Department of Chemistry

Development of tetrahydroisoquinoline analogues: Towards a treatment for Human African Trypanosomiasis

Danica Renae Cullen

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

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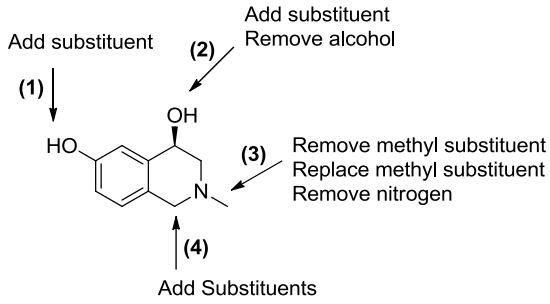
Abstract

Human African Trypanosomiasis (HAT) is a neglected disease endemic in sub-Saharan Africa. HAT is caused by the parasite *Trypanosoma brucei*, which is transmitted by the tsetse fly, and is fatal if left untreated. HAT occurs in two stages, the first being the haemolymphatic stage which progresses to the second stage once the parasite crosses the blood-brain barrier and enters the central nervous system. Currently effective treatments are available for the first stage of the disease, however treatment of the second stage is much more difficult. Only two drugs are currently available for treatment of stage two and they suffer from major drawbacks, namely toxicity and rigorous administration schemes which are not often possible in a rural setting. The lack of any new drugs being introduced for the treatment of HAT has led to growing resistance of the limited number of drugs which are currently available. New drugs are therefore desperately needed, which can effectively and efficiently treat HAT. This research describes the exploration of a new scaffold with the potential to be developed into an anti-HAT drug. The image below shows an isoquinoline scaffold which when substituted at the phenolic position with a benzyl or cyclohexylmethyl group showed preliminary activity against *T. b. rhodesiense* in the micromolar range.



In this research over 90 derivatives of the above isoquinoline scaffold were synthesised and evaluated for their *in vitro* activity against *T. b. rhodesiense* as well as their cytotoxicity towards mammalian cells. Synthesis of derivatives was focussed around modifications of four main parts of the scaffold which are summarised in the image above. Substitution of the phenol was thoroughly explored as well as

substitution directly at the aromatic ring at the same position (**1**). Modification of the benzylic alcohol (**2**) and the nitrogen atom (**3**) were explored, as well as the addition of substituents to the methylene carbon (**4**) and combinations of these. Synthesis of these derivatives and evaluation of their ability to inhibit *T. b. rhodesiense* allowed a structure-activity relationship to be developed for this isoquinoline scaffold. Five derivatives were identified with inhibition of *T. b. rhodesiense* in the sub-micromolar range with good selectivity over mammalian cells. These five derivatives provide good leads for further optimisation of this scaffold. All of the derivatives were also evaluated for their inhibition of two strains of *P. falciparum*, the causative agent of malaria. Two of these were found to be promising, showing inhibition of both strains of *P. falciparum* in the low micromolar range with good selectivity over mammalian cells.

A significant portion of the work described in this thesis has been published in three peer reviewed journals, as cited below:

Cullen, D. R.; Pengon, J.; Rattanajak, R.; Chaplin, J.; Kamchonwongpaisan, S.; Mocerino, M. *ChemistrySelect* **2016**, *1* (15), 4533–4538.

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Table of Contents

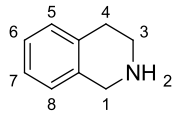
Abbreviations

Ac	acetyl	hr	hour
Ar	aryl	HRMS	high resolution mass spectrometry
ATP	adenosine triphosphate	Hz	Hertz
Bn	benzyl	IBX	2-iodoxybenzoic acid
BOC	*tert*-butyloxy dicarbonate	IC_{50}	half maximal inhibitory concentration
Bz	benzoyl	*J*	coupling constant
CNS	central nervous system	LCMS	liquid chromatography-mass spectrometry
DCM	dichloromethane	logD	logarithm of the distribution coefficient
DIAD	diisopropyl azodicarboxylate	logP	logarithm of the partition coefficient
DMF	*N*,*N*-dimethylformamide	m.p.	melting point
DMSO	dimethyl sulfoxide	*m/z*	mass to charge ratio
DPPF	1,1'-bis(diphenylphosphino) ferrocene	Me	methyl
EC_{50}	half maximal effective concentration	MEM	2-methoxyethoxymethyl
EGFR	epidermal growth factor receptor	min	minute
eq	equivalent	Ms	mesylate
Et	ethyl	NMR	nuclear magnetic resonance
GR	glutathione reductase	NTR's	nitroreductases
HAT	Human African Trypanosomiasis	ODC	ornithine decarboxylase
HMBC	heteronuclear multiple bond correlation	PFK	phosphofructokinase
HPLC	high performance liquid chromatography	Ph	phenyl
		ppm	parts per million
		Pr	propyl
		PS	petroleum spirits

QSAR	quantitative structure-activity relationship	Tf	triflate
		TFA	trifluoracetic acid
RF	retention factor	THF	tetrahydrofuran
RT	room temperature	TLC	thin layer chromatography
SAR	structure-activity relationship	TryR	trypanathione reductase
SI	selectivity index	TryS	trypanathione synthetase
T.b	*Trypanosoma brucei*	Ts	tosylate
TAO	trypanosome alternative oxidase	WHO	World Health Organisation
TBDPS	*tert*-butydiphenylsilyl	δ	chemical shift
t-Bu	*tert*-butyl	$[\alpha]_D$	specific rotation

Isoquinoline numbering

Throughout this document the isoquinoline scaffold is numbered according to IUPAC recommendations[1] as shown below.



1 Introduction

The health of over a billion people in some of the world's poorest countries is affected as a consequence of neglected tropical diseases. Neglected tropical diseases are a group of 17 communicable diseases which are present in tropical and subtropical countries worldwide.[2] The prevalence of these diseases is strongly dependant on control measures which are often neglected during periods of political instability, commonly leading to resurgence.[3] These diseases are considered neglected as they mostly affect impoverished populations in developing countries, and consequently interest from western governments and the pharmaceutical industry is low. As a result, research into these diseases is limited due to the prospect of little or no financial gain.[4–6] One of the most complex endemic neglected tropical diseases is known as Human African Trypanosomiasis, or more commonly African sleeping sickness.[2]

1.1 Human African Trypanosomiasis

Human African Trypanosomiasis (HAT) is a parasitic disease which occurs in sub-Saharan Africa. It is caused by the protozoan parasite *Trypanosoma brucei* which is transmitted by the tsetse fly.[3,7] It is a vector borne disease and is usually fatal if left untreated.[2]

1.1.1 Types of HAT

There are two subspecies of *Trypanosoma brucei* that are pathogenic for humans, *T. b. gambiense* and *T. b. rhodesiense*; a third type *T. b. brucei* infects only animals.[8] *T. b. gambiense* is prevalent in central and west Africa and causes a more chronic form of the disease. It is reported to be responsible for 98% of reported cases of HAT.[9] *T. b. rhodesiense* is prevalent in east and southern Africa and causes a more acute rapidly progressing form of the disease.[3]

1.1.2 Symptoms of HAT/clinical Features

For both types of HAT mentioned above there are two stages of infection: the haemolymphatic stage and the neurological stage. The haemolymphatic stage describes the stage where trypanosomes are restricted to the blood and lymphatic system.[3,9] Symptoms of this stage of the disease are generally non-specific and include malaise, headache, weight loss, fever, and fatigue.[5,10] The neurological stage is when trypanosomes cross the blood-brain barrier and invade the central nervous system (CNS).[9,11] One of the main symptoms of the second stage is a disruption of the sleep cycle, which gives this disease its more common name (sleeping sickness).[12] Many other symptoms can be observed, some of these being confusion, tremor, general motor weakness, psychiatric symptoms, as well as sensory and motor disturbances.[5,7,8] Due to the clinical manifestation of HAT the symptoms of both stages overlap and distinction between stages is difficult. Another consequence of the non-specific symptoms is misdiagnosis with other fever causing diseases and neuropsychiatric problems.[13,14] The symptoms of HAT are generally the same for the two forms of the disease, however they differ in terms of their severity and duration. *T. b. gambiense* is a more chronic form of the disease with an average duration of 3 years which is evenly divided between the first and second stages.[15] *T. b. rhodesiense* is a more acute form of the disease, with the first stage lasting only a few weeks, and leading to death within a few months.[16] Without treatment both types of HAT will ultimately lead to death.[3,5]

1.1.3 Transmission of HAT

The trypanosomes which cause HAT are transmitted by the tsetse fly from one mammalian host to another. Humans are the main reservoir for *T. b. gambiense*, while animals are the main reservoir for *T. b. rhodesiense*.[5,8] Trypanosome transmission begins with the tsetse fly feeding on an infected animal or human, followed by several differentiation steps of the trypanosome within the mid-gut of the fly. This leads to the development of an infective form of the trypanosome which subsequently reaches the fly's salivary glands and is transmitted to the human host by a bite.[3,5]

1.1.4 History

Reports of what is thought to be HAT have been recorded as early as the 14th century.[17] In the 20th century, multiple disastrous sleeping sickness epidemics were reported.[18] It was during these epidemics that the parasite which was responsible for the disease was discovered and linked with the tsetse fly.[17] Following this discovery, several control measures were set up which helped to control the disease. By the 1960s, the number of cases reported was very low,[19] which resulted in a slackening of control measures and eventually led to a resurgence of the disease by the 1990s. At this time the total number of cases of HAT was estimated to be 300,000.[20] By 2009, the number of reported cases of HAT had dropped to below 10,000 new cases.[21]

1.1.5 Current Situation

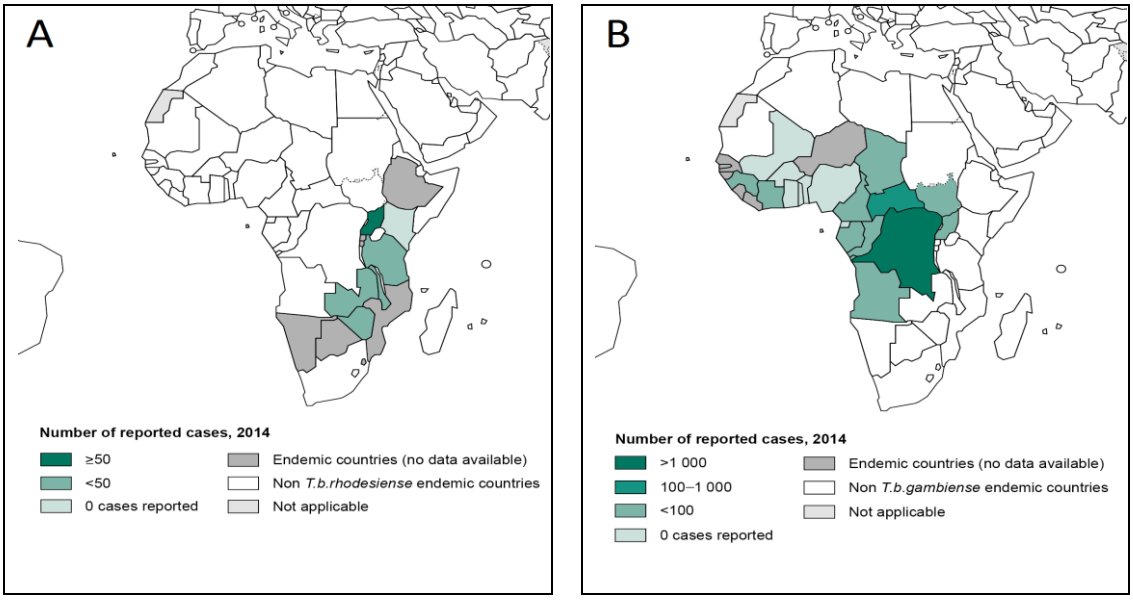


Figure 1 Map showing the number of reported cases of HAT in 2014. A: *T. b. rhodesiense*. B: *T. b. gambiense*. Image from WHO global health observatory map gallery.[22]

The current number of reported cases of HAT is summarised in **Figure 1**. In 2013, the number of reported cases of *T. b. gambiense* dropped to 6,228,[21] and the areas at high or very high risk dropped by 60% between 2008 and 2012.[23] The number of reported cases of *T. b. rhodesiense* in 2013 was less than 100, and the number of people at risk dropped by 95% during 2008-2012.[24] Although the number of cases of

T. b. rhodesiense has recently dropped dramatically, the zoonotic nature of this form of the disease means that it still holds its epidemic potential.[25]

1.1.5.1 Current treatments

Effective treatment of HAT relies on early detection while the patient is still in stage 1 of the disease, however most patients do not receive treatment until the disease has already progressed well past this point. This is due to two main reasons, the mild and non-specific symptoms present in the first stage of the disease, and the fact that the vast majority of people who are at risk are generally part of poor and neglected populations living in rural areas with limited access to healthcare.[2] Currently there are only 4 drugs registered for the treatment of HAT (see **Figure 2**).[26] Of these pentamidine **1** and suramin **2** are effective only in the first stage of the disease, against *T. b. gambiense* and *T. b. rhodesiense* respectively. However, neither of these drugs are effective against the second stage of the disease due to their inability to cross the blood-brain barrier, which results from the fact that they are highly charged at physiological pH.[27]

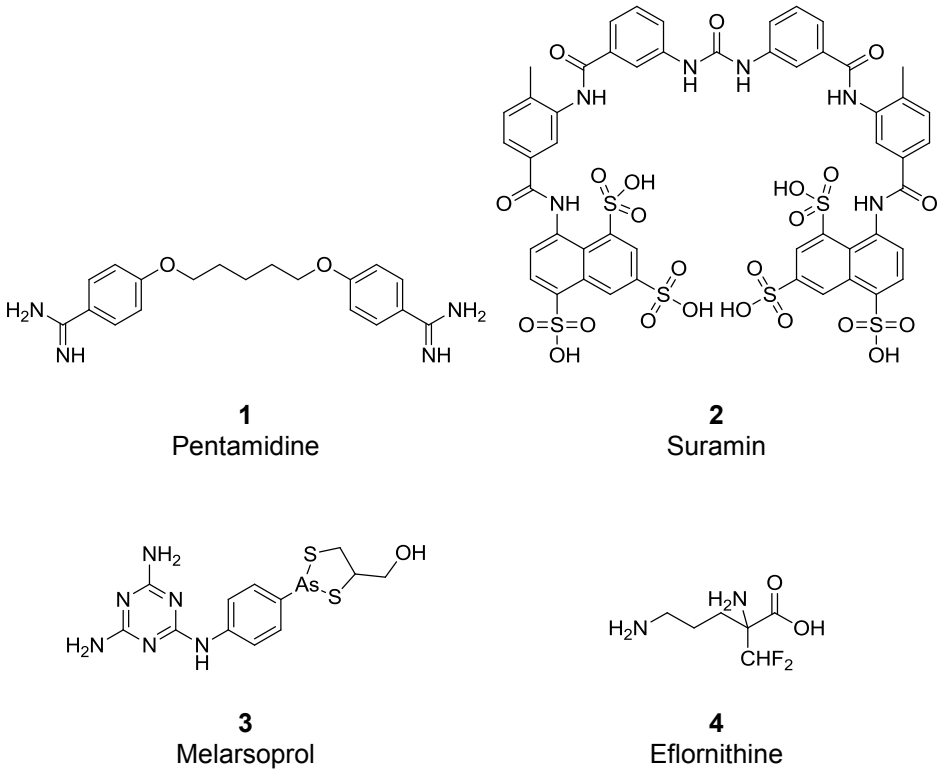


Figure 2 Four drugs registered for the treatment of HAT: pentamidine, suramin, melarsoprol, and eflornithine.

The second two drugs, melarsoprol **3** and eflornithine **4**, are used in the treatment of the second stage of the disease. Melarsoprol is effective against both types of the disease, however it is an arsenic based drug and is highly toxic. In approximately 5% of patients Melarsoprol causes adverse effects which lead to fatality.[20] Over the last decade there has been an increase in reports of melarsoprol resistance,[28] which is a cause for concern as it is currently the only effective treatment for *T. b. rhodesiense.* Eflornithine is less toxic than Melarsoprol, however it is only effective against *T. b. gambiense,* and is difficult to administer. Successful treatment with eflornithine requires that patients are administered one slow intravenous infusion of the drug every 6 hours for 14 days, resulting in a total of 56 infusions.[29] This rigorous administration scheme makes treatment with eflornithine expensive and difficult in a rural setting.[30] Recently a drug called nifurtimox **5** has been used in the treatment of HAT (**Figure 3**). Nifurtimox is an orally administered drug registered for the treatment of Chagas disease, a trypanosomal disease caused by the parasite *Trypanosoma cruzi,* which is endemic in Latin America.[31] Orally administered Nifurtimox is used in combination with intravenous eflornithine, resulting in a

significant reduction in the time and cost of treatment.[29] However, the combination therapy is still only effective against *T. b. gambiense,* and is still limited by the need for intravenous administration.[32] This combination therapy has been the only advance made in the treatment of HAT in the last 25 years.[32]

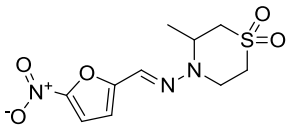


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Figure 3 Nifurtimox, a drug registered for the treatment of Chagas disease.

1.1.6 Significance

The drugs currently available to treat HAT are few, and suffer a number of drawbacks. Currently the only drug available to treat the second stage of *T. b. rhodesiense* is a toxic arsenic based drug which causes a number of adverse side effects which lead to death in some patients. The best available treatment for *T. b. gambiense* currently is the nifurtimox-eflornithine combination therapy. This is a step forward from the use of eflornithine by itself, however the treatment is still expensive and suffers from the drawback of requiring intravenous administration of the eflornithine. The lack of new drugs for the treatment of HAT in recent years has resulted in growing resistance to the currently available drugs, which are already limited in number and efficacy.[33] For these reasons it is important that new drugs are sought that work via different modes of action, and are cheaper and easier to administer than those currently available.

1.1.7 Current Clinical Trials

In the last 10 to 20 years there has been an increase in interest from the research community in novel treatments for HAT. Currently the most advanced candidate is an orally available drug by the name of fexinidazole **6** (**Figure 4**), which is administered orally once a day for 10 days.[34] In late 2012, it entered phase II/III clinical trials,[35] no outcomes have yet been reported. However, in 2016 additional

trials were started involving both adults and children as well as a phase IIIb trial including pregnant and lactating women.[36]

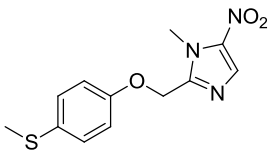

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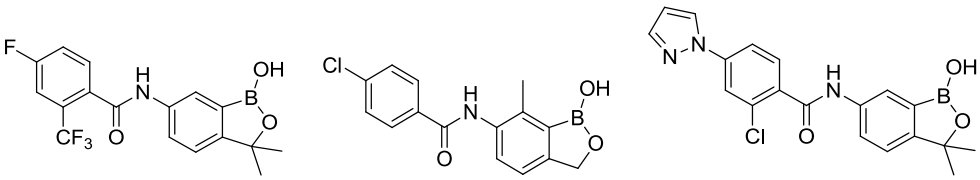
Figure 4 Structure of fexinidazole.

Another oral candidate is known as oxaborole SCYX-7158[37] **7** (**Figure 5**). The benefit of this candidate over fexinidazole is that it could potentially be given as a single oral dose due to its long half-life.[34] This candidate recently completed phase I clinical trials, and there are plans to proceed with phase II/III trials in 2016.[38] However, there have been no updates as yet on the commencement of these trials. As well as oxaborole SCYX-7158 there are two other similar candidates known as SCYX-1330682 and SCYX-1608210 **(Figure 5).**[39] The clinical development of these two candidates has currently been halted but will proceed in the event of any problems encountered with SCY-7158.[40,41]



7 SCYX-7158 **8** SCYX-1330682 **9** SCYX-1608210

Figure 5 Structure of oxaborole HAT candidates.

1.2 Recent HAT drug discovery

1.2.1 New molecules inspired by known antitrypanosomal agents

One approach to drug discovery is to take existing drugs or classes of compounds and use these as a starting point for drug discovery. This could include molecules that are known to be active against the intended target or a related target. This approach is usually known as target repurposing and has been coined by some as chemocentric drug discovey.[42]

1.2.1.1 Diamidines

There has been recent interest in diamidines (**Figure 6**) based on the currently used stage I HAT drug pentamidine **1**. Parfuramidine **10** was identified as a potentially orally available treatment for stage I HAT, and entered into clinical trials in 2000.[43] Parfuramidine advanced to phase III clinical trials but the trials were halted due to a later extended phase I trial which revealed delayed nephrotoxicity.[44] More recently an analogue of parafuramidine known as DB844 **11** has shown promising results in the oral treatment of second stage HAT, curing approximately 40% of cases in a monkey model.[45] A number of other diamidines have also been reported to have good antitrypanosomal activity with one such compound **12** resulting in 4/4 cures in a mouse model of *T. b. rhodesiense.*[46]

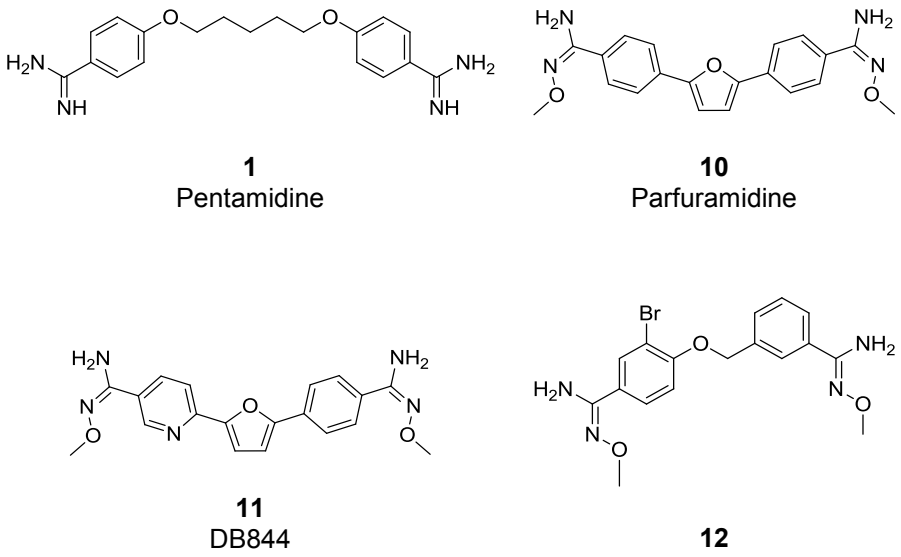


Figure 6 Recently reported diamidines showing activity for HAT.

1.2.1.2 Nitroheterocycles

Another area of interest in antitrypanosomal research are nitroheterocycles, inspired by the success of fexinidazole. Nitroheterocycles have been successful in the treatment of Chagas disease, a neglected parasitic disease endemic in areas of 21 Latin American countries, the current treatment for which is a nitroheterocycle known as benznidazole **13** (**Figure 7**).[2,9] In a general sense, the use of nitro containing compounds in drug discovery is usually avoided due to the high likelihood of toxicity issues arising,[47] however nitro groups are still found in many currently used drug molecules.[48–51] Many of these nitro containing drugs act as pro-drugs and must be activated within the pathogen, by nitroreductase enzymes (NTR), to have cytotoxic effects.[52] A parasite type I NTR is critical for trypanocidal activity of nitrohetereocycles. Parasites with lower levels of NTR were more resistant to nitro compounds, while those with elevated levels of NTR were hypersensitive. This enzyme, which is absent in mammalian cells, catalyses the two electron reduction of the nitro group to produce toxic metabolites.[52,53] It has been shown that nifurtimox acts in this way and is activated by these NTR's. Evidence has been reported which suggests that fexinidazole is also activated by the same NTR's.[53] This has raised concern that resistance could potentially be observed for fexinidazole before the drug has even been registered for use. This is because resistance seen in nifurtimox is believed to be due to down regulation of these NTR's and could be potentially be

translated to fexinidazole.[54] A laboratory generated *T. brucei* cell line resistant to nifurtimox was found to show cross resistance to fexinidazole.[47] Nitronaphthoquinones **14** have also been reported to have antitrypanosomal properties (**Figure 7**).[55] However, in this case it seems that the nitro group is not essential to *T. brucei* activity, rather it is the electron withdrawing nature of the nitro group that is important, with other electron withdrawing groups such as CF_3 and Cl also showing good activity. A class of nitroimidazoles **15** (**Figure 7**) have also been reported to show antitrypanosomal activity.[56] A SAR study was undertaken on a series of fifty 1-aryl-4-nitro-1*H*-imidazoles, with two of these compounds having curative action in mouse models of both *T. b. rhodesiense* and *T. b. brucei*. With no toxicity observed in this study, these compounds are promising leads for further development. A nitrotriazole based piperazide **16** has also been shown to have antitrypanosomal activity.[57] This compound was reported to be selectively active against *T. b. rhodesiense* with an IC_{50} of 0.23 μM. A number of similar compounds also exhibited antitrypanosomal activity but were not selective.

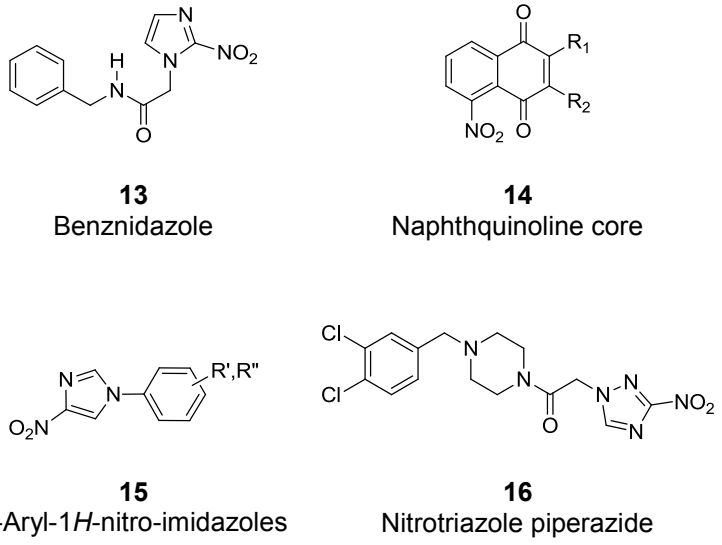


Figure 7 Nitroaryls showing anti-HAT activity.

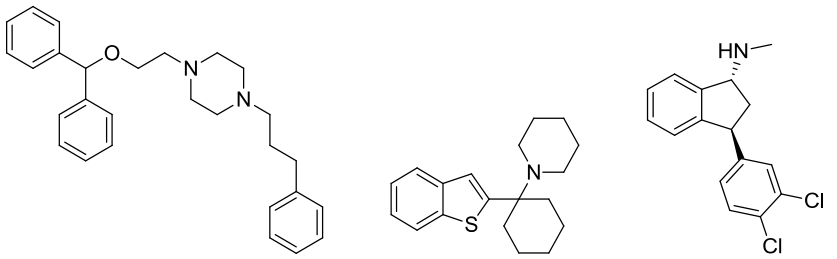
1.2.2 Target-based screening

Target-based screening is a popular drug discovery approach describing the identification and subsequent optimisation of a molecule that acts on a particular

target, usually an enzyme.[58] Generally such molecules are identified by high throughput screening methods against the desired target. Once identified the new lead compound can be optimised using structure based methods, including x-ray crystallography and computational modelling. This allows the binding mode of the lead compound to be explored and optimised. Target based screening is an important approach being used in the discovery of new anti-HAT agents.

1.2.2.1 Trypanothione reductase inhibitors

There has been a lot of recent interest into developing molecules to inhibit trypanothione reductase (TryR). TryR is an enzyme involved in the trypanothione based redox metabolism of *T. brucei* as well as some other parasites. In humans this system is not present and is instead carried out by glutathione and glutathione reductases (GR), and consequently it has been proposed as a good target for the selective inhibition of *T. brucei*.[59] A high throughput screen of the Sigma LOPAC1280 library of 1266 compounds was undertaken against TryR, with hits then being screened against *T. brucei* and human GR resulting in the identification of three new compounds (**Figure 8**) with properties warranting further investigation.[59] SAR studies were undertaken on one of these compounds, GBR-12935 **17**, which had an original EC_{50} of 9.3 μM against *T. brucei*. These studies resulted in the discovery of a competitive inhibitor of *Tb*TryR with a much improved potency against *T. brucei* (EC_{50} = 0.775 μM).[59] BTCP **18**, an analogue of a known anaesthetic drug phencyclidine, was also identified as a potential target. A small library of phencyclidine analogues were synthesised and inhibition of *Tb*TryR as well as *T. brucei* were determined. A detailed SAR was developed, however the activity of the compounds as compared to the original hit were only marginally improved and overall showed poor selectivity compared to mammalian cells.[60] The third hit compound indatraline **19**, a monoamine reuptake inhibitor, was derivatised in order to develop a SAR for this class of compound. However, it proved difficult to increase the potency of these derivatives as compared to indatraline, and it was discovered that the compounds showed a mixed mode of action which required further investigation.[61]



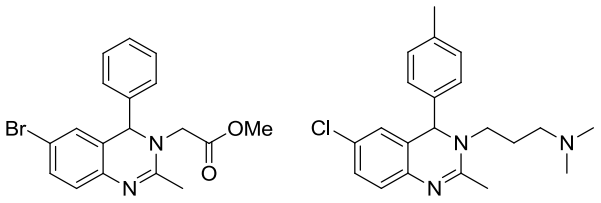
17
GBR-12935

18
BTCP

19
Indatraline

Figure 8 Three compounds identified from the LOPAC1280 library with TryR inhibition and trypanocidal activity.

A series of 3,4-dihydroquinazolines (**Figure 9**) has been reported as TryR inhibitors,[62] with the initial screening hit **20** having an IC_{50} of 6.8 μM against TryR and an EC_{50} of 40 μM against *T. brucei*. High resolution crystal structures of TryR alone, and TryR in complex with a number of inhibitors in this series were reported. These revealed that the enzyme undergoes a conformational change upon binding to the substrate, creating a new pocket which is then occupied by an aryl group on the ligand. This information on the structure and binding of TryR gave the opportunity to adopt a structure based design approach leading to more potent inhibitors, with the most potent inhibitor **21** having an IC_{50} of 0.23 μM against TryR and an EC_{50} of 0.73 μM against *T. brucei*, which provides a good starting point for further optimisation.[62]



20 **21**

Figure 9 A series of 3,4-dihydroquinazolines with activity against TryR.

A small library of 4-aminoquinoline heterodimers of three different structural classes was recently reported showing antitrypanosomal activity (**Figure 10**).[63] All of the compounds tested showed submicromolar IC_{50} values against *T. brucei*, with the most active compound having an IC_{50} of 0.12 μM, with good blood-brain barrier permeability. Mechanistic studies showed that inhibition of TryR is involved in the trypanocidal action of these compounds.[63]

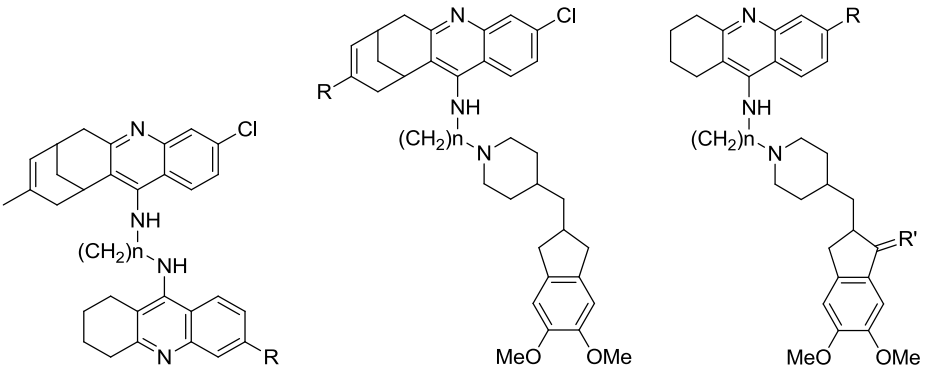


Figure 10 Three structural classes of 4-aminoquinoline heterodimers identified as having antitrypanosomal activity.

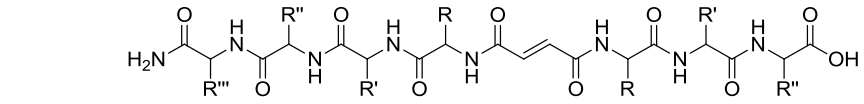
1.2.2.2 Rhodesain /cysteine protease Inhibitors

Another group of targets which have been popular recently in HAT drug discovery are cysteine proteases. Cysteine proteases have been suggested as good targets for the treatment of HAT. Parasitic organisms generally rely on cysteine proteases whereas humans rely on serine proteases, therefore cysteine proteases have been proposed as potential targets for selective antiparasitic drug design. Rhodesain is the major cysteine protease expressed by *T. b. rhodesiense*, and in the past few decades many compounds have been identified as rhodesain inhibitors.[64] There are three main classes of rhodesain inhibitors that have been reported, peptide-based inhibitors, peptidomimetic inhibitors, and nonpeptidyl inhibitors.

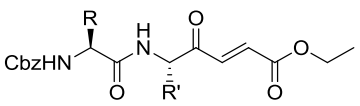
1.2.2.3 Peptide based rhodesain inhibitors

Peptide-based inhibitors are generally made up of a peptide segment for recognition by the enzyme, and what is termed as a warhead which is usually an electrophilic moiety that can undergo nucleophilic attack of the cysteine residue in the active site.[64] A series of heptapeptides **25** based on fumaric acid (**Figure 11**) have been identified as cysteine protease inhibitors via high throughput screening.[65] These peptides contain fumaric acid as the electrophilic moiety, which irreversibly binds to the active site cysteine residue of rhodesain via a conjugate addition reaction, effectively inhibiting rhodesain. Further studies of this series of inhibitors led to the identification of a number of compounds with inhibition of *T. b. brucei* in the

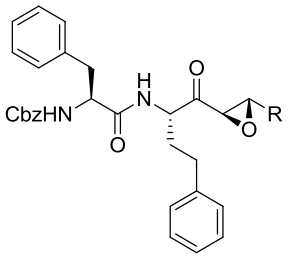
micromolar range, including a reversible inhibitor.[66] Another series of rhodesain inhibitors reported consists of dipeptidyl enoates **26** containing a 4-oxoenoate moiety acting as a Michael acceptor (**Figure 11**). These compounds have been shown to be potent rhodesain inhibitors, inhibiting rhodesain in the best case with an IC_{50} of 16.4 nM, however these compounds have yet to be tested *in vitro* against the parasite.[67] A rhodesain inhibitor **27** which combines a previously reported α-β-epoxy residue with a Cbz-Phe-HPhe sequence known to be selective for cruzain (cysteine protease present in *Trypanosoma cruzi*) has also been reported (**Figure 11**).[68] The best of these inhibitors was reported to have an IC_{50} for rhodesain of 3.5 nM and inhibition of *T. b. brucei in vitro* of 42%. Azadipeptide nitriles **28** have also been shown to inhibit rhodesain.[69] A library of azadipeptide nitriles (**Figure 11**) were recently shown to be nanomolar inhibitors of rhodesain, these compounds also showed trypanocidal effects, with the best compound showing an IC_{50} of 1.1 μM in a bloodstream form of *T. b. brucei*. Proteomics studies were also undertaken on these compounds confirming that rhodesain was the target.



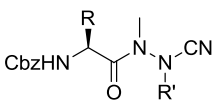
25
Heptapeptides



26
Dipeptidyl enoates



27
Dipeptidyl-α-β-epoxyesters



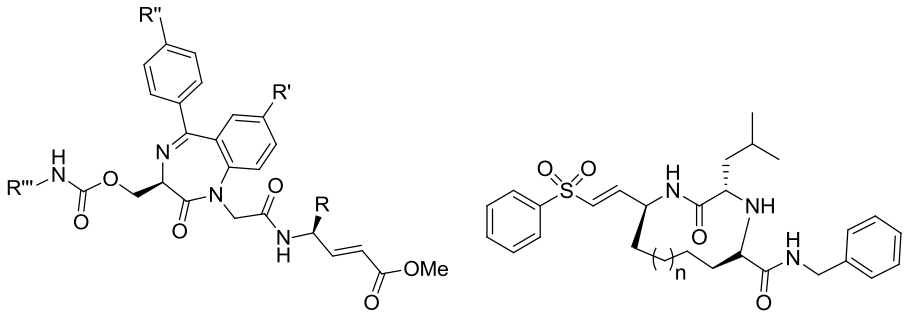
28
Azadipeptide nitriles

Figure 11 Peptide based inhibitors of rhodesain.

1.2.2.4 Peptidomimetic rhodesain inhibitors

Peptidomimetics are another class of cysteine protease inhibitors which have been of recent interest. Peptidomimetics mimic peptides but have an advantage over them in

that they can be designed with particular features giving them the potential to overcome some of the limitations of peptide based inhibitors. These features can include improving stability at physiological pH, improving selectivity through rigidity, as well as modifications allowing for better absorption through the blood-brain barrier. It is possible to achieve this in a number of ways including using unnatural amino acids, using amide bond isosteres, or locking the peptide into a rigid conformation.[64] Peptidomimetics based on a 1,4 benzodiazepine scaffold **29** have been reported as cysteine protease inhibitors (**Figure 12**).[64] It was suggested that these mimic a β-turn, which has been proposed as the active form of linear peptides. The most effective inhibitors of this kind included a vinyl ester as the warhead to inactivate rhodesain via a Michael addition. The most promising inhibitor from this series was reported to have excellent selectivity for rhodesain with an IC_{50} value of 4.8 μM for *T. b. brucei*. Another series of vinyl sulfone containing compounds **30** has also been shown to inhibit rhodesain.[70] In these compounds the peptide chain is locked to give a macrocyclic structure with a more rigid scaffold (**Figure 12**).



29
1,4-Benzodiazepine peptidomimetics

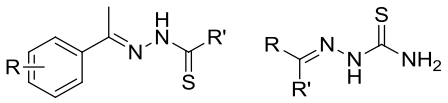
30
Macrocyclic peoptidomimetics

Figure 12 Peptidomimetic inhibitors of rhodesain.

1.2.2.5 Nonpeptidyl rhodesain inhibitors

The final class of rhodesain inhibitors that has been reported are nonpeptidyl inhibitors. A series of thiosemicarbazones (**Figure 13**) has been shown to inhibit rhodesain with good antitrypanosomal activity against *T. brucei*.[71] A library of thiosemicarbazones **31** was synthesised and screened against rhodesain as well as *T. b. brucei.* Of the compounds tested most showed activity against *T. b. brucei* in the low micromolar range. The best compound in this series showed no correlation in

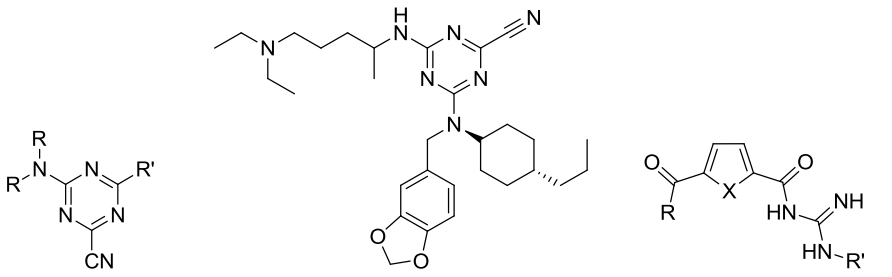
activity against *T. b. brucei* and inhibition of rhodesain indicating another mechanism of action. More recently another series of thiosemicarbazones **32** (**Figure 13**) was reported to show good inhibition of rhodesain. Of these compounds the best showed micromolar activity against *T. b. brucei* with good selectivity as compared to human cathespins.[72]



31 **32**

Figure 13 Two classes of thiosemicarbazone inhibitors of rhodesain.

Triazine nitriles have also been identified as inhibitors of rhodesain (**Figure 14**). High throughput screening identified a class of triazine nitriles **33** as inhibitors of rhodesain.[73] Initial hits were micromolar inhibitors of rhodesain, however they showed no activity against *T. b. brucei*. Activity against *T. b. brucei* was significantly improved by a number of structural modifications of the original hits, leading to compounds with activity against *T. b. brucei* in the micromolar range. Another series of triazine nitriles **34** has also been reported to have activity against rhodesain. Structure based design techniques and computer aided modelling were employed to design and synthesise a series of functionalised triazine nitriles. These compounds were found to show good inhibition of rhodesain but limited activity against the parasite.[74] Further structure based design resulted in compounds showing a significant improvement in antitrypanosomal activity with the best compound having an IC_{50} in the sub-micromolar range (**Figure 14**).[75] *N*-Protected guanidine compounds containing either a pyrrole or furan ring **35** (**Figure 14**) have also been reported to be antitrypanosomal, with the mechanism of action being inhibition of rhodesain. A structure activity relationship study of *N*-protected guanidines led to the development of rhodesain inhibitors with activity against *T. b. brucei* in the low micromolar range.[76]



33
Triazine nitriles 1

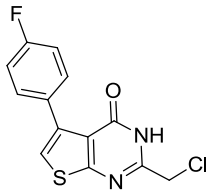
34
Triazine nitriles 2

35
Guanidine compounds

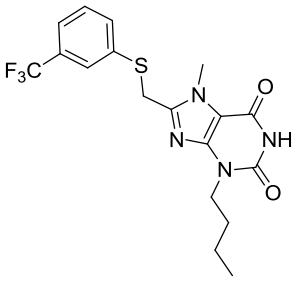
Figure 14 Triazine nitriles and guanidines with activity against rhodesain.

1.2.2.6 Tryparedoxin Inhibitors

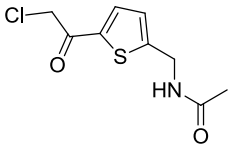
Tryparedoxin has also been identified as another important protein in the redox metabolism of *T. brucei*, and could be a possible target for *T. brucei* inhibition.[77] A high throughput screen and subsequent studies led to the identification of 12 covalent inhibitors of tryparedoxin, which were classed into 5 groups (**Figure 15**). The compounds were reported to show inhibition of *T. brucei* down to 1 μM with 83 fold selectivity as compared to HeLa (human cell line) cells.



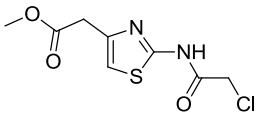
36
Thienopyrimidine-ones



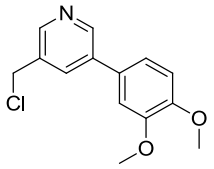
37
Purine diones



38
Chloroacetyl-thiophenes



39
Chloro-acetamides

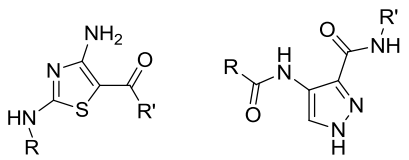


40
Chloromethyl-phenylpyridines

Figure 15 Representatives of five classes of compounds found to inhibit tryparedoxin.

1.2.2.7 GSK3 inhibitors

Recently a series of antitrypanosomal compounds which inhibit the *T. brucei* protein kinase GSK3 (TbGSK3) have been identified.[78] TbGSK3 has been shown to be important to the growth of *T. brucei* parasites *in vitro*, and is hence a potential target for the development of antitrypanosomal compounds. Initially high throughput screening identified a number of efficient inhibitors of TbGSK3 with sub-micromolar potency, two of these are shown in (**Figure 16**). The most active series was a series of 2,4-diaminothiazoles **41** which were found to be active against the parasite *T. b. brucei* with EC_{50} values in the sub-micromolar range. Aminopyrazole derivatives **42** have also been reported as TbGSK3 inhibitors.[79] A SAR investigation of an initial lead aminopyrazole led to the development of a series of aminopyrazole amides showing low nanomolar inhibition of TbGSK3 and high selectivity. However, activity against the parasite *T. b. brucei* was significantly lower with EC_{50} values in the micromolar range.

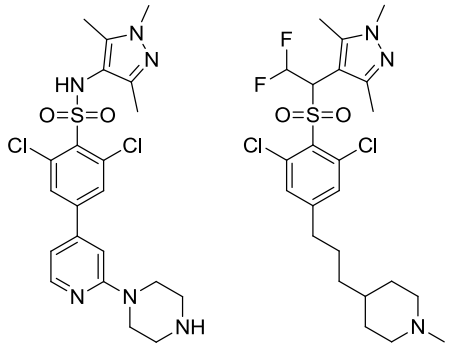


41 **42**

Figure 16 Diaminothiazoles and aminopyrazoles as TbGSK3 inhibitors.

1.2.2.8 *N*-Myristoyl transferase inhibitors

Pyrazole sulfonamide derivatives have been reported to inhibit *T. brucei N*-myristoyl transferase (*Tb*NMT).[80] There has been recent evidence that *Tb*NMT is a good target for the treatment of HAT due to it being essential for parasite growth.[81] Initial high throughput screening studies reported a pyrazole sulfonamide derivative **43** as an inhibitor of *Tb*NMT, however this compound showed very poor blood-brain barrier permeability (**Figure 17**).[80] More recently optimisation of this lead compound via an extensive SAR study, has led to a new lead compound **44** (**Figure 17**) with much improved blood-brain barrier permeability. However, this compound only proved partially efficacious when tested in a mouse model of stage 2 HAT.[82]

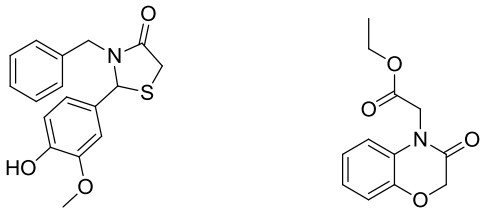


43 **44**

Figure 17 Pyrazole sulfonamide inhibitors of *N*-myristoyl transferase.

In the same high throughput screen thiazolidinone and benzomorpholine type compounds (**Figure 18**) were also reported as hits for *Tb*NMT. The thiazolidinone hit **45** was optimised by expanding the original hit into a series of compounds, resulting in the discovery of a new potential lead compound with an EC_{50} (*T. brucei*) of 6.3 μM, as well as discovery of the binding mode in the form of a crystal structure

which will be an important tool for future structure based optimisation.[83] The benzomorpholine hit **46** was also optimised using a structure based approach, as well as SAR studies. Compounds from this study showed very potent activity (EC_{50} *T. brucei* = 7 nM).[83]



45
Thiazolidinone series

46
Benzomorpholine series

Figure 18 Two series of initial Hit compounds for *Tb*NMT.

1.2.2.9 Trypanothione synthetase inhibitors

A series of indazoles which inhibit trypanathione synthetase (TryS) has been reported.[84] *Tb*TryS has been reported as being essential for *T. brucei* growth making it a good drug target.[85] A high throughput screen of a compound library containing over 62000 compounds was undertaken to identify inhibitors of *Tb*TryS. This resulted in the identification of six novel *Tb*TryS inhibitors. Three of these compounds **47, 48, 49** (**Figure 19**) were identified as having an overlapping pharmacophore for *Tb*TryS activity and were hybridised to give a new core scaffold **50** (**Figure 19**). Optimisation of this scaffold led to compounds with tenfold improved *Tb*TryS activity (<100 nM) over the original hits. However, these compounds failed to show good activity in cell based assays against *T. brucei*.

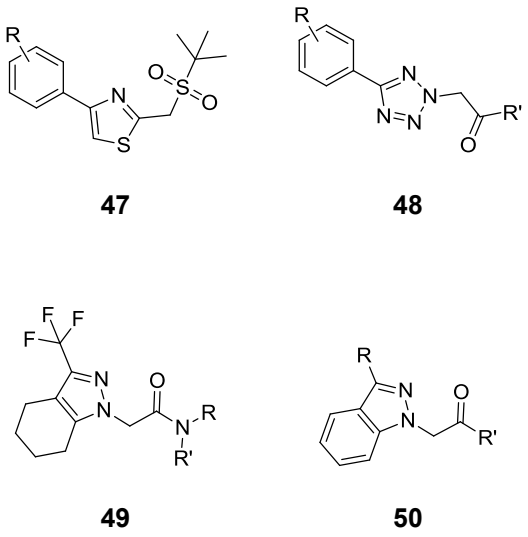


Figure 19 TryS inhibitors: Identification of three initial hit compounds and development of a new core scaffold.

1.2.2.10 Ornithine decarboxylase inhibitors

Another enzyme which has been targeted in HAT drug discovery is ornithine decarboxylase, which catalyses the first step of polyamine synthesis in *T. brucei.*[86] Eflornithine, which is currently used in the treatment of HAT, is an inhibitor of ornithine decarboxylase (ODC).[87] A high throughput screen for inhibitors of *Tb*ODC resulted in the identification of four novel series of *Tb*ODC inhibitors (**Figure 20**) with previously uncharacterised binding modes.[86] Of these series the benzothiazoles **51**, indoles **53**, and bisbiguanides **54** were shown to be good inhibitors of *Tb*ODC however they were nonselective inhibiting both *Tb*ODC and human ODC. The dithioamidines **52** showed the most promise having the ability to selectively inhibit *Tb*ODC over human ODC, with the potential to be optimised to improve potency.

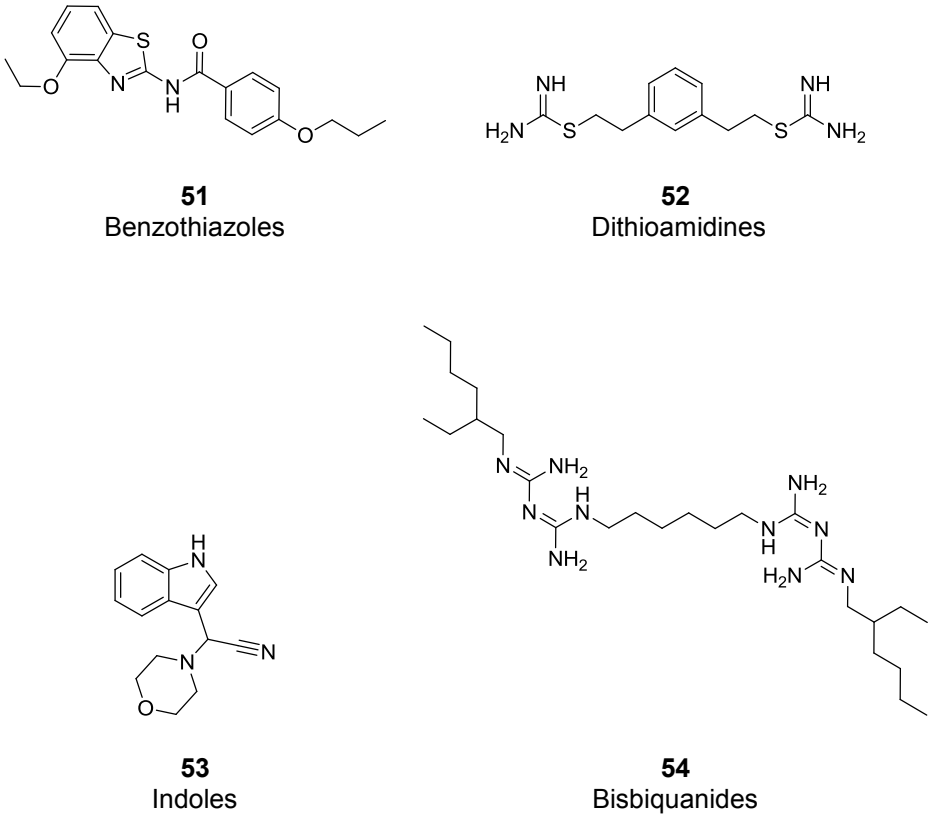
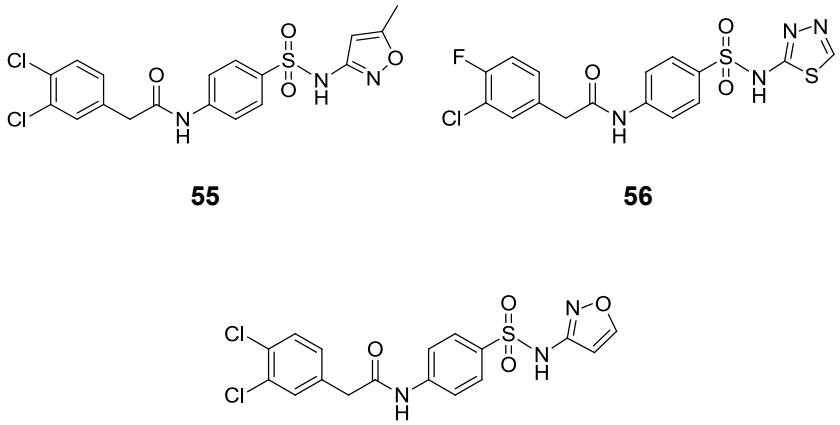


Figure 20 Ornithine decarboxylase inhibitors.

1.2.2.11 Phosphofructokinase Inhibitors

The *T. brucei* parasite is dependent on the metabolism of glucose for ATP generation, and the glycolytic enzyme phosphofructokinase (PFK) is essential for this process. Consequently PFK has been suggested as a potential drug target for HAT.[88] High throughput screening identified an amidosulfonamide **55** (**Figure 21**) with micromolar inhibition of TbPFK.[88] SAR and optimisation studies led to the most potent compound **56** in the series with an IC_{50} of 15 nM against *Tb*PFK, however this compound showed no activity against *T. b. rhodesiense*. Another compound **57** showed less potency for *Tb*PFK, with an IC_{50} of 0.37 μM, but had an ED_{50} of 16.3 μM against *T. b. rhodesiense* with low cytotoxicity (**Figure 21**). This compound represents a new potential lead for HAT.



55 **56**

57

Figure 21 Amidosulfonamide inhibitors of *Tb*PFK.

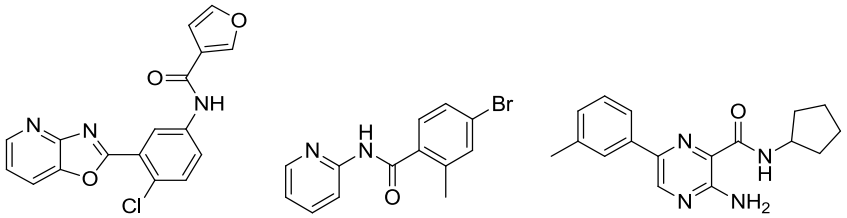
1.2.3 Phenotypic screening

Before the introduction of target based drug discovery phenotypic drug discovery was the main approach.[58] Phenotypic screening, similar to target based screening usually involves high throughput methods, however rather than screening molecules against specific targets and measuring a binding response, molecules are screened against a whole cell or organism and any phenotypic changes assessed.[42] Phenotypic changes can include any biological effect. In the case of HAT, parasite growth inhibition is usually the monitored phenotypic change. An advantage of phenotypic screening is that it can be used even when limited knowledge is known about the mechanism of the disease being targeted.

1.2.3.1 Oxazolopyridines, pyridyl benzamides and pyrazine carboxamides

Eight new compounds of five different chemical classes were identified as being potential candidates for HAT drug discovery via a high throughput screen of a library of 87,296 compounds.[89] From this screen three classes of compounds have been further optimised. An oxazolopyridine derivative was reported to have an IC_{50} of 0.22 μM for *T. b. brucei* and 0.59 μM for *T. b. rhodesiense*. A SAR study led to the identification of the most active compound **58** (**Figure 22**) with an IC_{50} of 91 nM for *T. b. rhodesiense* and much greater selectivity for *T. b. rhodesiense* as compared to a mammalian cell line.[90] A pyridyl benzamide with an initial IC_{50} of 12 μM was also

identified from this screen. Optimisation studies led to a significant improvement in activity with the best compound **59** (**Figure 22**) having an IC_{50} of 45 nM and a selectivity for *T. b. rhodesiense* over 4000 times greater than that of a mammalian cell line.[91] Pyrazine carboxamides were also identified as potential targets for HAT from this screen. The original hit compound was reported with an IC_{50} of 0.49 μM. Following SAR optimisation the best compound **60** (**Figure 22**) was reported to have an EC_{50} of 24 nM and a selectivity for *T. b. rhodesiense* 1500 times greater than that of mammalian cells.[92]



58 Oxazolopyridine

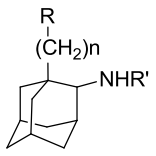
59 Pyridyl benzamide

60 Pyrazine carboxamide

Figure 22 Three compounds from the optimisation of hits identified through high throughput screening.

1.2.3.2 Adamantanes

A class of adamantanes has also been reported to have antitrypanosomal activity. The antitrypanosomal activity of substituted adamantanes has been correlated with hydrophobic substitutions on the adamantane ring. Alkyl aminoadamantanes (**Figure 23**) were reported to have antitrypanosomal activity with IC_{50} values as low as 90 nM, however no toxicity data was reported.[93,94] The most active adamantane was substituted with a guanylhydrazone and an alkyl chain 10 carbons in length. It is hypothesised that these molecules block a parasite membrane localised ion channel.[93]

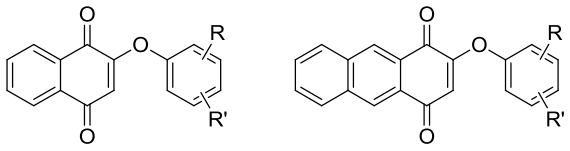


61

Figure 23 Adamantane derivatives showing antitrypanosomal activity.

1.2.3.3 Quinones

A small library of naphthoquinone **62** and anthraquinone **63** derivatives (**Figure 24**) has been reported to show antitrypanosomal activity.[95] The best compound showed an IC_{50} of 50 nM against *T. b. rhodesiense*, however most derivatives were found to be considerably cytotoxic. One derivative showed an IC_{50} of 80 nM and a selectivity index of 74, providing a potential hit compound. Through further study of this compound it was found that it involved a multi-target mechanism of action, including the ability to generate oxygen radicals. [96]

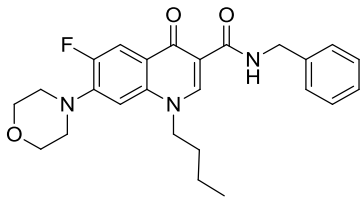


62 **63**

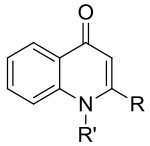
Figure 24 Naphthoquinone and anthraquinone derivatives with antitrypanosomal activity.

1.2.3.4 Quinolones

A library of 4-quinolone-3-carboxamides was synthesised and tested for antitrypanosomal activity.[97] Subsequent structure activity relationship studies led to the identification of a potent inhibitor of *T. b. rhodesiense* with an IC_{50} of 9 nM **64** (**Figure 25**), which is thought to act by inhibiting proteins involved in kinetoplast segregation. This compound was found to have low cytotoxicity but was unfortunately ineffective when administered orally in an animal model, however it is a promising structure for further optimisation. Another series of 4-(1*H*)-quinolone derivatives **65** has also been reported to have antitrypanosomal activity (**Figure 25**).[98] These compounds showed micromolar inhibition of *T. b. rhodesiense*, with the best compound having an IC_{50} of 1.07 μM, with good selectivity.



64
Quinolone carboxamide inhibitor

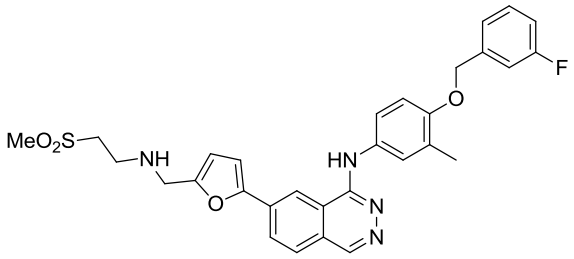


65
Quinolone inhibitor

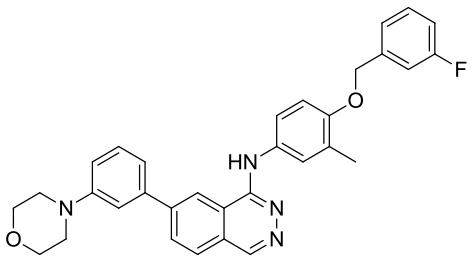
Figure 25 Quinolone inhibitors of *T. b. rhodesiense*.

1.2.3.5 Anilinoquinazolines

Lapatinib **66** is a 4-anilinoquinazoline registered as an epidermal growth factor receptor (EGFR) inhibitor, but was recently reported to show activity against HAT (**Figure 26**). Following this, lapatinib was optimised leading to the synthesis of a new potent HAT inhibitor **67** with an EC_{50} of 42 nM (**Figure 26**).[99] This compound was shown to have good selectivity and bioavailability as well as showing modest effects when tested in a mouse model of HAT. The method of action is unclear, however this compound provides a good starting point for further optimisation.



66
Lapatinib

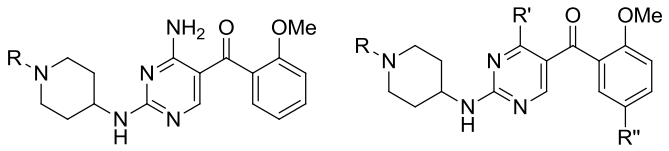


67

Figure 26 4-Anilinoquinazoline inhibitors of HAT.

1.2.3.6 Diaminopyrimidines

2,4-Diaminopyrimidines (**Figure 27**) have been shown to have activity against HAT, with kinase inhibition being suggested as the mode of action.[100] A SAR study of these 2,4-diaminopyrimidines **68** led to the discovery of three compounds which had IC_{50} values in the low micromolar to nanomolar range and were able to cure 100% of mice tested in a bloodstream model of *T. b. brucei*. The ability of these compounds to cross the blood-brain barrier was assessed through *in vitro* permeability studies. The compounds were found to show poor *in vitro* permeability, suggesting they would not be able to cross the blood-brain barrier. This led to the development of a series of 4-des-amino pyrimidines **69** (**Figure 27**) with improved *in vitro* permeability. Unfortunately this new set of compounds did not give consistent cure rates when tested in an animal model of bloodstream *T. b. brucei*.[101]

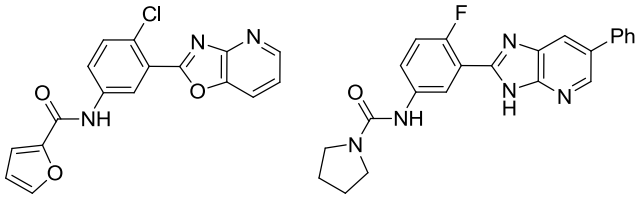


68 **69**

Figure 27 Diamino and Des-amino pyrimidines with HAT activity.

1.2.3.7 Imidazopyridines

A substituted 2-(3-aminophenyl)oxazolopyridine **70** was identified from a high throughput screen of 700,000 compounds as a potential lead compound for the treatment of HAT (**Figure 28**). This compound had an EC_{50} of 22 nM against *T. b. brucei in vitro*. Through the optimisation of this compound, imidazopyridines were identified as being highly potent antitrypanosomal compounds. The most potent of these, **71**, had an EC_{50} of 2 nM against *T. b. brucei in vitro* and was able to cure *T. b. rhodesiense* infected mice when administered orally.[102]



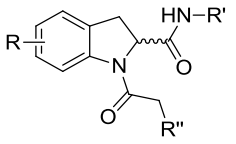
70
Oxazolopyridine

71
Imidazopyridine

Figure 28 Oxazolo and imidazopyridines with HAT activity.

1.2.3.8 Indoline carboxamide derivatives

A series of indoline-2-carboxamides (**Figure 29**) has been found to have potent activity against *T. b. brucei*.[103] This series of compounds was identified from screening of a focussed protease library against *T. b. brucei in vitro*. Optimisation of this series led to the development of nanomolar inhibitors of *T. b. brucei* with excellent selectivity over mammalian cells. One particular compound in the series was able to cure a stage one animal model of HAT. Some compounds in the series were found to be brain penetrant and were able to partially cure a stage two animal model of HAT.



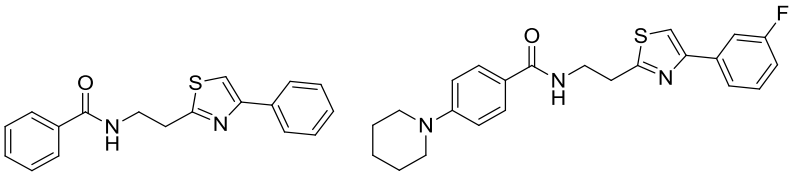
72

Figure 29 Indoline carboxamide derivatives with HAT activity.

1.2.3.9 Thiazol-2-ethylamines

A phenotypic high-throughput screen performed by the Genomics Institute of the Novartis Research Foundation identified 2-(benzamido)ethyl-4-phenylthiazole **73** as having inhibition of *T. brucei* below 0.63 μM and being non-toxic to mammalian cells.[104] Analogues of this were synthesised, and of these 42 out of 72 were found to be more potent inhibitors of *T. brucei* than the original hit compound. Of these a series of piperidyl derivatives were found to be the most promising, with one derivative **74** having an IC_{50} of 9 nM and excellent selectivity for *T. brucei* over

mammalian cells (SI>18,000). When tested *in vivo* some of these compounds were able to cause temporary reduction in parasitemia, however none were able to cure infected mice. The lack of potency *in vivo* was thought to be caused by poor metabolic stability of the compounds.

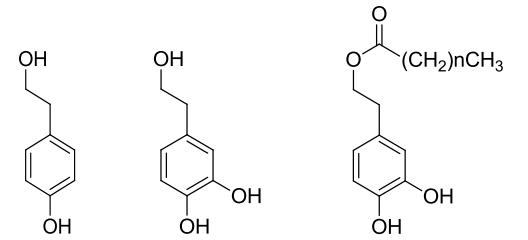


73 **74**

Figure 30 Thiazol-2-ethylamines with activity against *T. brucei*.

1.2.3.10 Tyrosol and hydroxytyrosol derivatives

Tyrosol **75** has been reported to have mild activity against *T. b. rhodesiense*.[105] More recently a study of derivatives of tyrosol **75** and hydroxyltyrosol **76** found that many derivatives showed good activity against *T. brucei*.[106] The most potent inhibitors were decanoate and dodecanoate esters of hydroxytyrosol **77** which exhibited sub-micromolar inhibition of *T. brucei*. Both derivatives were also reported to be more than hundredfold more selective for *T. brucei* than mammalian cells.



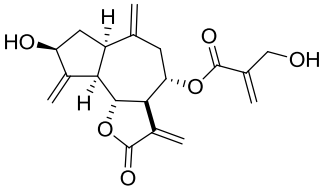
75 Tyrosol **76** Hydroxytyrosol **77** Where n=8 or 10

Figure 31 Structures of tyrosol and hydroxytyrosol.

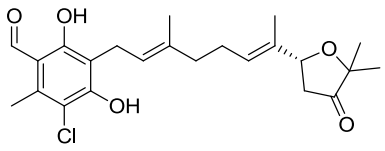
1.2.3.11 Natural products

There has been a lot of interest recently in the use of natural products in HAT drug discovery. Cynaropicrin **78** a natural product from the herb *Centaurea salmantica* L.

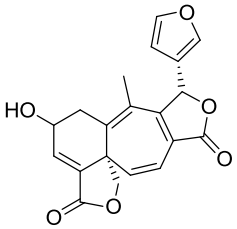
(Asteraceae), was identified through a high throughput screen of 1800 plant and fungal extracts as a potent *in vitro* inhibitor of HAT (**Figure 32**).[107] Cynaropicrin was reported to have an IC_{50} of 0.3 μM against *T. b. rhodesiense in vitro*, as well as having potent *in vivo* activity. The mechanism of action was later determined to be inhibition of trypanosomal ornithine decarboxylase as well as intracellular trypanothione depletion. [108] A SAR study was also undertaken but did not lead to the discovery of any derivatives with significantly increased activity as compared to cynaropicrin.[109] Another natural product ascofuranone **79** has also been shown to be active against *T. b. brucei in vivo*.[110] Ascofuranone acts by inhibiting the cyanide-insensitive trypanosome alternative oxidase (TAO). TAO is vital for trypanosome aerobic respiration but is not present in humans, and hence provides a potential selective target. Ascofuranone and its derivatives have been shown to have sub-nanomolar inhibition of TAO, providing an excellent lead compound for the treatment of HAT.[111] Analogues of salviandulin E **80**, originally isolated from the plant *Salvia leucantha (Lamiaceae),* have been reported to show antitrypanosomal effects.[112] Of these analogues the most potent was reported to have an IC_{50} of 0.14 μM against *T. b. brucei* with a good selectivity index when compared to mammalian cells.



78
Cynaropicrin



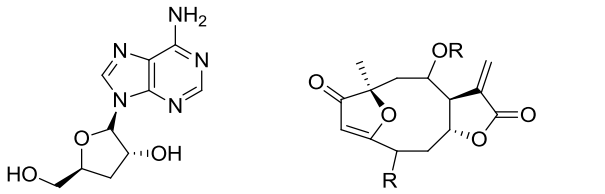
79
Ascofuranone



80
Salviandulin E

Figure 32 Natural products with anti-HAT activity.

Cordycepin **81** (**Figure 33**), isolated from the parasitic fungus *Cordyceps militari,* has been known to have antitrypanosomal properties since the 1970's.[113] More recently cordycepin was reported as a selective inhibitor of *T. b. brucei* with an IC_{50} of 32 nM *in vitro*, however it is inactive *in vivo*.[114] A SAR study of cordycepin led to the identification of 2-fluorocordycepin which was shown to retain reasonable activity and selectivity for *T. b. brucei in vitro*, and more importantly when tested *in vivo* was able to cure a mouse model of *T. b. brucei*. Sesquiterpene lactones (STL's) have been shown recently to have potent activity against *T. b. rhodesiense*.[115] A quantitative structure activity relationship (QSAR) analysis was undertaken on a set of 69 STL's for activity against *T. b. rhodesiense*.[116] This QSAR model was then used to predict the activity of a virtual library of 1750 STL structures. A group of furanoheliangolide type STL's **82** (**Figure 33**) were predicted to have high *in vitro* activity for *T. b. rhodesiense* and four representatives were then subjected to *in vitro* testing. Of these compounds all four showed activity against *T. b. rhodesiense* in the nanomolar range with the most potent compound having an IC_{50} of 15 nM and a selectivity index of 77.



81
Cordycepin

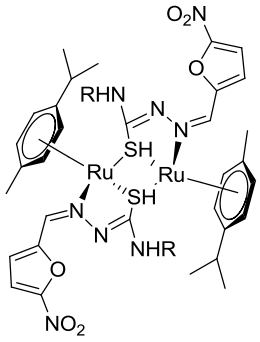
82
Furanoheliangolide type STL's

Figure 33 Natural products with anti-HAT activity.

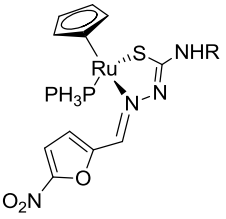
1.2.3.12 Organometallics

There have also been some reports in the literature of organometallic compounds having antitrypanosomal properties. Ruthenium compounds **83** and **84** have recently been reported to have antitrypanosomal activity (**Figure 34**).[117,118] These compounds incorporate a bioactive nitrofuran containing thiosemicarbazone ligand, which is known to have antitrypanosomal activity.[119,120] They showed activity against *T. b. brucei* with IC_{50} values in the low micromolar range and good selectivity over mammalian cells.

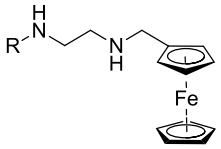
Ferrocenyl containing compounds **85** have also been shown to have activity against HAT (**Figure 34**).[121] The ferrocene group was incorporated into a benzyl diamine resulting in increased antitrypanosomal activity, with the best compounds having IC_{50} values against *T. b. brucei* in the low micromolar range.



83
Dimeric ruthenium compounds



84
Ruthenium compounds



85
Ferrocenyl diamines

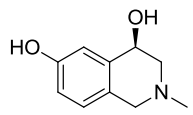
Figure 34 Organometallic compounds with antitrypanosomal activity.

There have been a number of promising compounds reported recently, many showing activity in the low nanomolar range *in vitro* and some also showing promising activity *in vivo*. Some particuarly interesting compounds are **46**, **59**, **60**, **64**, **67**, **71**, **74**, and **82** which all show activity below 50 nM against either *T. b. brucei* or *T. b. rhodesiense*. Of these **67** and **71** also show promising activity when administered orally in mouse models.

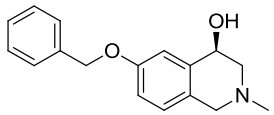
1.3 Preliminary work and lead compound

1.3.1 Lead Compound

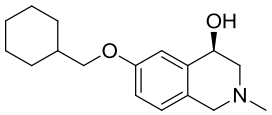
Unpublished work carried out by Epichem Pty Ltd has shown that two derivatives of (4*R*)-4,6-dihydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**86**) display antitrypanosomal activity (**Figure 35**). These compounds (**87** and **88**) were tested *in vitro* for activity against *T. b. rhodesiense* by the Murdoch University Parasitology group, and were found to have IC_{50} values of 4.9 and 4.8 μM respectively (**Figure 35**). The parent compound **86** did not show any activity. Isoquinoline **86** is a derivative of the common decongestant phenylephrine[122] and can be easily synthesised from phenylephrine via a Pictet-Spengler cyclisation with formaldehyde.



86



87
IC_{50} (*T. b. rhodesiense*) = 4.9 μM
IC_{50} (cytotoxicity) >100 μM



88
IC_{50} (*T. b. rhodesiense*) = 4.8 μM
IC_{50} (cytotoxicity) =60 μM

Figure 35 Lead compound and preliminary results.

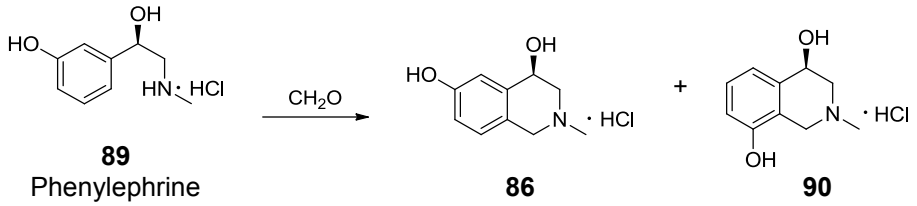
1.3.2 Research Aims

The aim of this research was to synthesise derivatives of **86** in order to develop a structure activity relationship, and potentially aid in the design of a new candidate for the treatment of HAT. The approach was to synthesise derivatives of **86** and evaluate these derivatives for their activity against *T. b. rhodesiense in vitro*. The biological results would then dictate the next series of derivatives that should be explored. The initial plan for the synthesis of derivatives of **86** is outlined below in section 1.3.2.2.

1.3.2.1 Synthesis of 86

Isoquinoline **86** can be easily synthesised from phenylephrine, making it a useful starting point for a potential drug candidate due to the ease of access to the starting material. A Pictet-Spengler cyclisation of phenylephrine hydrochloride with aqueous

formaldehyde (**Scheme 1**) gives the desired *para*[*] product (**86**) as well as the *ortho*[*] product (**90**), which can be readily separated from one another.[123] The *ortho* product precipitates from the reaction mixture and can be obtained by filtration, while the *para* product can be obtained by concentration of the filtrate and subsequent recrystallisation. However, for this research isoquinoline **86** was supplied by Epichem Pty Ltd.



89
Phenylephrine

86

90

Scheme 1 Synthesis of **86** via a Pictet Spengler cyclisation.

1.3.2.2 Modifications of lead compound

Due to the lack of any information about the mode of action of this compound, as well as the large number of potential derivatives, four key parts of the molecule were focused on when designing these derivatives as can be seen in **Figure 36**. Derivatives would be synthesised based on modifications to these four key parts of the molecule, and biological results would then dictate the next series of derivatives that should be explored. Focussing on the first part of the molecule the most obvious derivatives that could be synthesised are those substituted at the phenol, in order to explore the scope of the initial active compounds (**87** and **88**) mentioned previously. Conversion of the phenol to a triflate would also allow coupling directly to the aromatic ring eliminating the phenolic oxygen and providing information about the importance of the oxygen at this position. For the second part of the molecule the benzylic alcohol could be substituted in a similar way to the phenol or could be removed completely. With the possibility of adding substituents directly to the benzylic carbon and either removing the benzylic alcohol or leaving it in place. The third part of the molecule could be derivatised by removing the methyl group from the nitrogen to observe the effect of a secondary amine, or by replacing the methyl

[*] Relative to the phenolic OH.

group with a more bulky substituent. The nitrogen atom could also be removed completely to assess its importance in activity. For the fourth part of the molecule it is possible to add substituents to the methylene carbon by using different aldehydes in place of formaldehyde in the initial synthesis of the lead compound as described previously. This could provide an opportunity for adding substituents to the molecule without altering any of the other main functional groups. The exploration of combinations of these different modifications mentioned could also be of interest.

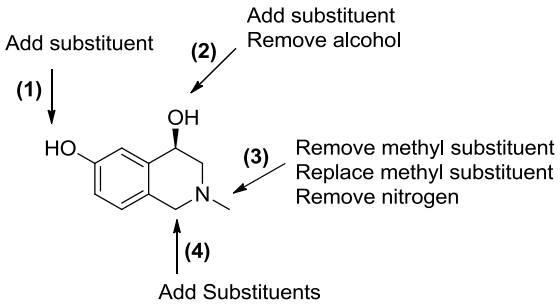
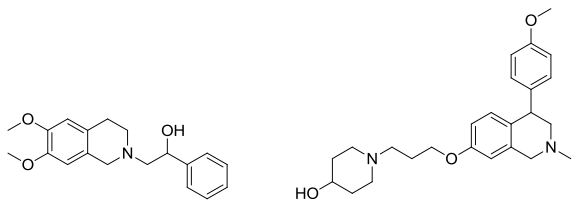


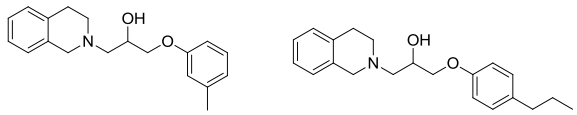
Figure 36 Four areas for potential modification of **86**.

1.4 Similar molecules

A similarity search was conducted using PubChem to survey if there were any similar molecules with reported activity towards other pathogens. A search for molecules with a Tanimoto threshold of greater than or equal to 90% was conducted for both compound **87** and **88**. This search resulted in the identification of 305 similar molecules for compound **87**. Of these four (**91** to **94**) were reported to have activity to against various targets (see **Figure 37**). The similarity search for compound **88** found 183 similar molecules, of these two (**91** and **92**) were reported to have activity against various targets.



91 **92**



93 **94**

Figure 37 Similar structures showing biological activity.

Compound **91** was reported, by the Broad Institute, to show activity against the RanGTP-Importin-beta complex.[124] The assay conducted was a fluorescence resonance energy transfer assay which resulted in compound **91** being reported to be active with an EC_{50} of 84.83 μM. The RanGTP-Importin-beta complex is a key regulator of protein transport into and out of the nucleus during interphase. It has also been implicated in several mitotic events including spindle assembly, kinetochore assembly, and nuclear envelope assembly. Inhibitors of the RanGTP-Importin-beta complex could have the potential to disrupt the Ran pathway at particular stages in mitosis and have potential therapeutic value in cancer treatment.[125] The Scripps Research Institute reported that compound **91** showed inhibition of the fructose-biphosphate aldolase (FBA) of mycobacterium tuberculosis.[126] FBA is a likely target in the inhibition of mycobacterium tuberculosis. It is responsible for catalysing the conversion of fructose biphosphate into glyceraldehyde phosphate and dihydroxyacetone phosphate in a reversible manner.[127] Compound **91** showed an inhibition of 40.93% at a concentration of 1μM. Compound **91** has also been reported to activate the chymotrypsin-like serine protease kallikrein-7 (K7) zymogen.[128] The Scripps Research Institute reported compound **91** with a 56.38% activation of K7 zymogen at a concentration of 7 μM. K7 has been associated with psoriasis and atopic dermatitis.[129] Elevated K7 expression has been observed in many cancer types[130–132] and has also been associated with the progression of Alzheimer's disease.[133,134] Activation of K7 zymogen could therefore lead to the development of

new drugs for skin diseases, cancer, and Alzheimer's disease. Compound **92** has been reported as acting as a dual histamine H_3/serotonin transporter ligand.[135–137] Serotonin reuptake inhibitors are commonly used to treat depression. However, these treatments can induce fatigue.[138,139] Histamine H_3 receptor antagonists are known to increase wakefulness.[140] Therefore, blocking both the histamine H_3 receptor and serotonin reuptake could potentially lead to better treatment of depression. Compound **92** was reported to have a K_i of 3.8 nM for human sodium dependant serotonin transporter and a K_i of 11 nM for human H_3.[135] Compound **93** has been reported as an inhibitor of the potassium ion channel Kir 2.1.[141] Potassium ion channels have been recognised as targets in the treatment of a number of disorders including cardiovascular, neurological, renal, and metabolic disorders.[142,143] Specifically, inhibition of the Kir 2.1 channel could lead to the development of treatments for arrhythmia, short and long-QT syndromes, and Andersen syndrome. Both compounds **93** and **94** were reported to be inhibitors of the D3 dopamine receptor.[144] Inhibition of this receptor represents a possible treatment for addiction and related disorders. It has also been suggested to be a potential treatment pathway for schizophrenia or psychosis as well as motor disorders associated with late stage Parkinson's disease treatment. There are a number of molecules similar to those discussed in this study which show potential in the treatment of various diseases. Testing of some of the compounds synthesised in this study against some of the targets mentioned above may uncover some interesting biological activities.

2 Substitution of the phenol and antitrypanosomal activity

The initial focus of this research was to synthesise analogues of **86** by substituting the phenol with various alkyl halides to form the corresponding ether derivatives (**Figure 38**). First to be explored was substituting the phenol with simple substituted benzyl groups, as well as increasing the chain length between the phenolic oxygen and the phenyl group. The phenol was also substituted with a cyclohexyl group having two different chain lengths, however phenyl substituents were the main focus due to the greater possibility of derivatisation. A range of nitrogen containing heterocycles was also explored as substituents for phenolic substitution, including some nitro-imidazoles. Also investigated were a number of biphenyls, obtained through Suzuki coupling reactions, as well as some biphenyl ethers, available through Chan-Lam coupling.

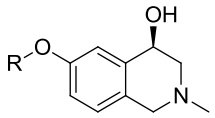
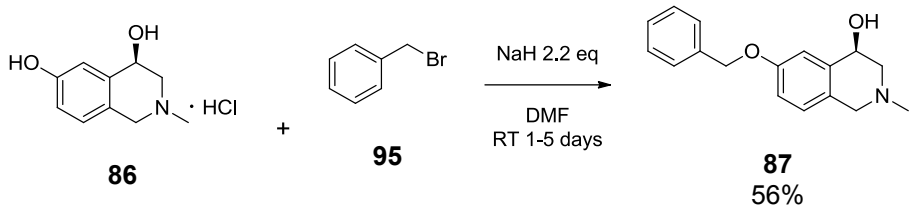


Figure 38 Substitution of the phenol.

2.1 Benzyl substituents

Substituents were added to the phenol via alkylation with the corresponding alkyl halides to give the corresponding ether derivatives. Since there are three potential sites on the tetrahydroisoquinoline **86** where alkylation could occur (the phenol, benzylic alcohol, and amine) care was taken to control the conditions in order to ensure selective alkylation of the phenol was favoured. This was accomplished by treating tetrahydroisoquinoline **86** with sufficient sodium hydride to completely deprotonate the phenol without also deprotonating the benzylic alcohol. Since isoquinoline **86** was used as the hydrochloride salt 2.2 equivalents of sodium hydride

were required. Substitution of the phenol with a benzyl group, in order to remake one of the preliminary active compounds **87** (see section 0, pg. 32)**,** was the starting point for phenolic substitution. Under the conditions described above, treatment of tetrahydroisoquinoline **86** with a slight excess of benzyl bromide in dimethylformamide gave the desired product **87** in 56% yield (**Scheme 2**). Use of a weak base such as potassium carbonate resulted in *N*-alkylation (i.e. formation of a quaternary ammonium salt).



Scheme 2 Synthesis of **87**.

The ^{1}H NMR spectrum of the benzyl substituted phenol **87** in deuterated chloroform is shown in **Figure 39**. This spectrum is discussed in detail below. For all of the derivatives substituted at the phenolic position reported herein their ^{1}H NMR spectra all showed similar patterns for the isoquinoline scaffold. On the spectrum, signal A can be seen as an AB quartet with a geminal coupling constant of 14.4 Hz, which represents the two methylene protons labelled A. The two signals labelled C can be assigned to the methylene protons closest to the OH group. From the spectrum these can be observed as a doublet of doublets and a doublet of doublet of doublets which are coupling to each other with a geminal coupling constant of 11.8 Hz. Separate signals are seen for each of these protons due to the twisted nature of the saturated ring, resulting from it being attached to the rigid aromatic ring. These protons are also coupling to signal D which represents the methine proton labelled D, all of these signals have a vicinal coupling constant of 2.8 Hz. Signal B corresponds to the *N*-methyl group which is downshifted (2.28 ppm) as compared to a regular methyl group. The three aromatic protons on the isoquinoline can be easily distinguished from one another based on their coupling patterns. Proton E can be seen as a doublet with 4 bond coupling (2.8 Hz) to proton F. Proton F is also coupled to proton G (8.4 Hz) and can be observed as a doublet of doublets, proton G can be seen as a doublet. As for the benzyl group, a singlet can be seen at 5.08 ppm corresponding to the

methylene protons which are slightly downshifted due to the attachment of the benzylic carbon to oxygen. Finally the aromatic protons of the benzyl group can be seen as a large multiplet labelled I. Substitution of the phenol was confirmed through HMBC which showed a correlation between the benzylic carbon labelled H and the aromatic ring of the isoquinoline, confirming that **86** had been substituted at the phenol and not at the benzylic alcohol.

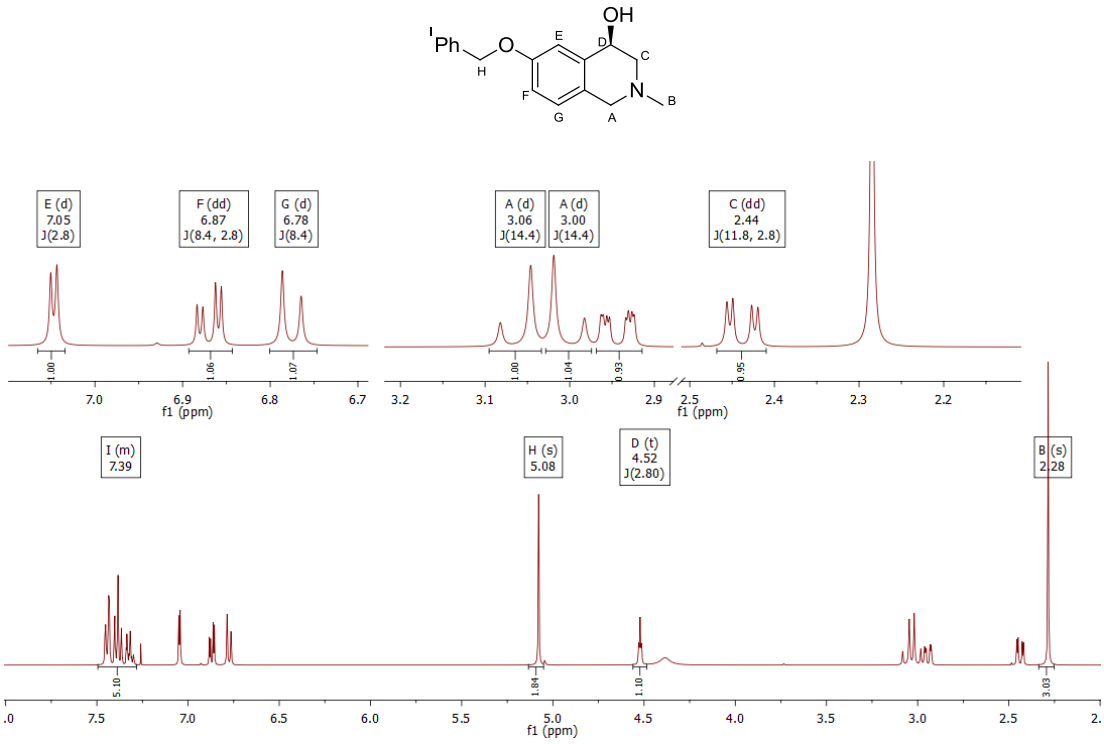
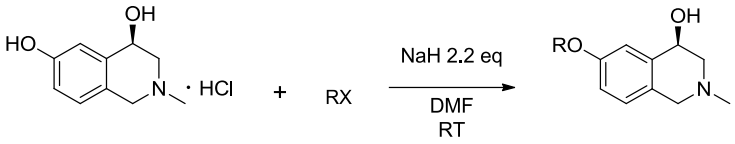


Figure 39 ^{1}H NMR spectrum of **87**.

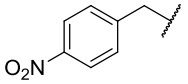
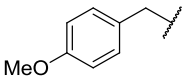
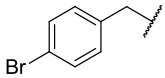
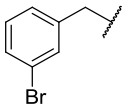
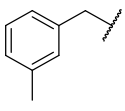
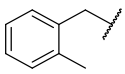
Some simple substituted benzyl groups were used as alkylating agents. Electron withdrawing, electron donating, and neutral groups were used in order to assess any effect, on anti-HAT activity, of these different groups on the phenyl ring. An electron withdrawing nitro group was chosen as well as an electron donating methoxy group. Some methyl substituted phenyl rings were also explored, as well as some bromo substituted benzyl groups which could be useful for further functionalisation. Synthesis of the aforementioned compounds was achieved as described above for the synthesis of **87**, from the corresponding alkyl bromides or chlorides. The alkyl halides and bromides used were from commercial sources except 1-(chloromethyl)-4-methoxybenzene and 1-(chloromethyl)-3-methylbenzene which were prepared from the corresponding alcohols according to standard procedures.[145] A summary of

the synthesised compounds can be found below (**Table 1**). All compounds were obtained in moderate to good yields, and substitution of the phenolic oxygen was confirmed by NMR spectroscopy as described above for benzyl derivative **87**.

Table 1 Synthesis of substituted benzyl derivatives.

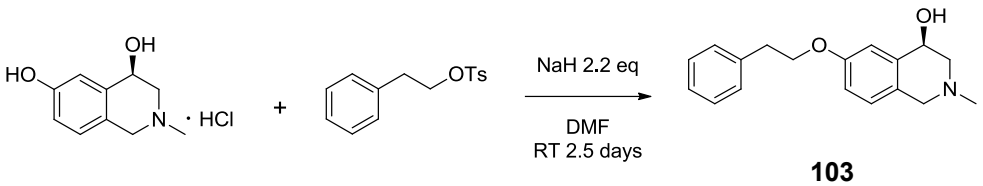


86

R	X	Reaction Time*	% Yield
 **96**	Br	2 hrs	58%
 **97**	Cl	5 days	29%
 **98**	Br	24 hrs	60%
 **99**	Br	2 days	65%
 **100**	Cl	2.5 days	66%
 **101**	Cl	24 hrs	43%

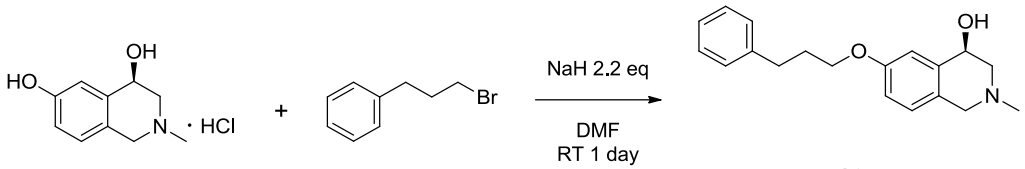
*Reaction conditions were not optimised.

Increasing the length of the chain between the phenolic oxygen and the phenyl ring to two and three carbons in length was also explored (see **Scheme 3** and **Scheme 4**). This was achieved as described above, using the corresponding alkyl tosylate and alkyl bromide respectively to give derivatives **103** and **105** in moderate yield. The alkyl tosylate **102** was prepared from 2-phenylethanol according to standard procedures.[146] 1-Bromo-3-phenylpropane **104** was obtained from a commercial source.



86 **102** **103** 40%

Scheme 3 Synthesis of phenylethyl derivative **103**.

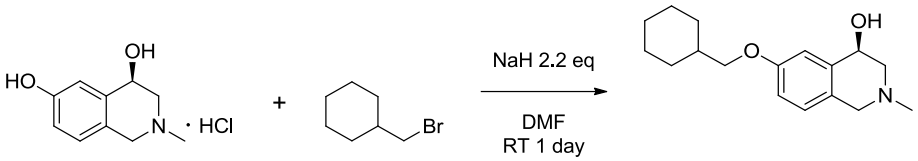


86 **104** **105** 58%

Scheme 4 Synthesis of phenylpropyl derivative **105**.

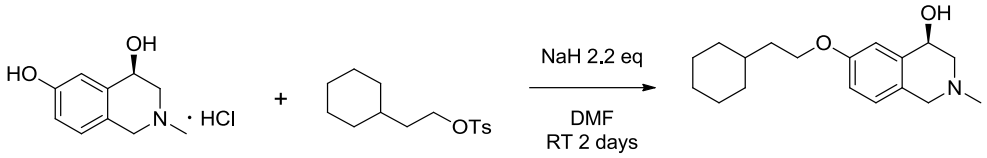
2.2 Cyclohexyl substituents

Compound **88**, with a cyclohexylmethyl group substituted at the phenolic position (see **Figure 35**, pg. 33), was also synthesised along with the cyclohexylethyl compound (see **Scheme 5** and **Scheme 6**). These were synthesised as described above, using the corresponding bromide or alkyl tosylate respectively, to give the desired ether products **88** and **108** in moderate yields. (Bromomethyl)cyclohexane **106** was obtained from a commercial source. Alkyl tosylate **107** was synthesised from 2-cyclohexylethanol according to standard procedures.[146]



86 **106** **88** 49%

Scheme 5 Synthesis of cyclohexylmethyl derivative **88**.



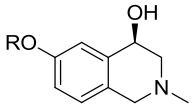
86 **107** **108** 58%

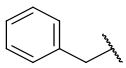
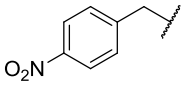
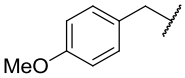
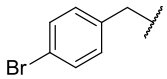
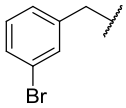
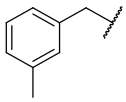
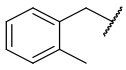
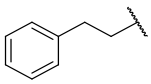
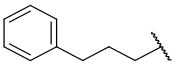
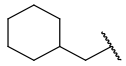
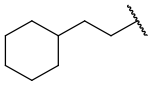
Scheme 6 Synthesis of cyclohexylethyl derivative **108**.

2.3 Antitrypanosomal activity of benzyl and cyclohexyl derivatives

The compounds mentioned above as well as the parent isoquinoline **86** were evaluated for their cytotoxicity to *T. b. rhodesiense* and mammalian cells. The parent isoquinoline **86** showed no toxicity to *T. b. rhodesiense* or mammalian cells. Nitrophenyl derivative **96** and methoxyphenyl derivative **97** showed almost identical activity against *T. b. rhodesiense,* with both also having comparable activity to benzyl substituted derivative **87**. This showed that having a substituent in the *para* position on the phenyl ring increases the activity slightly, however there is no difference in having an electron withdrawing or donating group. Having a bromo substituent on the phenyl ring in either the *para* or *meta* (**98** or **99**) position increases the activity against *T. b. rhodesiense* by tenfold, while still maintaining reasonable selectivity against mammalian cells. A methyl group on the phenyl ring in either the *meta* or *ortho* (**100** or **101**) position had no effect on activity. Increasing the chain length between the phenolic oxygen (**103** and **105**) and the phenyl ring seemed to have no significant effect on activity. Cyclohexyl derivatives **88** and **108** showed more activity than the corresponding benzyl derivatives, however again the length of the chain seemed to have no effect.

Table 2 *In vitro* activity of benzyl and cyclohexyl derivatives.



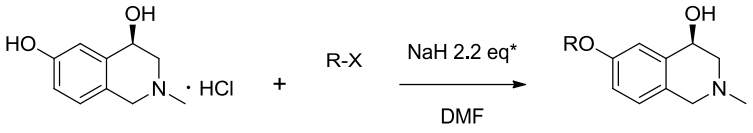
No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
86	H	>100	>100	
87		25.6 ± 0.9	>100	>3.9
96		16.9 ± 1.2	>50	>3.0
97		17.5 ± 0.7	>50	>2.9
98		2.5 ± 0.1	37.0 ± 6.0	14.8
99		2.2 ± 0.1	60.3 ± 34.8	27.4
100		20.3 ± 0.9	>50	>2.5
101		20.7 ± 0.6	>100	>4.8
103		17.9 ± 1.7	>50	>2.8
105		18.7 ± 0.9	>50	>2.7
88		2.8 ± 0.1	65.6 ± 2.3	23.4
108		2.5 ± 0.1	>50	>20

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

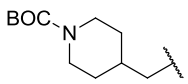
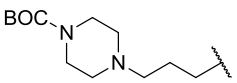
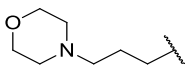
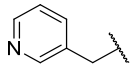
2.4 Nitrogen-containing heterocycles

Nitrogen-containing heterocycles are a common motif in many biologically active compounds including some anti-HAT agents.[9,34,55–57] With this in mind a range of nitrogen containing-heterocycles was substituted onto the phenol of **86** in order to provide some information about the effect on biological activity of having a nitrogen atom in the phenyl or cyclohexyl ring. The nitrogen-containing heterocycles that were explored include piperidine, piperazine, morpholine, and pyridine. The specific derivatives that were synthesised were based on availability of starting materials (see **Table 3**).

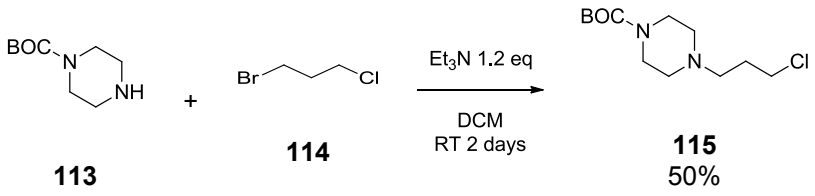
Table 3 Phenolic substitution of nitrogen-containing heterocycles.



86

R	X	Reaction time	% Yield
 **109**	OMs	24 hrs	**32%**
 **110**	Cl	24 hrs	**76%**
 **111**	Cl	3 days	**17%**
 **112** *3.2 eq of NaH used	Cl	2 days	**58%**

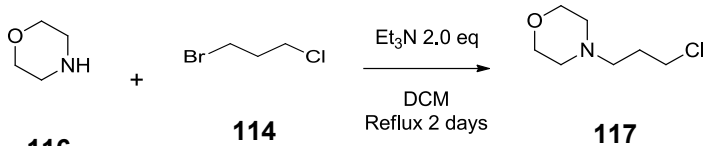
The piperidine derivative **109** was synthesised from the mesylate of the corresponding BOC protected piperidine, as described previously. The mesylate was prepared from commercially available BOC protected 4-piperadinemethanol under standard conditions.[147] The piperazine derivative **110** was synthesised from the chloride of the corresponding BOC protected piperazine **115** (see **Scheme 7**), as described previously. A propyl chain was used as the linking group between the nitrogen atom of the heterocycle and the phenol, avoiding issues associated with installation of an ethyl group, namely elimination. This was achieved by reacting the BOC protected piperazine **113** with 1-bromo-3-chloropropane, as described in **Scheme 7**, to give the chloropropylpiperazine **115** in moderate yield.



113 **114** **115** 50%

Scheme 7 Synthesis of chloropropylpiperazine **115**.

The morpholine derivative **111** was synthesised from *N*-3-chloropropylmorpholine as described previously to give the morpholine derivative in 17% yield. The poor yield can be attributed to difficulty in purification. *N*-3-Chloropropylmorpholine was synthesised by reacting morpholine **116** with 1-bromo-3-chloropropane **114** as described in **Scheme 8** to give *N*-3-chloropropylmorpholine **117** in good yield. A propyl linker was used in this case for the same reason as described above for **110**.



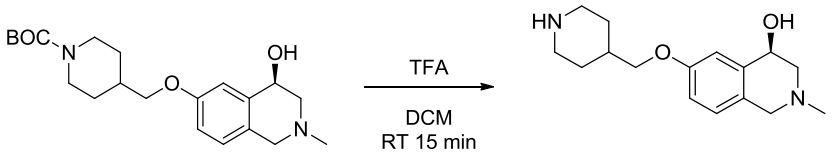
116 **114** **117** 78%

Scheme 8 Synthesis of *N*-3-chloropropylmorpholine.

The pyridine derivative was synthesised from commercially available 2-(chloromethyl)pyridine hydrochloride using a slightly modified procedure than described for the previous substitution reactions. Due to the starting material being available as the HCl salt, the pyridine salt was treated with 3.2 equivalents sodium hydride prior to the addition of isoquinoline **86,** in order to neutralise the HCl salt of

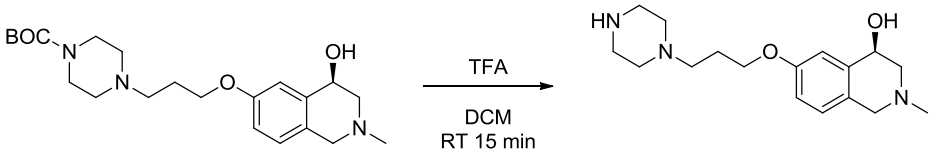
both the isoquinoline and the pyridine as well as deprotonating the phenol. This was necessary to avoid the extra step involved in neutralizing the salt, and allowing the reaction to be done in one pot with only one addition of base, while still taking care to selectively deprotonate only the phenol. Following this modified procedure pyridine derivative **112** was obtained in 58% yield.

Derivatives **109** and **110** were then deprotected with trifluoroacetic acid (see **Scheme 9** and **Scheme 10**)[148] to give the corresponding secondary amines **118** and **119** in 83% and 44% yield respectively.



109 **118** 83%

Scheme 9 BOC deprotection of **109**.

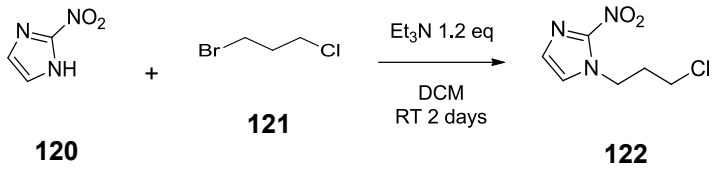


110 **119** 44%

Scheme 10 BOC deprotection of **110**.

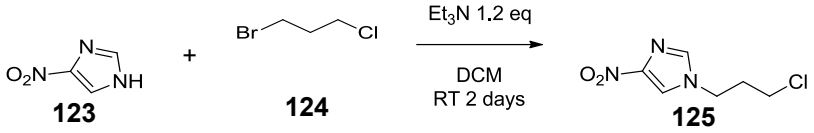
2.4.1 Nitroimidazoles

Nitroimidazoles are another motif that can be found in some successful anti-Hat compounds,[9,34,56] and as such two nitroimidazole derivatives of **86** were synthesised. 2-Nitroimidazole and 4-nitroimidazole were substituted with 1-bromo-3-chloropropane to give the corresponding chloropropyl derivatives as seen in **Scheme 11** and **Scheme 12**. The ^{1}H NMR spectra for derivatives **122** and **125** showed the expected signals for the product as well as another set of signals. The second set of signals were determined to be the terminal alkene product, resulting from elimination of one of the halides. The spectra showed a multiplet at ~6 ppm and two doublets of doublets at ~5.1 ppm typical of a terminal alkene.



120 **121** **122**

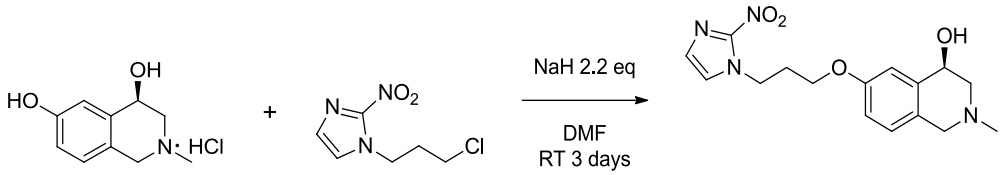
Scheme 11 Synthesis of chloropropyl imidazole derivative **122**.



123 **124** **125**

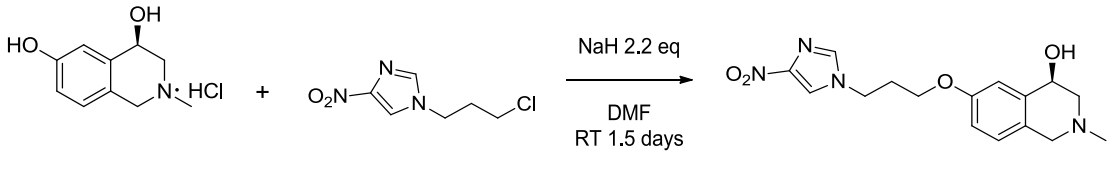
Scheme 12 Synthesis of chloropropyl imidazole derivative **125**.

The chloropropyl imidazole derivatives were then used as alkylating agents for phenolic substitution. Phenolic substitution with 3-chloropropyl-2-nitroimidazole using conditions similar to that described previously gave derivative **126** in 11% yield (see **Scheme 13**). The 4-nitroimidazole derivative **127** was obtained in better yield (see **Scheme 14**). The high polarity of these compounds resulted in difficulty in purification and streaking on the column during chromatography. These factors attributed to the low yields, especially in the case of **126**.



86 **122** **126** 11%

Scheme 13 Synthesis of nitroimidazole derivative **126**.



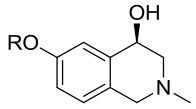
86 **125** **127** 37%

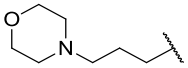
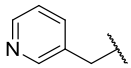
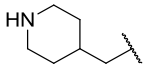
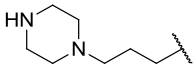
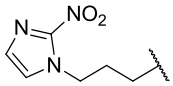
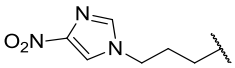
Scheme 14 Synthesis of nitroimidazole derivative **127**.

2.5 Antitrypanosomal activity of nitrogen-containing heterocycles

Evaluation of the above mentioned nitrogen-containing heterocycles for their cytotoxicity to *T. b. rhodesiense* and mammalian cells showed very little activity (**Table 4**). The pieridine and piperazine derivatives (**118** and **119**) showed no activity against *T. b. rhodesiense*. Interestingly the pyridine derivative **112** proved to be inactive, despite its similarity to benzyl derivative **87**. This suggests the possibility of a hydrophobic pocket in which the benzyl derivative can fit favourably, while the introduction of a polar nitrogen atom into the ring results in this interaction being unfavourable. Significantly, at physiological pH the nitrogen atom would be protonated making the pyridine group charged and polar, possibly resulting in an unfavourable interaction between the positively charged pyridine group and another positively charged residue in the active site. Conflictingly, the morpholine derivative **111,** which also contains a polar nitrogen atom which would also be protonated at physiological pH as well as a polar oxygen, showed some activity. However, the chain length is increased by 2 carbons relative to the pyridine derivative which could account for this change in activity, although the nitrogen atom is still the same number of bonds from the phenolic oxygen in both the pyridine and morpholine derivative. Synthesis of some carboxylic acid derivatives which would be negatively charged at physiological pH could prove interesting. Of the nitroimidazole derivatives the derivative with the nitro group in the 2 position (**126**) showed some activity, while the 4-nitro derivative **127** appears to be inactive.

Table 4 *In vitro* activity of nitrogen-containing heterocycles.

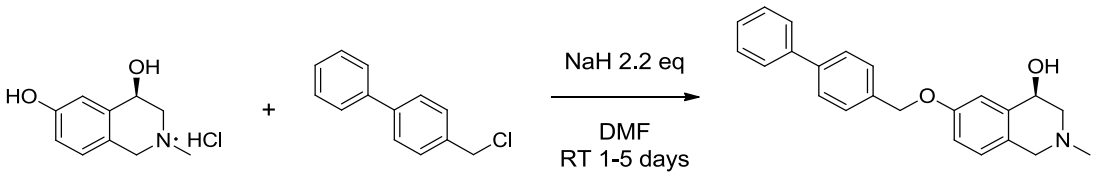


No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
111		27.6 ± 0.2	>50	1.8
112		>50	>50	
118		>100	>100	
119		>100	>100	
126		21.7 ± 1.0	>50	2.3
127		>50	>50	

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

2.6 Biphenyls

A biphenyl group was substituted onto the phenolic oxygen using conditions as described previously to give **129** in 54% yield. This derivative proved to have interesting anti-HAT activity, and so a range of substituted biphenyls was explored.

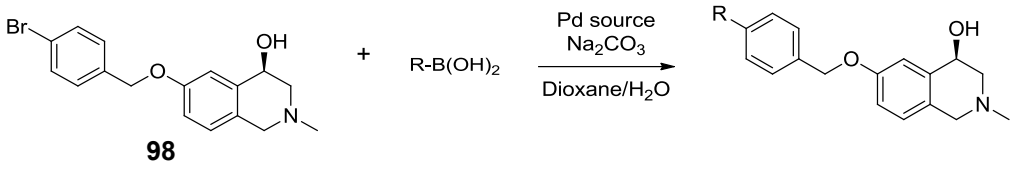


86 **128** **129**

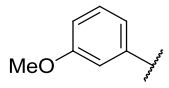
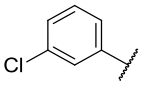
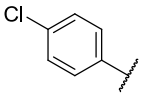
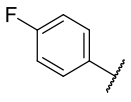
Scheme 15 Synthesis of biphenyl derivative **129**.

Suzuki coupling, which involves the coupling of an aryl halide and a boronic acid in the presence of a palladium catalyst, is a common way to access biphenyls.[149,150] In this case aryl bromide substituted isoquinoline **98** was the aryl halide used in the coupling reaction. This was coupled with a range of boronic acids to give the corresponding biphenyl derivatives (**Table 5**).

Table 5 Synthesis of para-biphenyl derivatives.

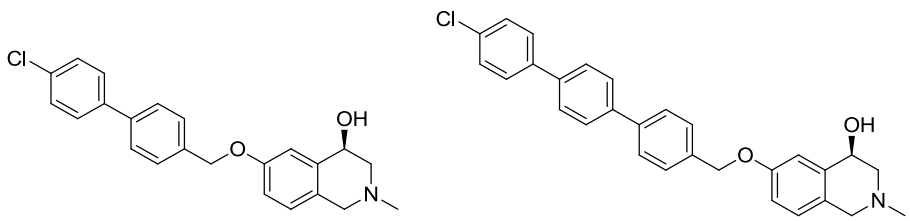


98

R	Pd source	Reaction conditions	% Yield
 **130**	$Pd(PPh_3)_4$	Microwave reactor 160°C 13 mins	**19%**
 **131**	$Pd(dppf)Cl_2$	Reflux 6 hrs	**84%**
 **132**	$Pd(dppf)Cl_2$	Microwave reactor 140°C 30 mins	**64%**
 **133**	$Pd(dppf)Cl_2$	Reflux 6 hrs	**75%**

Initially the palladium catalyst that was used for the Suzuki coupling reactions above was tetrakis(triphenylphosphine)palladium(0). Using this catalyst and under the reaction conditions described in **Table 5**, biphenyl **130** was obtained in poor yield

and was difficult to purify by chromatography. The use of the same catalyst and reaction conditions in the synthesis of biphenyl **132** gave similar results. Analysis of the reaction mixture of biphenyl **132** via LCMS showed a major and minor peak with *m/z* [M+H]+ of 380.20 and 456.20 respectively. The first peak, with a *m/z* [M+H]+ of 380.20, corresponds to the desired product as expected. Surprisingly the second peak, with a *m/z* [M+H]+ of 456.20, corresponds to the overcoupled product **134** as seen in **Figure 40**.

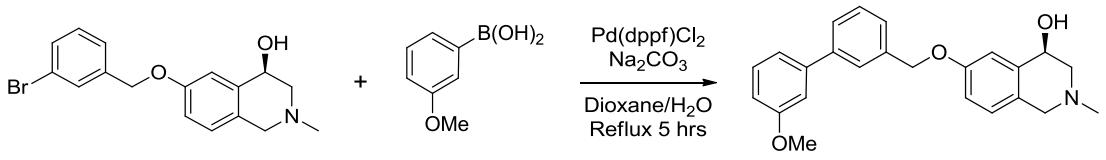


132

134
m/z [M+H]$^+$ expected = 456.16

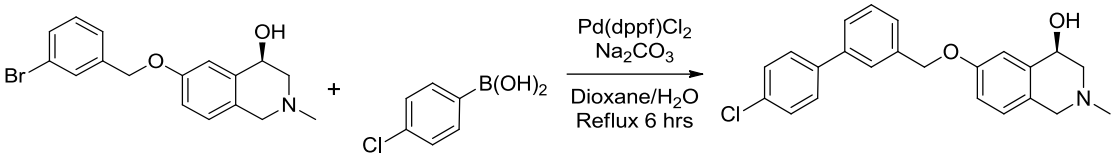
Figure 40 Structure of **133** and resulting overcoupled product.

Changing the catalyst to bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl_2) eliminated the overcoupled by-product and also increased the yield and ease of purification of the desired product. Therefore in the synthesis of the rest of the biphenyl derivatives Pd(dppf)Cl_2 was used as a catalyst, and the remaining biphenyl derivatives were obtained in good yields using the conditions described in **Table 5**. Confirmation of the products was obtained through observation of the extra aromatic peaks seen in the ^{1}H and ^{13}C NMR spectra, corresponding to the newly introduced aromatic rings. Two biphenyl derivatives were also synthesised using aryl bromide substituted isoquinoline **99**, to give some *meta*-biphenyl derivatives (**136** and **138**). This was achieved as described in **Scheme 16** and **Scheme 17** using Pd(dppf)Cl_2 as the palladium source to give the desired biphenyl derivatives in good yields. Confirmation of the products was obtained through observation of the extra aromatic peaks seen in the ^{1}H and ^{13}C NMR spectra, corresponding to the newly introduced aromatic rings.



99 **135** **136** **49%**

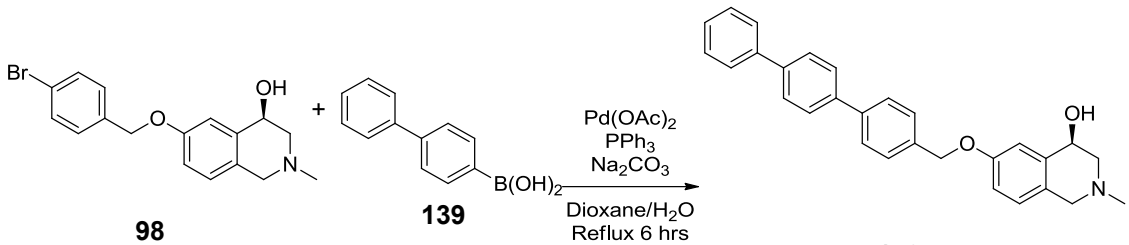
Scheme 16 Synthesis of *meta*-biphenyl derivative **136**.



99 **137** **138** 66%

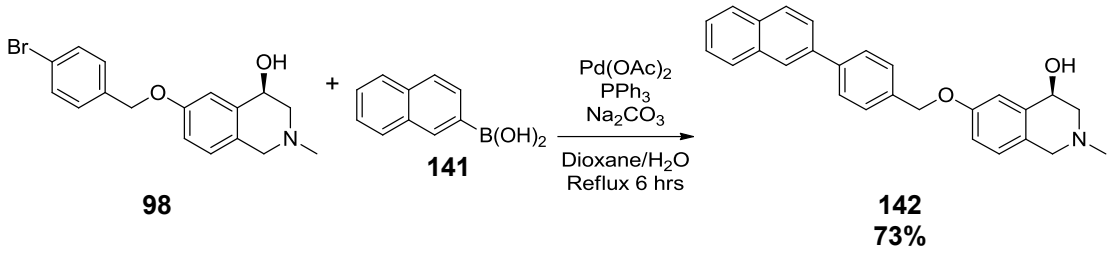
Scheme 17 Synthesis of *meta*-biphenyl derivative **138**.

Also synthesised by Suzuki coupling were triphenyl and naphthyl derivatives **140** and **142** (see **Scheme 18** and **Scheme 19**). These derivatives were synthesised in the same way described above using the 4-bromobenzyl derivative **98** as the aryl halide and the corresponding boronic acid. Palladium acetate was used as the palladium source with the addition of triphenylphosphine, to give triphenyl derivative **140** in 37% yield and naphthyl derivative **142** in 73% yield.



98 **139** **140** **37%**

Scheme 18 Synthesis of triphenyl derivative **140**.

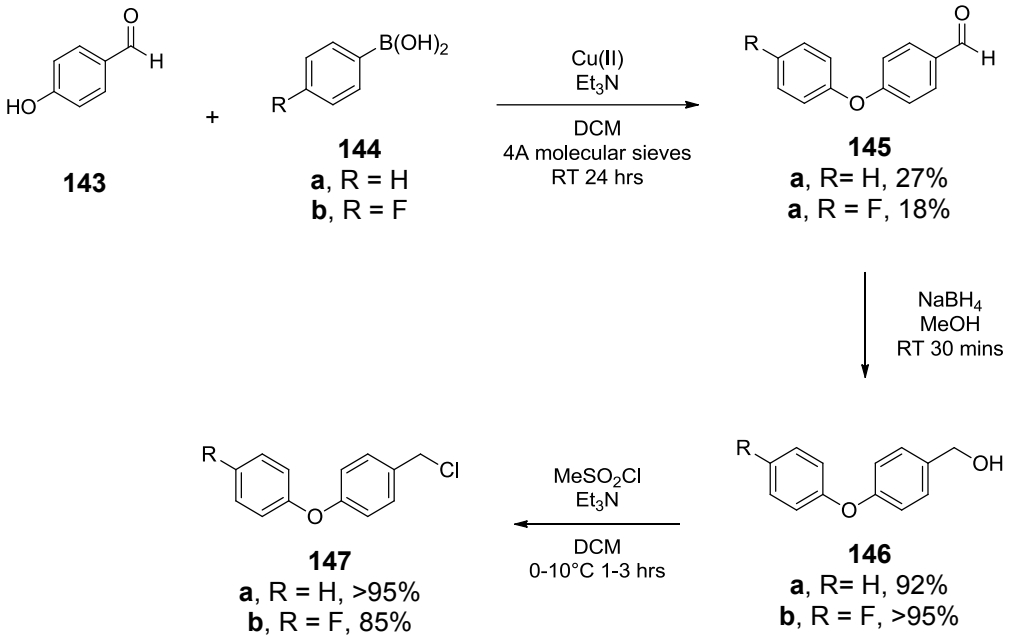


Scheme 19 Synthesis of naphthyl derivative **142**.

2.7 Diphenyl ethers

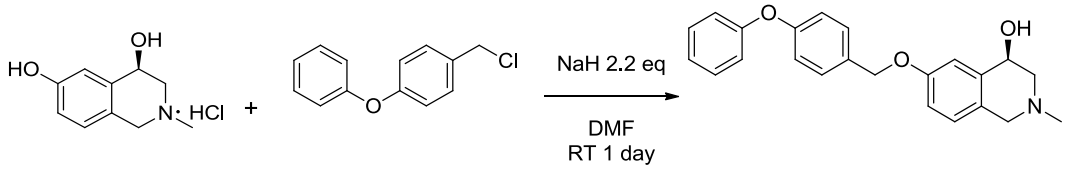
Two diphenyl ether derivatives were also synthesised as potentially interesting phenolic substituents, these were accessed via a Chan-Lam coupling. Chan-Lam coupling involves in this case the coupling of an arylboronic acid with an O-H containing compound in air. The reaction is facilitated by a stoichiometric amount of copper(II), and can be undertaken at room temperature.[151]

Table 6 Diphenyl ether synthesis.



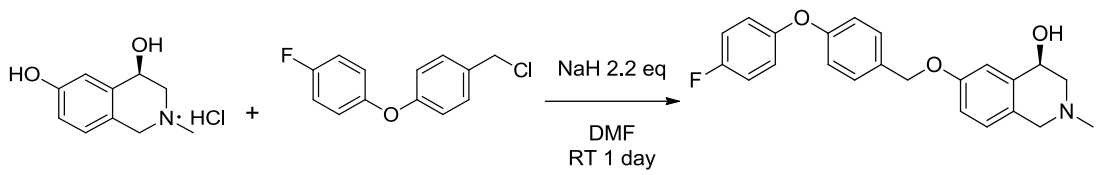
The synthesis of diphenyl ether derivatives began with Chan-Lam coupling[152] of 4-hydroxybenzaldehyde **143** with the corresponding arylboronic acid in the presence of

a stoichiometric amount of copper(II) acetate and excess triethylamine. The reaction was undertaken at room temperature and the reaction mixture stirred open to air with the addition of 4Å molecular sieves to keep the reaction anhydrous. In this way, the diphenyl ethers **145a** and **145b** were obtained in low yields. The product was confirmed by ^{1}H NMR spectroscopy which showed 4 signals corresponding to a total of 9 protons as expected for the product as well as the formation of a new spot by TLC (EtOAc:PS; 1:9). In order for these diphenyl ethers to be used as phenolic substituents it was necessary to convert the aldehyde into a good leaving group. This was achieved by first reducing the aldehyde to an alcohol using sodium borohydride,[153] to give the corresponding benzyl alcohols **146a** and **146b** in excellent yields. Conversion of the aldehyde to the alcohol was confirmed by ^{1}H NMR spectroscopy which showed the disappearance of the aldehyde signal (~ 10 ppm) as well as the upfield shift of the aromatic protons on the benzylic ring, and a new signal at ~ 4.7 ppm corresponding to the benzylic protons. Following this, the alcohols were reacted with mesyl chloride, however rather than the expected mesylates the chlorides (**147a** and **147b**) were obtained. Conversion of the alcohols to the chlorides was confirmed based on there being no significant change in the ^{1}H NMR spectra accompanied by the formation of a new spot by TLC (EtOAc:PS; 1:9) with a large difference in RF (~ 0.7) value. If the mesylate were being formed a new peak in the ^{1}H NMR spectrum would be observed for the methyl protons. What most likely occurred was the formation of the desired mesylate followed by the displacement of the mesylate by a chloride ion, this displacement has been reported to occur with tosylation using tosyl chloride.[154] Confirmation of the chloride products could also be achieved through mass spectroscopy, however this was not undertaken due to limited access to mass spectrometry facilities. With the chloride also being a reasonably good leaving group these chloro derivatives were used in the phenolic substitution reaction with isoquinoline **86,** as described in **Scheme 20** and **Scheme 21**, to give the corresponding ethers **148** and **149** in moderate yields.



86 **147a** **148** 37%

Scheme 20 Synthesis of diphenylether derivative **148**.



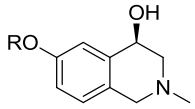
86 **147b** **149** 66%

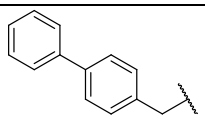
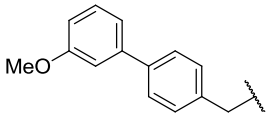
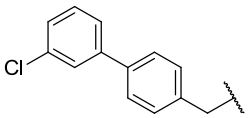
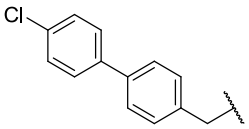
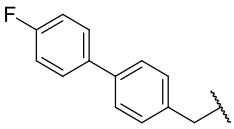
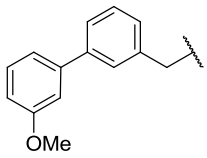
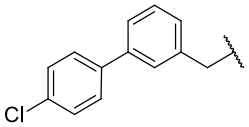
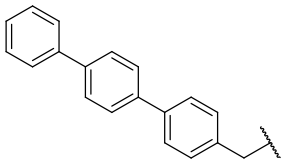
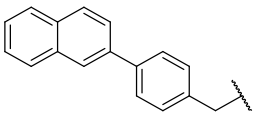
Scheme 21 Synthesis of diphenylether derivative **149**.

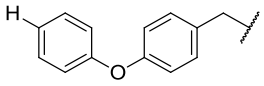
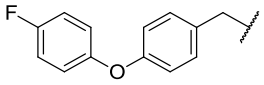
2.8 Antitrypanosomal activity of biphenyl and diphenyl ether derivatives

Evaluation of the biphenyl and diphenyl ether derivatives discussed above for their activity against *T. b. rhodesiense* and mammalian cells showed some interesting results. As compared to the original lead compound, benzyl substituted isoquinoline **87** (IC_{50} = 25.6 ± 0.9), biphenyl **129** showed a tenfold increase in activity against *T. b. rhodesiense*. However, this is accompanied by a significant increase in cytotoxicity. The substituted biphenyl derivatives (**130-133**) all showed almost identical activity to unsubstituted biphenyl derivative **129** with similar cytotoxicity. Exceptions to this are substituted biphenyl derivatives **132** and **133** which showed increased activity against *T. b. rhodesiense*, both of these derivatives have more of a linear structure as compared to the other substituted biphenyl derivatives. In the case of biphenyl derivative **132** an almost tenfold increase in antitrypanosomal activity is observed, as compared to the unsubstituted biphenyl derivative. However, the cytotoxicity remains comparable resulting in a significant increase in selectivity for *T. b. rhodesiense* over mammalian cells (SI = 86.1). Derivatives **136** and **138** also showed similar activity to unsubstituted biphenyl derivative **129**. Derivatives **140** and **142** showed good activity against *T. b. rhodesiense* with IC_{50} values in the submicromolar range, however they were also highly toxic to mammalian cells. The two diphenyl ether derivatives **148** and **149** showed almost identical activity. In comparison to unsubstituted biphenyl derivative **129,** the activity against *T. b. rhodesiense* was almost identical, however a significant increase in cytotoxicity was observed.

Table 7 *In vitro* activity of biphenyl and diphenyl ether derivatives.



No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
129		2.9 ± 0.1	23.0 ± 2.1	7.9
130		2.8 ± 0.1	10.8 ± 4.2	3.9
131		2.8 ± 0.1	25.5 ± 3.0	9.1
132		0.28 ± 0.01	24.1 ± 4.3	86.1
133		1.4 ± 0.1	33.8 ± 16.7	11.9
136		2.9 ± 0.1	24.3 ± 3.8	8.4
138		2.8 ± 0.1	27.3 ± 2.6	10.5
140		0.28 ± 0.01	0.28 ± 0.04	1
142		0.24 ± 0.01	0.31 ± 0.01	1.3

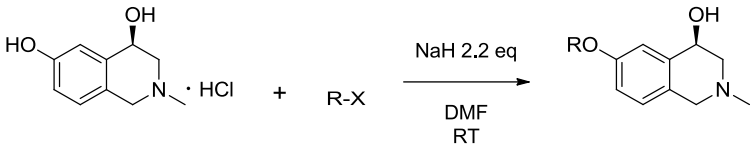
No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
148		2.7 ± 0.2	3.4 ± 0.8	1.3
149		2.7 ± 0.2	5.6 ± 0.1	2.1

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

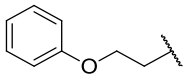
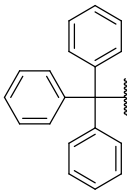
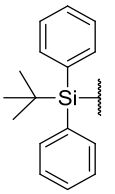
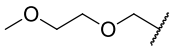
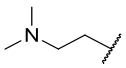
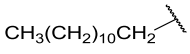
2.9 Other phenolic substituents

A number of other groups were also substituted onto the phenolic oxygen to give the corresponding ether derivatives (**Table 8**). 2-Phenoxyethanol was treated with tosyl chloride according to standard procedures[146] to give the tosylate which was then used in the phenolic substitution reaction to give the corresponding ether derivative **150** in 65% yield. Trityl chloride was used in the phenolic substitution reaction to give the corresponding triphenylmethyl derivative **151** in 21% yield. Difficulties in purifying this derivative, namely loss of the trityl group through purification by column chromatography due to its acid sensitive nature, resulted in a lower than expected yield. Treatment of the phenol with *tert*-butylchlorodiphenylsilane gave the TBDPS protected phenol **152** in excellent yield. Treatment of the phenol with methoxyethoxymethyl chloride gave the MEM protected phenol **153** in 61% yield. Substitution with 2-chloro-*N*,*N*-dimethylethylamine gave the corresponding ether **154** in 52% yield. Alkylation of the phenol with 1-bromododecane gave the dodecyl ether **155** in good yield.

Table 8 Other derivatives synthesised by phenolic substitution.



86

R	X	Reaction time	% Yield
 **150**	OTs	5 days	**65%**
 **151**	Cl	3 days	**21%**
 **152**	Cl	2.5 days	**80%**
 **153**	Cl	24 hrs	**61%**
 **154**	Cl	2 days	**52%**
 **155**	Br	24 hrs	**74%**

Finally, treatment of 2 equivalents of isoquinoline **86** with 1 equivalent of diethylene glycol bis(*p*-toluenesulfonate) gave the isoquinoline dimer **157** in moderate yield. Diethylene glycol bis(*p*-toluenesulfonate) was prepared according to a literature

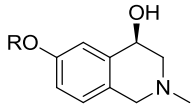
procedure.[155] The rationale behind making this derivative was that this derivative being a dimer joined by a long chain looks similar to pentamidine (**1** see pg. 5), which is used to treat type 1 HAT, and other pentamidine inspired HAT active compounds (**10** to **12** see pg. 9).

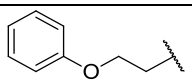
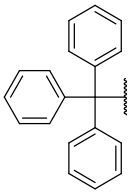
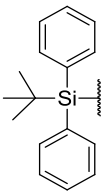
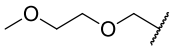
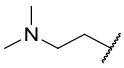
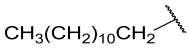
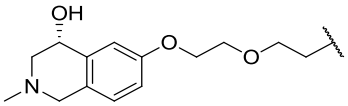
86 **156** **157** 48%

2.10 Antitrypanosomal activity of other phenolic substituents

Evaluation of the above mentioned derivatives (**150**-**157**) for their activity *in vitro* against *T. b. rhodesiense* and mammalian cells showed that both the TBDPS derivative **152** and dodecyl derivative **155** had good activity against *T. b. rhodesiense*. However, this activity is accompanied by increased cytotoxicity with these derivatives having poor selectivity for *T. b. rhodesiense* over mammalian cells with selectivity indexes of 6.8 and 7.8 respectively. Trityl derivative **151** also showed some activity but interestingly was approximately tenfold less active than the TBDPS derivative which has similar bulk on the phenol. This could be due to possible hydrolysis of the trityl group *in vitro*. This was again accompanied by high cytotoxicity. Derivative **150** was somewhat active while derivatives **153**, **154**, and **157** showed no antitrypanosomal activity.

Table 9 *In vitro* activity of other phenolic derivatives.



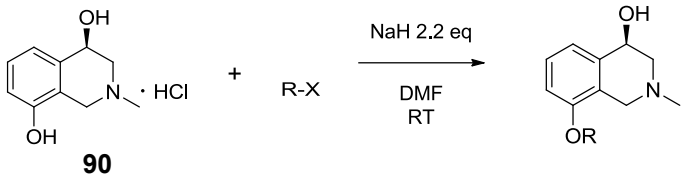
No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
150		17.9 ± 0.2	>100	5.6
151		20.8 ± 0.4	87.9 ± 7.1	4.2
152		2.8 ± 0.1	19.1 ± 0.6	6.8
153		>50	>50	
154		>50	>50	
155		2.4 ± 0.1	18.8 ± 3.7	7.8
157		>100	>100	

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

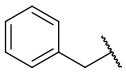
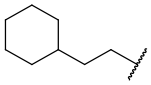
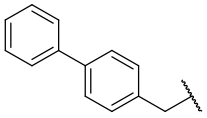
2.11 Derivatives of isoquinoline 90 and their antitrypanosomal activity

From the synthesis of the parent isoquinoline **86** via a Pictet-Spengler cyclisation the *ortho* isomer **90** is also obtained (see **Scheme 1**, pg. 34). A small number of derivatives of this isoquinoline were synthesised to compare to the derivatives of isoquinoline **86**. The phenolic oxygen was substituted in the same way described above instead using isoquinoline **90.** Four derivatives were synthesised, the methoxy **158**, benzyl **159**, cyclohexylethyl **160**, and the biphenylmethyl **161** to give a range of different derivatives.

Table 10 Derivatives of isoquinoline **90**.

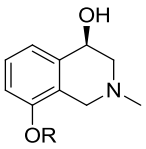


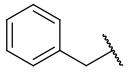
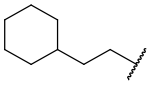
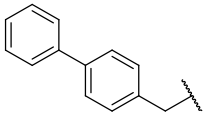
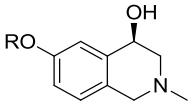
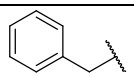
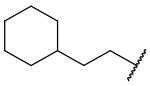
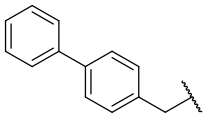
90

R	X	Reaction time	% Yield
 **158**	I	24 hrs	**30%**
 **159**	Br	24 hrs	**68%**
 **160**	OTs	24 hrs	**50%**
 **161**	Cl	24 hrs	**45%**

The above compounds were evaluated for their activity against *T. b. rhodesiense* and mammalian cells *in vitro*. Interestingly, the benzyl substituted derivative **159** showed no activity, while biphenyl substituted derivative **161** showed comparable activity to the biphenyl derivative of isoquinoline **86** (derivative **129**) but with less toxicity to mammalian cells. The methyl derivative **158** showed no activity, however the cyclohexylethyl derivative **160** showed comparable activity and cytotoxicity to the same derivative of isoquinoline **86** (derivative **108**). The inactivity of the benzyl and methyl derivatives and activity of the biphenylmethyl and cyclohexylethyl could be due to the size or reach of the substituted groups, with both the cyclohexylethyl and biphenylmethyl groups being slightly larger than the benzyl group. Synthesis of the phenylethyl and phenylpropyl derivatives could potentially provide some insight into this.

Table 11 *In vitro* activity of derivatives of **90**.



No.	R	IC_{50} *T. b. rhodesiense*[a] *(µM)*	Cytotoxicity[b] IC_{50} (µM)	Selectivity Index[c] (SI)
90	H	>100	>100	
158		>100	>100	
159		67.8 ± 0.5	>100	>61.5
160		13.0 ± 0.2	62.7 ± 9.1	4.8
161		3.1 ± 0.1	>50	>16
				
87		25.6 ± 0.9	>100	>3.9
108		2.5 ± 0.1	>50	>20
129		2.9 ± 0.1	23.0 ± 2.1	7.9

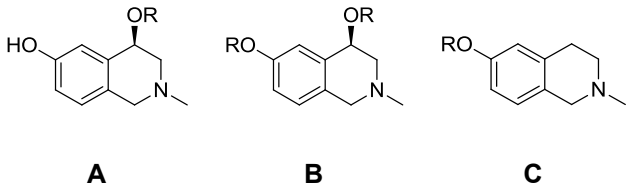
[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

2.12 Summary of derivatives substituted at the phenol

In summary, 37 derivatives of isoquinoline **86** substituted at the phenolic position with various motifs have been synthesised and evaluated for their *in vitro* antitrypanosomal activity against *T. b. rhodesiense* and mammalian cells. Substituting the phenol with substituted benzyl groups results in no significant difference in activity as compared to the unsubstituted benzyl group, an exception being bromobenzyl substituents (**98** and **99**) which increase activity against *T. b. rhodesiense* tenfold. Increasing the chain length between the phenolic oxygen and the phenyl group has no effect. Cyclohexyl substituents showed good activity, with increased activity as compared to their phenyl counterparts. Derivatives substituted with a biphenyl group at the phenol showed the best activity against *T. b. rhodesiense,* however they generally showed a high level of cytotoxicity. An exception being derivative **132,** which corresponds to the *p*-chloro biphenyl.

3 Modification of the benzylic alcohol and the effect on antitrypanosomal activity

Modification of the benzylic alcohol was the next area of interest. Derivatives of **86** were synthesised by substituting the benzylic alcohol with a range of substituents to give the corresponding ethers (**Figure 41 A**). The effect of substituting both the benzylic and phenolic oxygens with various groups was also examined (**Figure 41 B**). Finally removal of the benzylic alcohol was explored to give the deoxy version of **86**, including substitution of the phenol of this deoxy derivative (**Figure 41 C**) in order to assess the effect of the benzylic alcohol on biological activity.

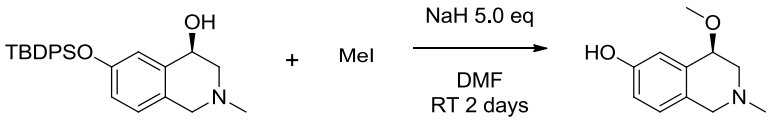


A **B** **C**

Figure 41 Modification of the benzylic alcohol.

3.1 Substitution of the benzylic alcohol

Substitution of the benzylic alcohol of **86** was first attempted using a large excess of sodium hydride and one equivalent of the desired alkyl halide. The rationale being that both the phenol and benzylic alcohol would be fully deprotonated, and since the benzylic alcohol should be the superior nucleophile substitution would occur preferentially at the benzylic alcohol as opposed to the phenol. However, under these conditions the disubstituted product was isolated. This was confirmed through the ^{1}H NMR spectrum which showed double the number of aromatic signals expected in the region in which the benzyl group is observed. Following this result it was decided that a protecting group would need to be installed on the phenol before the substitution reaction could be undertaken.

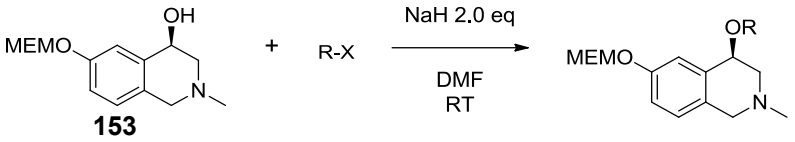


152 **162**

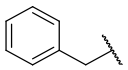
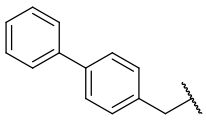
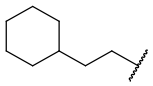
Scheme 22 Synthesis of **162**.

A *tert*-butydiphenylsilyl (TBDPS) group was installed onto the phenol as described previously (see **Table 8** pg. 60) to give the TBDPS protected phenol **152.** This was deprotonated using an excess of sodium hydride, subsequent addition of a slight excess of methyl iodide then gave the desired methyl ether derivative as the free phenol rather than the expected TBDPS protected phenol. The instability of the TBDPS group on phenols under strongly basic conditions[156] was rationalised as the reason for its loss. Substitution of the benzylic alcohol was confirmed via HMBC which showed a correlation between the signal for the methyl hydrogens and the methine carbon (4) of the saturated ring, and no correlation was seen between the methyl hydrogens and the aromatic ring. Using benzyl bromide in place of methyl iodide in the above reaction gave a complex mixture from which a small amount of product substituted with a benzyl group at the phenol, rather than at the benzylic alcohol, was isolated. This result was inconsistent with the synthesis of the methyl ether derivative **162** which was obtained under these same conditions as the free phenol. It can be rationalised that in the case of the methyl ether, due to the higher reactivity of methyl iodide as compared to benzyl bromide, the substitution reaction was able to take place on the benzylic alcohol before the TBDPS group came off the phenol. In the case of the benzyl ether the TBDPS group was probably removed under the strongly basic conditions before the substitution reaction with benzyl bromide could take place. This also explains why the phenolic substituted product was obtained rather than the product substituted at the benzylic alcohol. To overcome this problem the 2-methoxyethoxymethyl (MEM) group was used in place of the TBDPS group due to its stability in the presence of strong bases.[156]

Table 12 Synthesis of benzyl substituted derivatives.



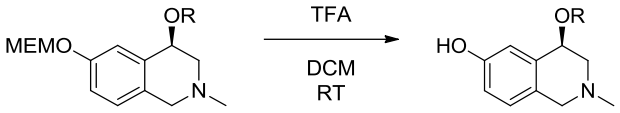
153

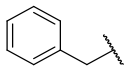
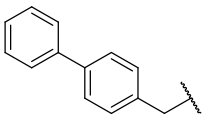
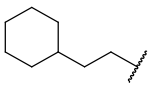
R	X	Reaction time	% Yield
 **163**	Br	1.5 hrs	**36%**
 **164**	Cl	1 hr	**83%**
 **165**	OMs	4 hrs	**46%**

A MEM group was installed onto the phenol as described previously (see **Table 8** pg. 60) to give the MEM protected phenol **153**. Deprotonation of the benzylic alcohol with an excess of sodium hydride followed by substitution with the corresponding alkylating agents gave the desired ether products. It was found that if the reaction mixture was left for too long then a complex mixture was obtained; 1-4 hours was the optimum time. The benzyl **163**, biphenylmethyl **164**, and cyclohexylethyl **165** derivatives were synthesised in this way to give the desired products in moderate to good yields (see **Table 12**). This was confirmed through observation of the ^{1}H NMR spectra which showed extra signals for the corresponding alkyl groups. The MEM group was easily removed using trifluoroacetic acid (TFA)[157] to give the free phenol derivatives **166**, **167**, and **168** in moderate yields (see **Table 13**). Removal of the MEM group was confirmed through ^{1}H NMR spectroscopy by the loss of the signals attributed to the protons of the MEM

group as well as the new signal at ~9.2 ppm corresponding to the phenolic proton (DMSO-d_6).

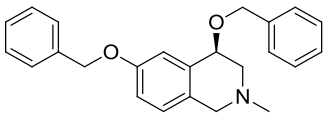
Table 13 MEM deprotection.



R	Reaction time	% Yield
 **166**	45 min	**50%**
 **167**	1 hr	**32%**
 **168**	1 hr	**53%**

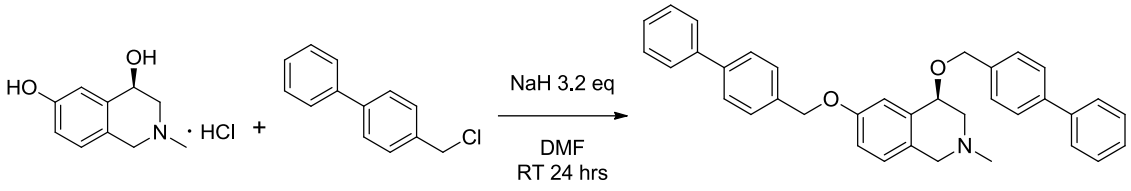
3.2 Disubstituted derivatives

So far derivatives substituted at either the phenolic or benzylic alcohol have been synthesised. Derivatives substituted at both of these positions to give a disubstituted product were explored next. From the synthesis of benzyl substituted derivative **87** (see **Scheme 2** pg. 40) a small amount of the disubstituted product **169** was also isolated from the reaction mixture via column chromatography. This was confirmed through ^{1}H NMR spectroscopy which showed a multiplet integrating for 10 protons in the region where the aromatic protons on the benzyl groups are expected (7.3-7.5 ppm).



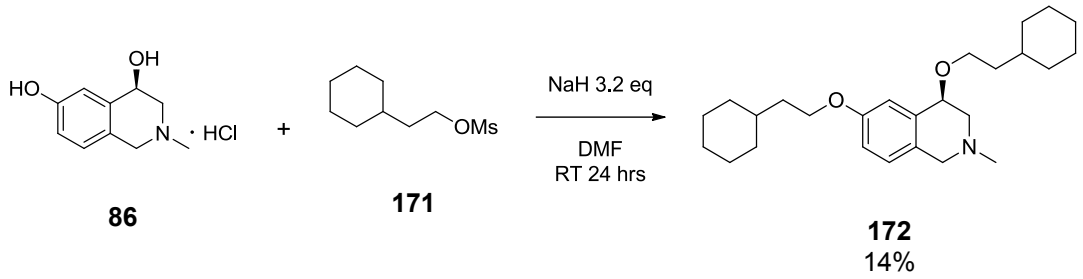
169

The biphenylmethyl and cyclohexylethyl disubstituted derivatives were also synthesised. This was achieved through deprotonation of both the phenol and benzylic alcohol with a slight excess of sodium hydride, followed by substitution with the appropriate alkylating agent. Following this procedure the desired disubstituted products **170** and **172** were obtained in poor yield (see **Scheme 23** and **Scheme 24**). TLC indicated a large amount of the monosubstituted product in the reaction mixture. If these derivatives were to be synthesised in future an improved procedure would need to be explored to improve the poor reaction yields. Confirmation of these products was obtained through the ^{1}H NMR spectra which showed the correct integration for having two of the corresponding alkyl groups on the molecule.



86 **128** **170** 7%

Scheme 23 Synthesis of biphenyl-disubstituted derivative **170**.



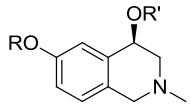
86 **171** **172**
14%

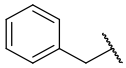
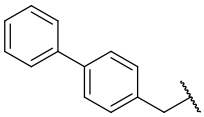
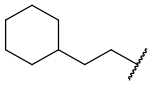
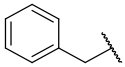
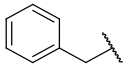
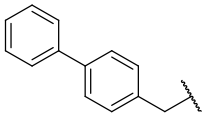
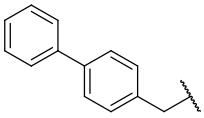
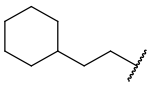
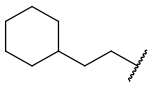
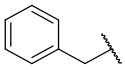
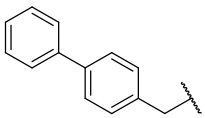
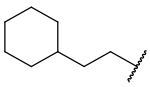
Scheme 24 Synthesis of cyclohexylethyl-disubstituted derivative **172**.

3.3 Antitrypanosomal activity of benzylic alcohol substituted derivatives and disubstituted derivatives.

The benzylic alcohol substituted and disubstituted derivatives above were evaluated *in vitro* for their activity against *T. b. rhodesiense* and mammalian cells. Both methyl and benzyl substituted derivatives **162** and **166** showed no anti-HAT activity, however both the biphenyl **167** and cyclohexyl **168** derivatives showed moderate activity against *T. b. rhodesiense* with no cytotoxicity to mammalian cells. Both the biphenylmethyl and cyclohexylethyl groups are larger and have a longer reach as compared to the benzyl group which could be contributing to their observed activity. The disubstituted derivatives (**169**, **170**, and **172**) showed almost identical activity. A comparison with the corresponding phenol substituted (i.e. mono substituted) derivatives (**87**, **129**, and **108**) showed the disubstituted benzyl derivative **87** having significantly increased activity while conflictingly the biphenyl **170** and cyclohexyl **172** derivatives had almost identical activity to their counterparts. Although the biphenyl disubstituted derivative **170** was more cytotoxic.

Table 14 *In vitro* activity of benzylic alcohol substituted derivatives and disubstituted derivatives.

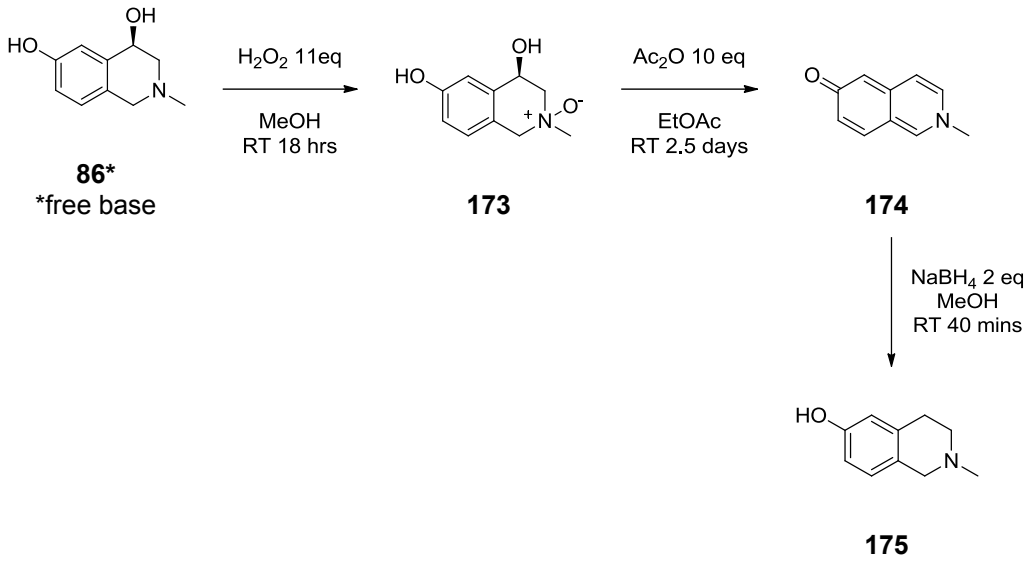


No.	R	R'	IC_{50} *T. b. rhodesiense*[a] (μM)	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
162	H		>100	>100	
166	H		>50	>50	
167	H		6.4 ± 1.1	>50	>7.8
168	H		19.1 ± 0.2	>50	>2.6
169			2.8 ± 0.2	23.5 ± 1.4	8.4
170			2.8 ± 0.2	>10	3.6
172			2.3 ± 0.2	23.6 ± 1.5	10.3
87		H	25.6 ± 0.9	>100	>3.9
129		H	2.9 ± 0.1	23.0 ± 2.1	7.9
108		H	2.5 ± 0.1	>50	>20

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

3.4 Removal of the benzylic alcohol and phenolic substitution

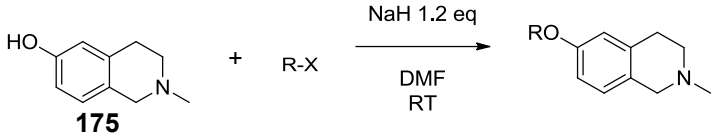
Removal of the benzylic alcohol from isoquinoline **86** would allow information to be obtained on the importance of the benzylic alcohol for anti-HAT activity. The benzylic alcohol of **86** was removed serendipitously while attempting to remove the *N*-methyl group of **86** via a Polonovski reaction (see section 5.1.1 pg. 94). Isoquinoline **86** as the free base was treated with an excess of aqueous hydrogen peroxide to give the *N*-oxide **173** , as a mixture of two diastereomers (7:3), in >99% yield. Formation of the *N*-oxide was confirmed through ^{1}H NMR spectroscopy which showed two sets of signals corresponding to the two diastereomers of **173**. The downfield shift of the protons on the saturated ring as well as the downfield shift of the *N*-methyl signal from 2.5 to ~3.4 confirmed the *N*-oxide had been formed. Treatment of the *N*-oxide with an excess of acetic anhydride was expected to furnish the *N*-acetyl derivative via a Polonovski reaction, however this was not observed. A very polar (TLC 15% MeOH, 2% sat. NH_3, in DCM) bright yellow compound which fluoresced under UV light was obtained. This compound was determined to be the isoquinolone **174**, which was isolated in 64% yield. Other than the *N*-methyl signal the ^{1}H NMR spectrum of this compound showed only signals in the aromatic region. The ^{13}C NMR spectrum also showed only aromatic signals, apart from the *N*-methyl signal, with a signal at ~180 ppm corresponding to a carbonyl carbon which fits with the structure proposed for **174**. A search of the literature revealed that this compound had been reported previously by Fourneau et al.[158] The structure of isoquinolone **174** was then confirmed by comparison with the reported ^{1}H NMR spectrum. Fourneau et al. also reported that reaction of this isoquinoline **174** with potassium borohydride gave the saturated isoquinoline **175**. Following treatment of isoquinoline **174** with an excess of sodium borohydride the desired 4-deoxy derivative **175** was obtained. This was confirmed by ^{1}H NMR spectroscopy which showed two triplets for the two sets of coupling methylene protons (position 3 and 4). The protons on the methylene carbon at position 1 were also observed as a singlet as opposed to two doublets in the starting material.



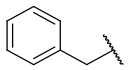
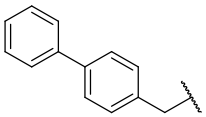
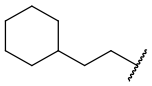
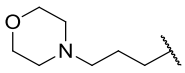
Scheme 25 Removal of the benzylic alcohol.

Substitution of the phenol of deoxy isoquinoline **175** was undertaken similarly to that described previously. The phenol was deprotonated using a slight excess of sodium hydride, followed by substitution with the corresponding alkylating agent. Following this procedure the benzyl **176**, biphenylmethyl **177**, cyclohexylethyl **178**, and *N*-propylmorpholine **179** derivatives of **175** were synthesised in moderate to good yield (see **Table** 15). Synthesis of these derivatives was confirmed via ^{1}H NMR and ^{13}C NMR spectroscopy which showed new signals for the new substituents in the appropriate regions of the spectrum.

Table 15 Phenolic substitution of deoxyisoquinoline **175**.



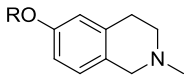
175

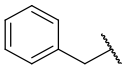
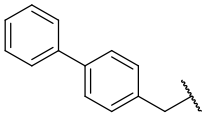
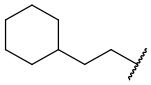
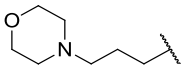
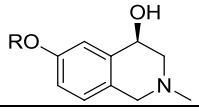
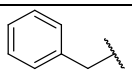
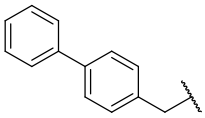
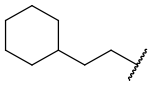
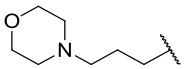
R	X	Reaction time	% Yield
 **176**	Br	2 days	**69%**
 **177**	Cl	2 days	**30%**
 **178**	OTs	2.5 days	**82%**
 **179**	Cl	24 hrs	**57%**

3.5 Antitrypanosomal activity of phenolic substituted derivatives of 175

Deoxyisoquinoline **175** and its phenolic substituted derivatives were evaluated for their activity against *T. b. rhodesiense* and mammalian cells. Deoxyisoquinoline **175** showed no activity against *T. b. rhodesiense.* This result was expected as the oxy version **86** showed no activity. All derivatives showed some inhibition of *T. b. rhodesiense* with reasonable selectivity as compared to mammalian cells. Comparison of these derivatives (**176-179**) with the corresponding derivatives with the benzylic alcohol still intact (**87**, **129**, **108**, and **111**) showed no significant difference. The benzyl derivative **176** was slightly more active than its counterpart with the benzylic alcohol intact. The biphenyl **177**, cyclohexyl **178**, and morpholine **179** derivatives showed almost identical activity to their counterparts with the benzylic alcohol intact. These results suggest that the benzylic alcohol is not having a significant effect on the anti-HAT activity of this series of compounds, and is unlikely to be important to the mode of action.

Table 16 *In vitro* activity of phenolic substituted derivatives of **175**.

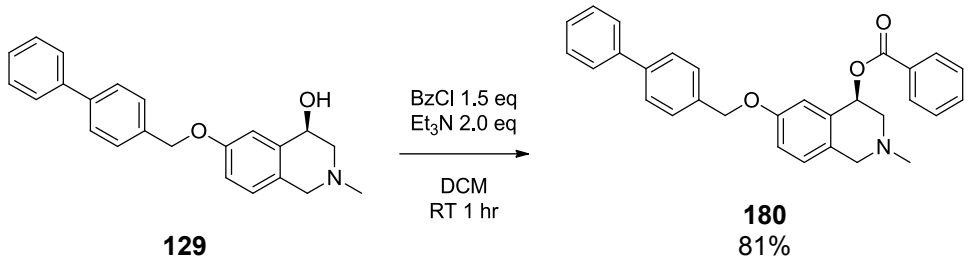


No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
175	H	>100	>100	
176		4.4 ± 0.3	>100	22.7
177		2.3 ± 0.1	16.5 ± 2.8	14.2
178		2.9 ± 0.1	25.0 ± 3.9	8.6
179		25.9 ± 2.2	>50	>1.9
				
87		25.6 ± 0.9	>100	>3.9
129		2.9 ± 0.1	23.0 ± 2.1	7.9
108		2.5 ± 0.1	>50	>20
111		27.6 ± 0.2	>50	1.8

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

3.6 Changing the stereochemistry

Although from the results above it seems that the benzylic alcohol has no effect on anti-HAT activity, when substituted, the resulting derivatives still showed some activity. Therefore it was thought that it might be valuable to look at the stereochemistry of the benzylic alcohol. So far it has been assumed that the benzylic alcohol retains the original stereochemistry from its original synthesis from (*R*) phenylephrine. The benzoate of **129** and its enantiomer were synthesised in order to provide a comparison of the two possible positions of the benzylic alcohol *R* and *S*. Biphenyl substituted phenol **129** was used rather than isoquinoline **86** as it showed good anti-HAT activity and would provide a basis to make a comparison. Synthesis of the benzoate was achieved through a simple esterification reaction with benzoyl chloride to give the desired benzoate **180** in 81% yield (**Scheme 26**). The ^{1}H NMR spectrum **180** showed the methine proton on the same carbon as the benzylic alcohol (position 4) shift downfield significantly from the starting material (4.62 - 6.22 ppm) confirming the attachment of the electron withdrawing benzoyl group to the benzylic alcohol. The ^{13}C NMR spectrum also showed a peak for the carbonyl carbon at 166.8 ppm.

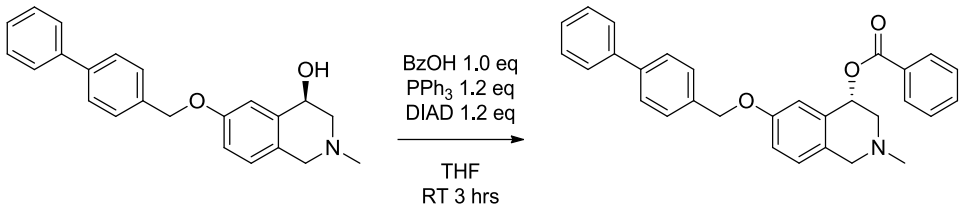


129 **180** 81%

Scheme 26 Synthesis of the benzoate of **129**.

The use of Mitsunobu chemistry[159,160] allowed for the synthesis of the benzoate of **129** with inverted stereochemistry. The Mitsunobu reaction involves the conversion of in this case a secondary alcohol to an ester, with inversion of stereochemistry, using an azodicarboxylate and triphenyl phosphine. Benzoic acid was used as the nucleophile in order to furnish the benzoyl ester. DIAD (diisopropyl azodicarboxylate) was used as the azodicarboxylate which reacts with triphenylphosphine to form a phosphonium intermediate which then bonds to the

alcohol. Substitution of the benzoic acid and elimination of triphenylphosphine oxide then generates the stereochemically inverted ester. Treatment of **129** with benzoic acid in the presence of DIAD and triphenylphosphine[161] gave the desired benzoate **181** in 42% yield. The ^{1}H and ^{13}C NMR spectra of this derivative were both identical to derivative **180**. Optical rotation was used to confirm that the stereochemistry of derivatives **180** and **181** were opposite. The specific rotation for derivative **180** was measured at +29.8° which is approximately opposite to that measured for derivative **181** at -37.4°, confirming the stereochemistry of both derivatives. Chiral HPLC for each of these derivatives showed only one peak with the elution times being significantly different for derivative **180** (12.73 min) and **181** (10.21 min) again confirming that the two opposite isomers had been synthesised (see chapter 7, pg. 125 for details).



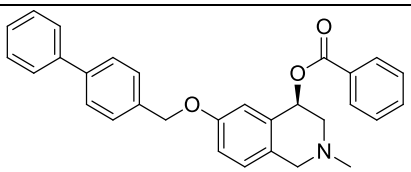
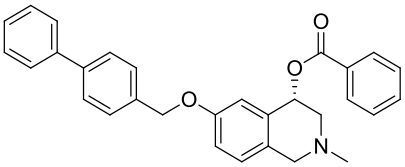
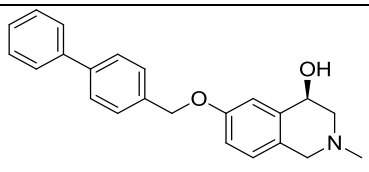
129 **181** 42%

Scheme 27 Synthesis of the Mitsunobu benzoate of **129**.

3.7 Effect of changing the stereochemistry on antitrypanosomal activity

Evaluation of derivatives **180** and **181** for their activity against *T. b. rhodesiense* and mammalian cells gave identical results. There was no difference seen between the activity of the derivative with the original stereochemistry **180** and that with inverted stereochemistry **181** against *T. b. rhodesiense*. Hovever, both derivatives proved to be very cytotoxic, with equivalent cytotoxicities. Comparison of these derivatives against biphenyl derivative **129** showed that they were slightly less active and considerably more toxic to mammalian cells. These results suggest that the stereochemistry of the benzylic alcohol has no effect on the anti-HAT activity, as was expected from the previous results which showed that the benzylic alcohol plays no role in the anti-HAT activity.

Table 17 *In vitro* activity of **180** and **181** derivatives.

No.	Structure	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
180		16.4 ± 0.7	10.5 ± 4.1	0.6
181		16.3 ± 0.7	12.9 ± 2.3	0.8
129		2.9 ± 0.1	23.0 ± 2.1	7.9

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

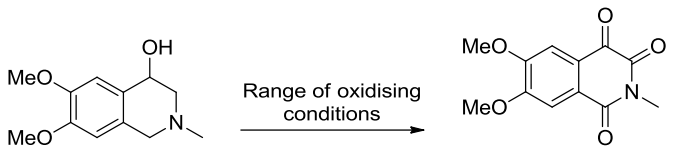
3.8 Grignard chemistry

Conversion of the benzylic alcohol to a ketone would provide further opportunity to add substituents to this part of the molecule through Grignard chemistry. Some difficulty was encountered in the oxidation of the benzylic alcohol to the ketone. Oxidation of **105** using 2 equivalents of IBX gave a complex mixture, although the ^{1}H NMR spectrum of the crude sample showed the disappearance of the signal corresponding to the methine proton, there was no other evidence of the desired product being formed. Isolation of a pure compound through column chromatography was not possible. Oxidation with manganese dioxide also gave a mixture of products however the major product was isolated and was determined to be the trione **182** (see **Scheme 28**). The ^{1}H NMR spectrum of **182** showed no signals in the aliphatic region apart from those associated with the propyl chain and the *N*-methyl signal. However, the aromatic signals corresponding to the isoquinoline were still present in the spectrum but they were shifted downfield significantly. The ^{13}C NMR spectrum showed four signals in the region of 150 to 180 ppm where it would be expected to find the carbon signals associated with the three carbonyl groups as well as the quaternary aromatic carbon attached to the oxygen.

105 **182**

Scheme 28 Attempted oxidation of the benzylic alcohol with MnO_2.

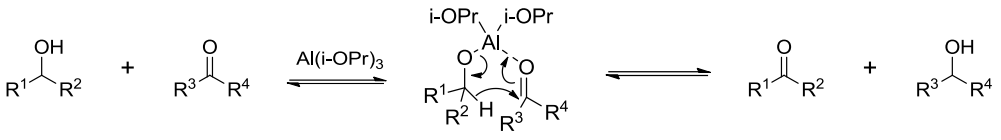
A similar reaction has been reported by Lesèche et al. in the oxidation of a similar isoquinoline (see **Scheme 29**).[162] Considering all of the above data along with the HRMS data the structure of compound **182** can be confirmed. Lesèche et al. reported their attempt to oxidise 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**184**) using a number of different oxidation methods (**Scheme 29**), from which they found that an Oppenauer oxidation was the only successful method. It was rationalised that Oppenauer oxidation may provide a successful method to convert the benzylic alcohol of **105** to a ketone.



183 **184**

Scheme 29 Reactions reported by Lesèche et al.

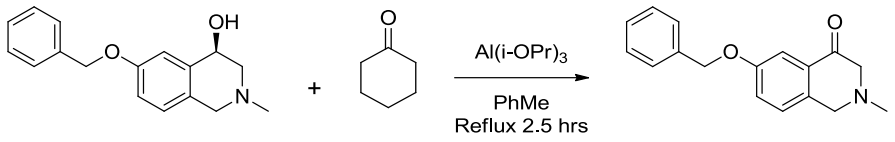
Oppenauer oxidation involves the conversion of a secondary alcohol to a ketone using aluminium isopropoxide as a catalyst and excess of a ketone reagent, which acts as a hydride acceptor.[163] The mechanism (see **Scheme 30**) involves one of the isopropoxide groups on the aluminium being replaced with the alcohol which generates isopropyl alcohol. Coordination of the excess ketone to the aluminium complex results in a six-membered transition state where the α-hydrogen on the alcohol shifts to the ketone, resulting in formation of the desired ketone.[164,165]



Scheme 30 Mechanism of the Oppenauer oxidation.

Following the procedure reported by Lesèche et al. isoquinoline **87** was subjected to Oppenauer oxidation, using excess cyclohexanone as the hydride acceptor. The procedure involves a distillation setup which allows for azeotropic drying of the solvent but more importantly allows for the removal of the isopropanol and cyclohexanol formed in the reaction preventing them from taking place in the reaction and being oxidised themselves. Initial attempts showed some of the desired product being formed however isolation of the product from the reaction mixture via column chromatography resulted in decomposition. By carefully monitoring the reaction via TLC and ensuring it went to completion (it was required to keep adding more toluene so the reaction mixture did not dry out) 85% yield (crude) of what was believed to be the desired product was obtained. The ^{1}H NMR spectrum showed two large singlets at 3.69 and 3.30 ppm which correspond to the two methylene signals. Due to the methylene protons now being in more similar environments for isoquinolone **186** as compared to isoquinoline **87** it would be expected that these signals now appear as singlets. The peak for the methine proton of **87** was also no

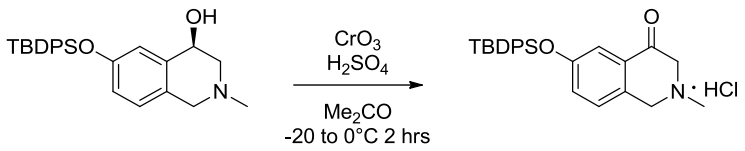
longer seen in the spectrum. The ^{13}C NMR spectrum of **186** showed a carbonyl signal at 194.7 ppm. Conversion of isoquinone **186** to the HCl salt gave a more stable product as judged by no decomposition observed by ^{1}H NMR spectroscopy over a period of 24 hours, however it could not be purified successfully.



87 **185** **186**

Scheme 31 Oppenauer oxidation of **87**.

Gensler et al.[166] reported a method of successfully oxidising a similar isoquinoline using Jones reagent. Although Lesèche et al. had no success with this procedure another example was later reported by Domínguez et al.[167] in which they were successful in using a modified procedure of that reported by Gensler et al. Using this procedure the TBDPS protected isoquinoline **152** was treated with Jones reagent at -20°C and stirred for 10 minutes. Upon workup some of the desired product was obtained however a large amount of starting material still remained. Due to the difficulty in purifying the product it would be ideal if all of the starting material was converted in the reaction. It was found that stirring the reaction mixture at -20°C and then allowing the reaction mixture to slowly warm to 0°C (approximately 2 hrs) gave a better result (see **Scheme 32**). However, the best result that was obtained was a mixture of product and starting material in a ratio of 3:2. Through workup of the reaction it was possible to extract the HCl salt from the reaction mixture using ethyl acetate, the product was obtained as a yellow solid which was quite hygroscopic making it difficult to work with.

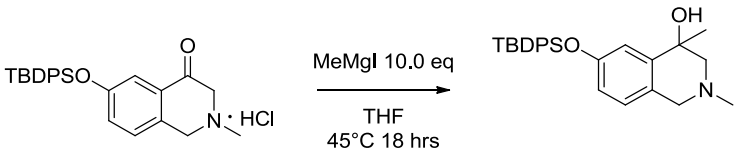


152 **187**

Scheme 32 Jones oxidation of **152**.

The product of the Jones oxidation (as the mixture of ketone and starting material) was used in a Grignard reaction, as the starting material should not affect the reaction. Since the ketone was isolated as the HCl salt it was necessary to use an

excess of Grignard reagent to allow for the reaction with the HCl salt. Initially attempts using methylmagnesium iodide (MeMgI) were unsuccessful resulting in complex mixtures being formed. Due to the hygroscopic nature of the HCl salt it was found that drying it under high-vacuum before introducing the Grignard reagent seemed to give a better result. The methylated product was successfully synthesised using 10 equivalents of MeMgI (**Scheme 33**). Workup with a sat. ammonium chloride solution, to quench the excess Grignard reagent without protonating the tertiary amine, and subsequent chromatography gave the desired product **188** in 41% yield. The ^{1}H NMR spectrum showed a new signal at 1.29 ppm corresponding to the new methyl group, while the signals for the methylene protons are seen as two doublet of doublets and two doublets showing that the methylene protons now have axial and equatorial arrangements. This coupled with HRMS data confirms that the desired Grignard product was successfully formed.



187 **188** 41%

Scheme 33 Grignard reaction using MeMgI.

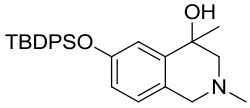
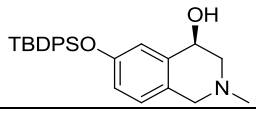
Multiple attempts of the same reaction using phenylmagnesium iodide as the Grignard reagent gave complex mixtures which were not purified and this reaction was abandoned. Further work is needed to optimise the reaction conditions and allow a variety of Grignard reagents to be used. It would also be useful to revisit both the Oppenauer and Jones oxidations in order to try and improve the synthesis of the ketone. Optimisation of the reaction conditions would potentially allow the ketone to be synthesised and isolated more effectively which would also potentially improve the outcome of the Grignard reactions, as well as allowing for a variety of other transformations of the ketone.

3.8.1 Antitrypanosomal activity of derivative 188

The ketone was not submitted for biological testing as a pure sample could not be obtained. However, the Grignard derivative **188** was evaluated for its activity against

T. b. rhodesiense and mammalian cells. This derivative showed some activity to *T. b. rhodesiense* (see **Table 18**) although there was no increased activity as compared to the TBDPS phenol substituted isoquinoline **152**. It would be interesting to see how using larger substituents in a Grignard reaction would affect the anti-HAT activity of this type of derivative.

Table 18 *In vitro* activity of derivative **188**.

No.		IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
188		2.7 ± 0.1	22.2 ± 1.1	8.2
152		2.8 ± 0.1	19.1 ± 0.6	6.8

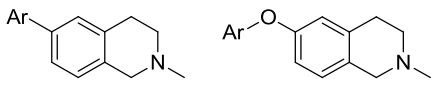
[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

3.9 Summary of derivatives modified at the benzylic alcohol

In summary, 15 derivatives were synthesised which were modified at the benzylic alcohol. Substitution at the benzylic alcohol gave mixed results with larger substituents, such as a biphenylmethyl and cyclohexylethyl group, showing some activity. Disubstitution (i.e. substitution at both the phenol and benzylic alcohol) did not seem to improve activity as compared to derivatives substituted only at the phenol. Derivatives substituted at the phenol with the benzylic alcohol removed showed comparable activity to derivatives substituted at the phenol with the benzylic alcohol still intact, suggesting the benzylic alcohol is not important for activity. Changing the stereochemistry of the benzylic alcohol also had no impact on activity supporting the idea that the benzylic alcohol is not important in activity.

4 Synthesis of analogues modified at the phenolic position and their antitrypanosomal activity

Modification of isoquinoline **86** at the phenolic position has been explored thoroughly (see chapter 2), however no information has been obtained regarding whether the flexible ether linkage is important for activity. Derivatives synthesised where the aromatic ring (position 6) is directly substituted forming a new carbon-carbon bond (see **Figure 42 A**) would provide more rigid derivatives and also potentially provide some information regarding the size and shape of the receptor site. Also synthesised were derivatives through the formation of diaryl ethers at the phenolic position (see **Figure 42 B**). These derivatives do not have a methylene carbon linking the phenolic oxygen to the aryl substituent, providing derivatives with slightly increased rigidity compared to the benzyl ethers.



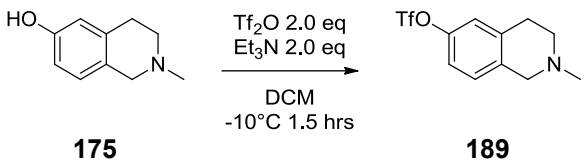
A **B**

Figure 42 Modification of position 6.

4.1 Direct substitution onto the aromatic ring at the phenolic position 6

Synthesis of derivatives where the aromatic ring (position 6) is directly substituted forming a new carbon-carbon bond, was achieved through Suzuki coupling. Since it was determined from previous results that the benzylic alcohol played little or no part in anti-HAT activity (see section 3.5 pg.77), it was decided to use the deoxyisoquinoline derivative **175,** which corresponds to the derivative with the benzylic alcohol removed, for the synthesis of these derivatives. This would simplify

the synthesis and was not expected to affect the biological activity. The first step required conversion of the phenol to a triflate. The triflate being a pseudo halide could then be used in Suzuki coupling reactions.[149] Reaction of deoxyisoquinoline **175** with triflic anhydride gave the expected triflate in 36% yield. Confirmation of the triflate was obtained through NMR spectroscopy. The ^{1}H NMR spectrum showed a downfield shift of the aromatic protons attributed to the de-shielding effect of the triflate group.

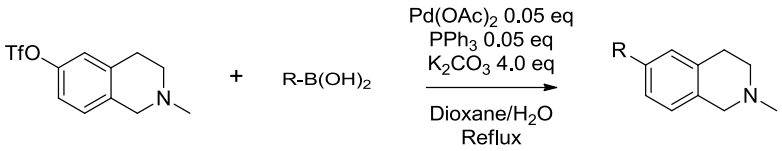


175 **189**
36%

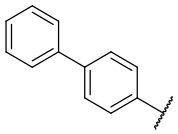
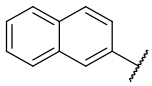
Scheme 34 Synthesis of the triflate of **189**.

Suzuki coupling of triflate **189**, using palladium acetate and triphenylphosphine to generate the palladium(0) source, with the corresponding boronic acids gave the expected diaryl derivatives. The ^{1}H NMR spectra showed the signals corresponding to the aromatic hydrogens on the isoquinoline scaffold that are closest to the new formed bond (positions 5 and 7) have shifted downfield slightly (0.3-0.6 ppm shift) caused by the attachment of the new aryl group. HRMS data also confirms the desired products had been formed.

Table 19 Derivatives synthesised by Suzuki coupling of triflate **189**.

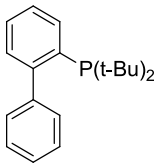


189

R	Reaction time	% Yield
 **190**	6 hrs	**33%**
 **191**	7 hrs	**52%**
 **192**	6 hrs	**43%**

4.2 Synthesis of diaryl ethers at the phenolic position 6

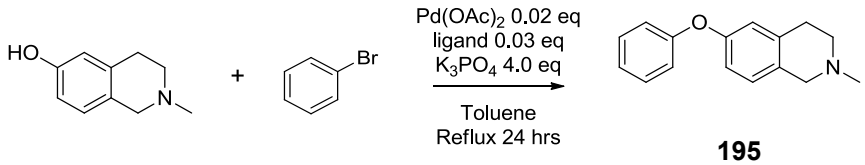
Synthesis of diaryl ethers at the phenolic position was achieved through Buchwald-Hartwig cross coupling. Buchwald-Hartwig cross-coupling is the palladium catalysed cross coupling of phenols and aryl halides to form diaryl ethers.[168] An electron rich phosphine ligand is also essential in this reaction. 2-(Di-*tert*-butylphosphino)biphenyl **193** was the ligand used in this case.



193

Figure 43 2-(di-*tert*-butylphosphino)biphenyl.

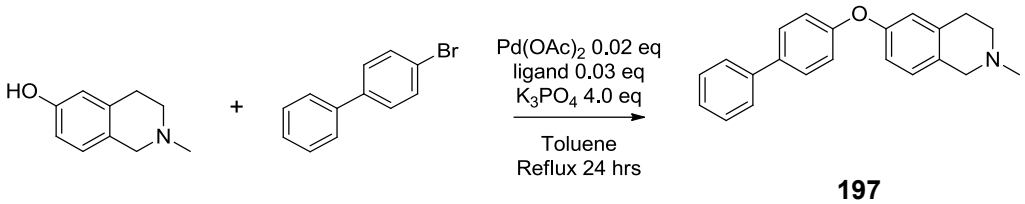
Coupling of phenol **175** with bromobenzene gave the expected diaryl ether product **195** in low yield (**Scheme 35**). The ^{1}H NMR spectrum of **195** showed a slight downfield shift of the aromatic protons on the isoquinoline scaffold attributed to the coupling of the phenyl ring to the phenolic oxygen, as well as new signals integrating for 5 protons in the aromatic region corresponding to the phenyl ring.



175 **194** **195** **22%**

Scheme 35 Synthesis of diaryl ether **195** by Buchwald-Hartwig coupling.

Coupling of phenol **175** with 4-bromobiphenyl also gave the expected aryl ether **197** in low yield (**Scheme 36**). Again a slight downfield shift of the aromatic protons on the isoquinoline scaffold was observed in the ^{1}H NMR spectrum attributed to the attachment of the biphenyl group to the phenol, as well as new signals integrating for 9 protons in the aromatic region.



175 **196** **197** **37%**

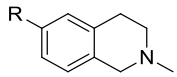
Scheme 36 Synthesis of diaryl ether **197** by Buchwald-Hartwig coupling.

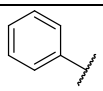
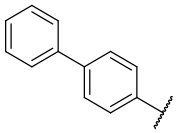
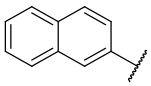
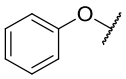
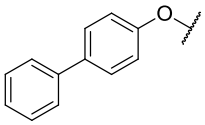
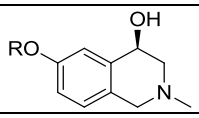
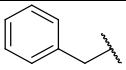
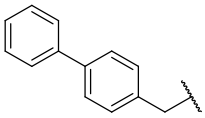
4.3 Antitrypanosomal activity of derivatives modified at the phenolic position

The above diaryl and diaryl ether derivatives were evaluated for their *in vitro* activity against *T. b. rhodesiense* and mammalian cells. The diaryl derivatives showed good anti-HAT activity with the biphenyl derivative **191** being tenfold more active than the phenyl **190** and naphthyl **192** derivatives. Both the phenyl and biphenyl derivatives showed an approximate tenfold increase in activity against *T. b. rhodesiense* as compared to the phenolic substituted benzyl **87** and biphenyl methyl **129** derivatives discussed in chapter 2, with reasonable selectivity as compared to mammalian cells.

This suggests that the increased rigidity of the molecule is favourable to activity. As for the diaryl ether derivatives (**195** and **197**) both showed activity against *T. b. rhodesiense* similar to the corresponding phenolic substituted derivatives **87** and **129**.

Table 20 *In vitro* activity of diaryl and diaryl ether derivatives.



No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
190		3.0 ± 0.1	>50	16.7
191		0.27 ± 0.01	15.6 ± 0.3	57.8
192		2.7 ± 0.1	24.1 ± 2.2	8.9
195		19.8 ± 0.6	>100	5.1
197		2.7 ± 0.1	22.3 ± 0.4	8.3
				
87		25.6 ± 0.9	>100	>3.9
129		2.9 ± 0.1	23.0 ± 2.1	7.9

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

5 Modification of the nitrogen atom and its impact on antitrypanosomal activity

The impact of the nitrogen atom in the isoquinoline ring and its substitution were explored in order to see how these affected anti-HAT activity. Removal of the *N*-methyl would give the secondary amine allowing us to gain information on the importance of the *N*-methyl and the effect of a secondary amine as opposed to a tertiary amine. It would also provide the opportunity to substitute the nitrogen atom with different alkyl groups (**Figure 44 A**) and explore the effect on anti-HAT activity of having something larger than a methyl group on the nitrogen atom. Substitution of the phenol of the secondary amine derivative (**Figure 44 B**) would also be possible, again providing information on the effect of a secondary amine. It is also possible to substitute the nitrogen atom and also substitute the phenol (**Figure 44 C**) providing some disubstituted derivatives which may be of interest. Finally removing the nitrogen atom from the ring completely (**Figure 44 D**) would provide information on the importance of the nitrogen atom for activity.

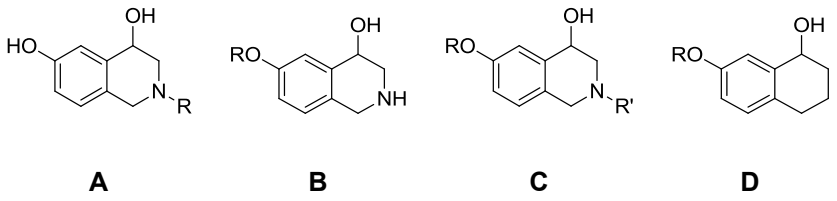


Figure 44 Modification of the nitrogen atom.

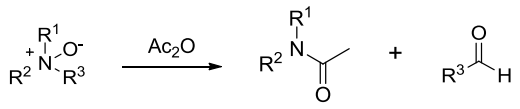
5.1 *N*-Demethylation of isoquinoline 86

There are a number of different ways to achieve *N*-demethylation of amines.[156] One of the most common ways of *N*-demethylation is the Polonovski reaction. Classical and non-classical Polonovski reaction conditions were used in an attempt to *N*-demethylate isoquinoline **86**. After multiple unsuccessful attempts to demethylate isoquinoline **86** it was decided that rather than demethylating the isoquinoline it

would be better to instead synthesise the desired de-methylated product via a Pictet-Spengler cyclisation from nor-phenylephrine.

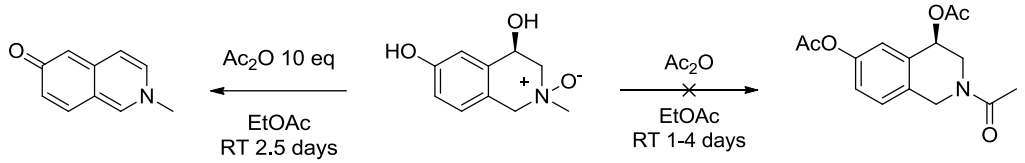
5.1.1 Polonovski reaction

The Polonovski reaction describes the reaction of a tertiary *N*-oxide with an activating agent, most commonly acetic anhydride, which results in the formation of an acetamide and an aldehyde (see **Scheme 37**). [169] The secondary amine can then be obtained by hydrolysis or reduction of the acetamide.



Scheme 37 Classical Polonovski reaction.

The *N*-oxide **173** was synthesised as described previously (see **Scheme 25** pg. 75). Treatment of the *N*-oxide **173** with 4 equivalents acetic anhydride under Polonovski reaction conditions[170] was expected to give the tri-acetyl compound **198**. However, after workup of the reaction a complex mixture was obtained. Under the same conditions treatment of *N*-oxide **173** with 10 equivalents of acetic anhydride also gave a complex mixture observed by ^{1}H NMR spectroscopy, isoquinolone **174** was isolated as the major product as described previously (see **Scheme 25** pg. 75).



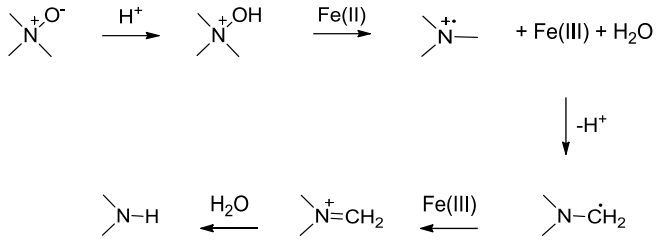
174 **173** **198**

Scheme 38 Attempted Polonovski reaction of **173**.

5.1.2 Non-classical Polonovski reaction

After little success of *N*-demethylation using classical Polonovski reaction conditions attention was turned to using non-classical conditions. A non-classical Polonovski reaction was reported by Scammells et al.[171] where *N*-demethylation of an opiate alkaloid is achieved using an $FeSO_4 \cdot 7H_2O$ mediated Polonovski reaction. In this

example rather than using acetic anhydride as an activating agent an iron(II) salt is used. The proposed mechanism involves coordination of iron(II) to the protonated *N*-oxide which undergoes a one electron reduction resulting in cleavage of the N-O bond and formation of an aminium radical cation. This radical cation then loses an α-proton and reorganises to form a carbon centred radical which is subsequently oxidised by iron(III) to form an iminium ion. Hydrolysis of the iminium ion then gives the desired secondary amine (**Scheme 39**).



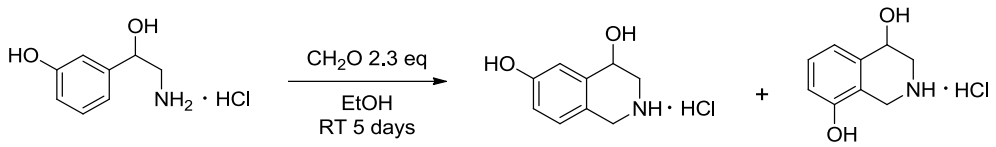
Scheme 39 Proposed mechanism of the non-classical iron mediated Polonovski reaction.

After treatment of *N*-oxide **173** with 1 equivalent of concentrated HCl to give the protonated *N*-oxide and treatment with $FeSO_4 \cdot 7H_2O$, according to the procedure proposed by Scammells et al.,[171] the *N*-oxide was recovered as well as some of the original isoquinoline **86**. This was apparent by TLC which showed two spots in the reaction mixture corresponding to the *N*-oxide and a new spot corresponding to isoquinoline **86**. Comparison of the ^{1}H NMR spectra of the *N*-oxide and isoquinoline **86** also confirmed this.

5.1.3 Pictet-Spengler cyclisation with nor-phenylephrine

After multiple unsuccessful attempts to demethylate isoquinoline **86** it was decided to instead synthesise the demethylated version. This was achieved through a Pictet-Spengler cyclisation of nor-phenylephrine. The Pictet-Spengler cyclisation describes the condensation of a β-arylethylamine with a carbonyl compound followed by cyclisation; the cyclisation occurs through an iminium intermediate.[172] Treatment of racemic nor-phenylephrine hydrochloride **199** with formaldehyde gave the desired *para* cyclised product **200**, as well as the *ortho* cyclised product **201** as a mixture of isomers (3:1) which were separated by crystallisation.[173] The ^{1}H NMR spectra for

both the *para* and *ortho* products showed only 3 aromatic protons consistent with the cyclised product, nor-phenylephrine showed 4 aromatic protons. For the *para* product the aromatic region showed two doublets and a doublet of doublets consistent with the isoquinoline being substituted in the 6 position. For the *ortho* product the aromatic region showed two doublet of doublets and a multiplet consistent with the isoquinoline being substituted in the 8 position. Both spectra also showed two new signals in the region of 4.2-4.5 ppm which can be observed as two doublets and correspond to the new methylene protons of the isoquinoline (position 1).



199

200
(33%)

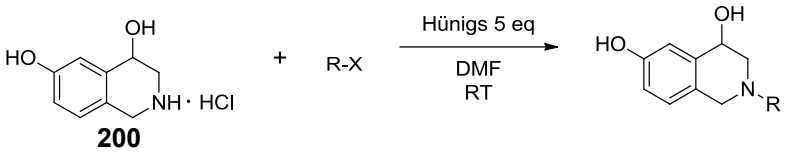
201
(12%)

Scheme 40 Pictet-Spengler cyclisation of nor-phenylephrine.

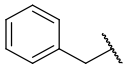
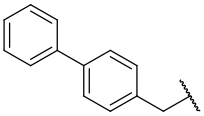
5.2 Substitution of the nitrogen atom

Availability of the 'demethylated' isoquinoline **200** now allowed for different substituents to be added to the nitrogen atom in order to assess the effect on anti-HAT activity. Substituents were added to the nitrogen atom via a simple alkylation reaction with the appropriate alkylating agents in the presence of Hünigs base. Hünigs base was used to prevent disubstitution and formation of the quaternary ammonium salt.[174] Alkylation with a range of alkyl halides gave the corresponding tertiary amine derivatives in moderate to good yields (**Table 21**). The ^{1}H NMR spectra of these derivatives showed an upfield shift of the signals for both sets of methylene protons on the isoquinoline scaffold consistent with alkylation of the nitrogen atom. Derivative **204** has been reported previously as the hydrochloride salt.[175]

Table 21 Substitution of the nitrogen atom.

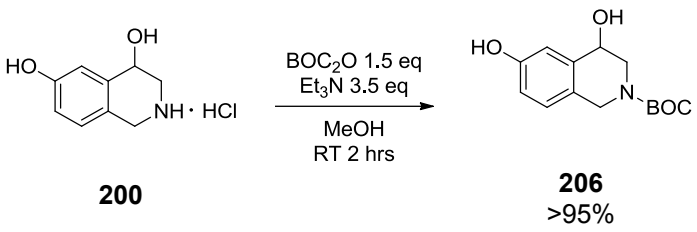


200

R	X	Reaction time	% Yield
 **202**	Br	1.5 days	**55%**
 **203**	Br	1.5 days	**47%**
 **204**	Br	24 hrs	**88%**
 **205**	Cl	24 hrs	**67%**

5.3 Substitution of the phenol

Substitution of the phenol of the 'demethylated' isoquinoline **200** was the next area of interest. Substituting the phenol would allow for information to be gained on the effect of a secondary amine as opposed to a tertiary amine in the isoquinoline scaffold. Since the isoquinoline with an unsubstituted phenol showed no anti-HAT activity, substituting the phenol would allow a comparison to be made with other active compounds and determination of the impact of the secondary amine. Substitution of the phenol first required protection of the amine to prevent the substitution reaction taking place at the amine instead of the phenol. Reaction of isoquinoline **200** with BOC-anhydride[176] gave the BOC protected amine **206** in excellent yield. The ^{1}H NMR spectrum showed a new peak at 1.50 ppm which integrates for 9 protons and corresponds to the *tert*-butyl group of the BOC protecting group.

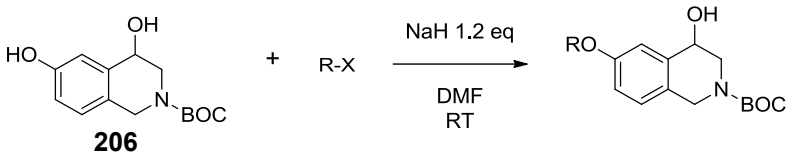


200 **206** >95%

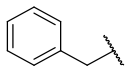
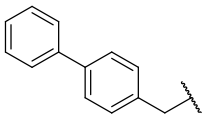
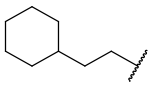
Scheme 41 BOC protection of isoquinoline 200.

Substitution of the phenol of the BOC protected isoquinoline **206** with a range of alkylating agents as described previously then gave the desired ether derivatives in moderate to good yields (**Table 22**).

Table 22 Substitution of the phenol of **206.**

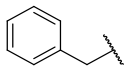
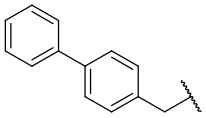
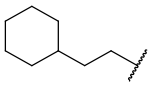


206

R	X	Reaction time	% Yield
 **207**	Br	24 hrs	**83%**
 **208**	Cl	3 days	**83%**
 **209**	OTs	3 days	**39%**

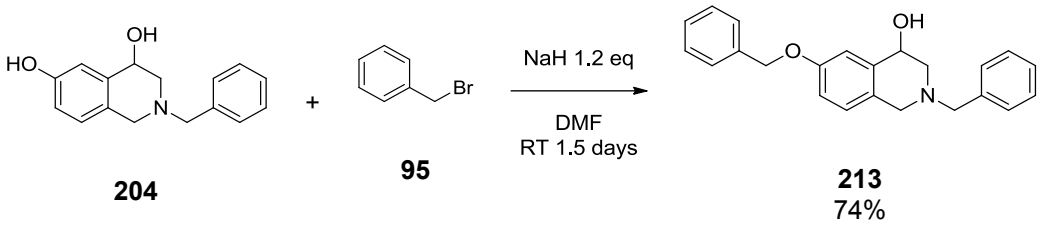
Following this the BOC protected isoquinolines (**207-209**) were deprotected by treatment with trifluoroacetic acid[148] to give the secondary amines (**210-212**) in moderate to excellent yields (**Table 23**). The ^{1}H NMR spectra showed the upfield shift of the methylene protons adjacent to the nitrogen atom in the isoquinoline scaffold (position 3) consistent with removal of the BOC group.

Table 23 BOC deprotection of derivatives **207**-**209**.

R	% Yield
 **210**	**41%**
 **211**	**55%**
 **212**	**>95%**

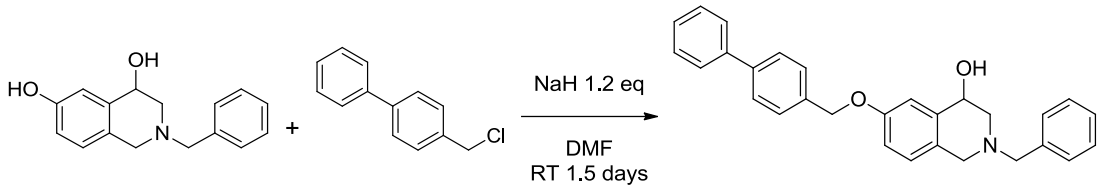
5.4 Substitution of the nitrogen atom and phenol

As well as substituting both the nitrogen atom and phenol separately, substitution of both the nitrogen atom and phenol on the same molecule could potentially show some interesting biological activity. The simplest way to achieve this was to take the *N*-substituted derivative **204** and alkylate the phenol. The phenol of derivative **204** was substituted with both a benzyl and biphenylmethyl group as described in **Scheme 42** and **Scheme 43** below to give the phenolic and nitrogen disubstituted derivatives **213** and **214** in good yields.



204 **95** **213** 74%

Scheme 42 Synthesis of derivative **213**.



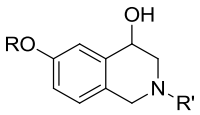
204 **128** **214** 70%

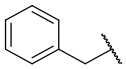
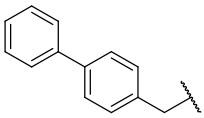
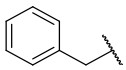
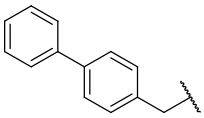
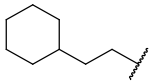
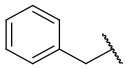
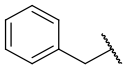
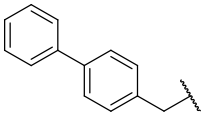
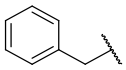
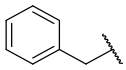
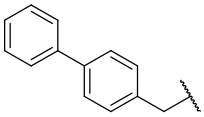
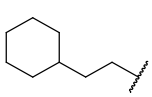
Scheme 43 Synthesis of derivative **214**.

5.5 Antitrypanosomal activity of *N*-modified derivatives

The synthesised *N*-modified derivatives were evaluated for their *in vitro* activity against *T. b. rhodesiense* and mammalian cells. The '*N*-demethylated' isoquinoline **200** showed no activity against *T. b. rhodesiense*. Derivatives substituted at the nitrogen atom with an ethyl **202** or propyl **203** group also showed no activity, however when the nitrogen atom was substituted with a benzyl group some activity was seen. *N*-Biphenylmethyl derivative **205** showed increased activity with and IC_{50} in the low micromolar range. Derivatives with a secondary amine in the isoquinoline core and substituted at the phenol with a benzyl **210** and cyclohexylethyl **212** group showed comparable activity to their counterparts with a tertiary amine in the isoquinoline core (**87** and **108** as reported previously). The derivative substituted at the phenol with a biphenyl methyl group **211** showed a tenfold increase in activity against *T. b. rhodesiense* as compared to its counterpart **129**, with comparable cytotoxicity to mammalian cells, making it almost 80 times more selective for *T. b. rhodesiense* than mammalian cells. This increase in activity is potentially due to increased solubility. As for derivatives substituted at the nitrogen atom with a benzyl group and at the phenol, the benzyl derivative **213** showed increased activity as compared to the corresponding *N*-methyl derivative **87**. The biphenyl derivative showed almost identical activity to its *N*-methyl counterpart **129**.

Table 24 *In vitro* activity of *N*-modified derivatives.

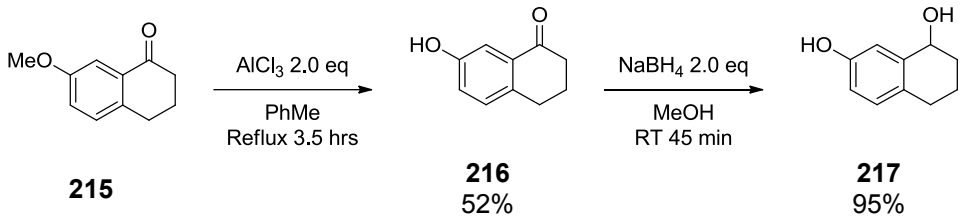


No.	R	R'	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
200	H	H	>100	>100	
202	H		>100	>100	
203	H		>100	>100	
204	H		70.5 ± 0.5	>100	1.4
205	H		5.4 ± 0.7	>50	9.3
210		H	17.4 ± 2.3	>50	2.9
211		H	0.25 ± 0.02	20.8 ± 0.8	83.2
212		H	2.5 ±0.2	>50	20
213			8.4 ± 1.1	31.8 ± 6.7	3.8
214			2.7 ± 0.1	14.8 ± 5.5	5.5
87		Me	25.6 ± 0.9	>100	>3.9
129		Me	2.9 ± 0.1	23.0 ± 2.1	7.9
108		Me	2.5 ± 0.1	>50	>20

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

5.6 Derivatives without a nitrogen atom

It was suspected that the nitrogen atom in the isoquinoline scaffold was important to anti-HAT activity. In order to confirm this a core scaffold without a nitrogen atom was synthesised, giving a tetrahydronaphthalene. This was achieved following a literature procedure starting from commercially available 7-methoxy-1-tetralone **215**.[177] This was demethylated using aluminium chloride to give the phenol **216** in 52% yield. Reduction of the ketone **216** using sodium borohydride then gave the desired product **217** in 95% yield.

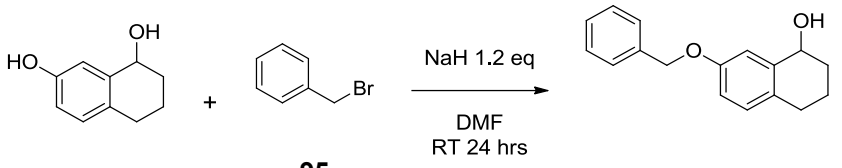


215 **216** 52% **217** 95%

Scheme 44 Synthesis of the core scaffold without a nitrogen atom.

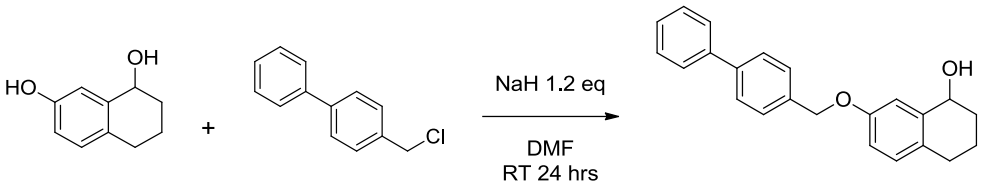
5.6.1 Substitution of the phenol

The phenol of this scaffold was then substituted with a benzyl (**Scheme 45**) and a biphenylmethyl (**Scheme 46**) group to allow a comparison of anti-HAT activity with the isoquinoline derivatives. This was achieved as described above to give the desired ether derivatives in good yields. This was confirmed through ^{1}H NMR spectroscopy by the slight downfield shift of the signals for the aromatic protons of the core scaffold, and the additional signals for the benzyl/biphenylmethyl groups.



217 **95** **218** 84%

Scheme 45 Benzyl substitution of **113**.



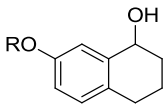
217 **128** **219** 87%

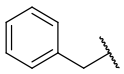
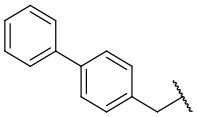
Scheme 46 Biphenylmethyl substitution of **217**.

5.6.2 Antitrypanosomal activity

The above derivatives were evaluated for their *in vitro* activity against *T. b. rhodesiense* and mammalian cells (**Table 25**). The core scaffold with the nitrogen atom removed **217** showed no anti-HAT activity, as was expected. Substitution at the phenol of this scaffold (**218** and **219**) did not improve the activity, therefore confirming the importance of the nitrogen atom in the scaffold for anti-HAT activity.

Table 25 *In vitro* activity of naphthyl derivatives.



No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
217	H	>100	>100	
218		65.9 ± 0.6	39.0 ± 10.4	0.6
219		>100	>100	

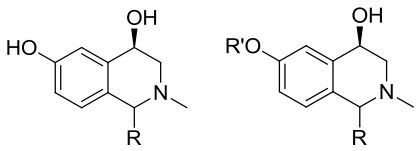
[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

5.7 Summary of derivatives modified at the nitrogen atom

In summary, 14 derivatives were synthesised with modifications at the nitrogen atom. Derivatives substituted at the nitrogen atom with larger groups such as a benzyl group showed some activity, with the biphenylmethyl derivative showing activity in the low micromolar range. Substituting the phenol of *N*-demethylated derivatives gave comparable results to derivatives where the nitrogen atom was methylated. An exception to this was derivative **211** substituted with a biphenylmethyl group at the phenol, which showed a tenfold increase in activity as compared to the *N*-methyl version. Substituting both the phenol and nitrogen atom did not increase activity as compared to *N*-methyl derivatives substituted at the phenol. Derivatives with no nitrogen atom in the scaffold showed no activity, confirming the importance of the nitrogen atom for activity.

6 Addition of substituents via Pictet-Spengler cyclisations and the effect on antitrypanosomal activity

It is possible to add substituents to position 1 of the isoquinoline scaffold by using functionalised aldehydes in the place of formaldehyde in the Pictet-Spengler cyclisation with phenylephrine. This provides an opportunity to add substituents to this position without altering the rest of the molecule (**Figure 45 A**). Synthesis of these derivatives would also allow for them to be substituted at the phenol (**Figure 45 B**) in order to allow a comparison of anti-HAT activity to the original phenolic substituted derivatives.



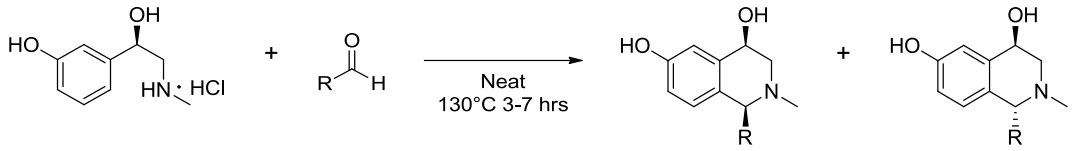
A **B**

Figure 45 Substitution of position 1.

6.1 Pictet-Spengler Cyclisations

The Pictet-Spengler cyclisations were originally attempted using previously reported conditions,[178] involving reflux of phenylephrine and the aldehyde in ethanol. The reaction was attempted with both benzaldehyde and acetaldehyde and in both cases no reaction was observed. The reaction mixture was heated at reflux for multiple days however still no reaction was observed. TLC and ^{1}H NMR spectra showed only starting material. Heating phenylephrine hydrochloride **89** with 1 equivalent of the aldehyde neat at 130°C was successful in giving the desired cyclised products (**Scheme 47**). Using any aldehyde other than formaldehyde in this cyclisation has been reported to give only the *para* substituted product,[173] and only formation of the

para cyclised product was observed. This is obvious from the substitution pattern in the ^{1}H NMR spectra which showed a small doublet (J = 2.5 Hz), a large doublet (J = 8.4 Hz), and a doublet of doublets (J = 8.4, 2.5 Hz) consistent with this 1,2,4-substitution pattern.† However, two isomers were observed from the reaction with almost identical ^{1}H NMR spectra. In most cases these two isomers were separated by column chromatography and represent the two diastereomers (**Scheme 47**), where isomer A is that which elutes first by chromatography and isomer B is that which elutes second.



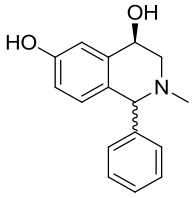
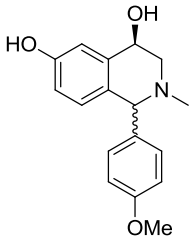
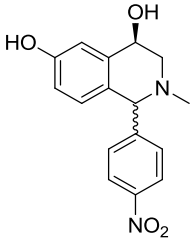
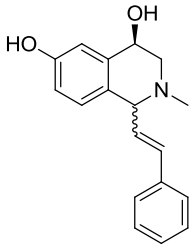
89

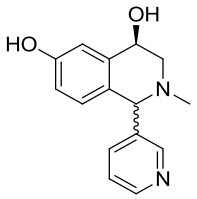
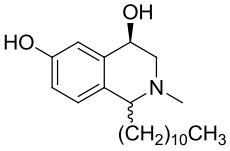
Scheme 47 Pictet-Spengler cyclisation using a range of aldehydes.

The cyclisation as described above was performed using a number of different aldehydes (see **Table 26**). Due to the reaction conditions the choice of aldehydes was restricted to those with high boiling points. Below is a summary of the derivatives synthesised. The two diastereomers were successfully separated via column chromatography (>90% purity by NMR) in most cases except for the pyridine and the undecyl derivatives. Derivative **220** has been reported in the literature, although the separated diastereomers were not reported.[179,180]

† Coupling constants reported here correspond to compound 220A, however the coupling pattern is consistent for all other derivatives (i.e. compounds 220-225).

Table 26 Derivatives synthesised by Pictet-Spengler cyclisation.

Structure	Isomer A	Isomer B
 **220**	**15%**	**21%**
 **221**	**17%**	**29%**
 **222**	**36%**	**32%**
 **223**	**9%**	**21%**

Structure	Isomer A	Isomer B
 **224**	**11%**	Contaminated with residual isomer A
 **225**	**43%** As a mixture of isomers A and B (66:34 by ^{1}H NMR)	

The ^{1}H NMR spectra of the cyclised derivatives showed a new signal between the region of 3.7 ppm and 4.9 ppm (depending on the particular derivative) corresponding to the new methine proton at position 1 of the cyclised product. In the case of derivative **222** a singlet is observed at ~4.3 ppm (see **Figure 46**) for both isomers A and B. Almost identical ^{1}H NMR spectra are observed for isomers A and B. The signals for the proton on the benzylic alcohol and the proton next to the benzylic alohol (position 4) are significantly downshifted (by ~0.3 ppm in the case of **222**) for isomer B as compared to isomer A. This is consistent for all derivatives. Interestingly the two methylene protons at position 3 are observed as two doublets of doublets for isomer A and as a doublet of doublets and an apparent triplet for isomer B (see expanded regions of spectra in **Figure 46**). This is consistent for all of the derivatives.

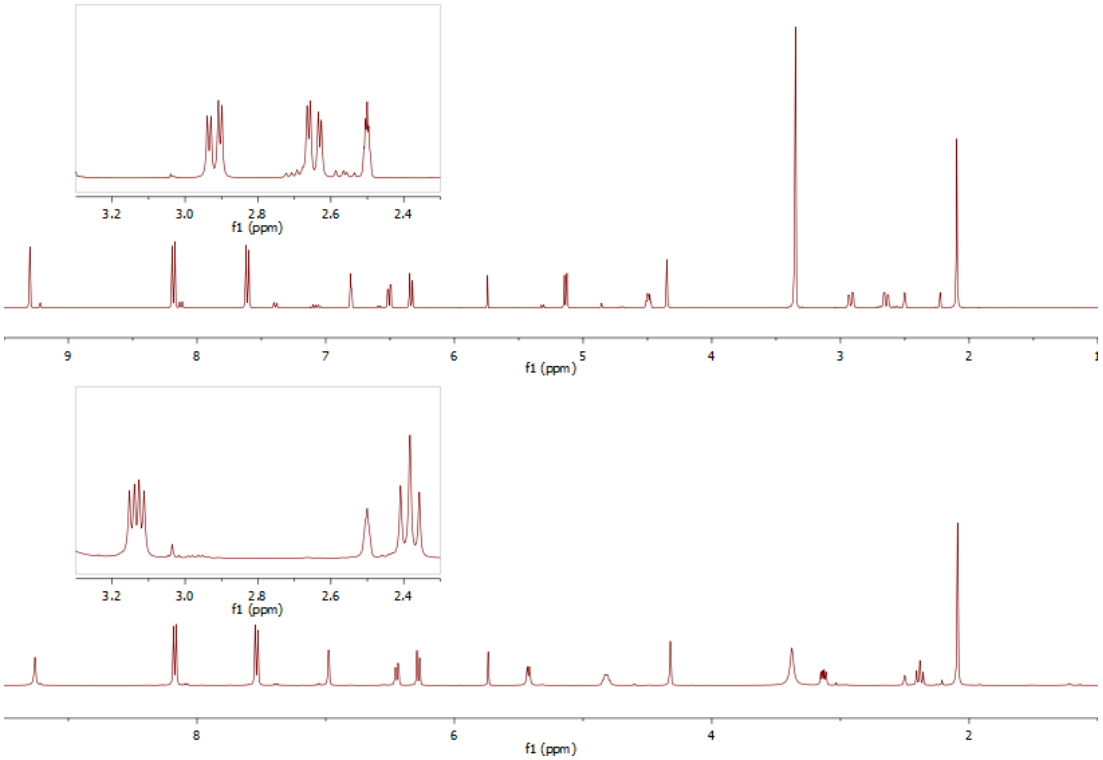


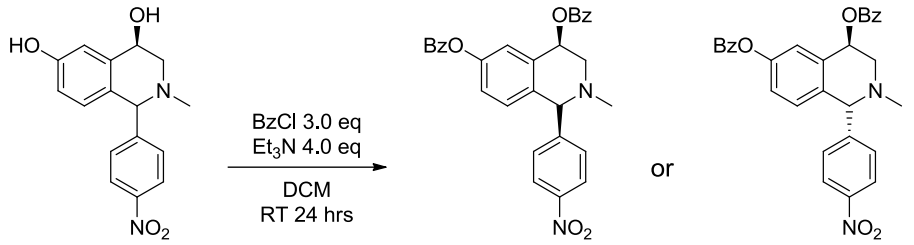
Figure 46 ^{1}H NMR spectra of **222**219 isomers A (top) and B (bottom).

6.2 Stereochemistry of cyclised products

To assign the correct structures to isomers A and B of the above derivatives, attempts were made to grow a single crystal of each of the isomers in order to determine the structure by x-ray crystallography. However, these attempts were not successful. To overcome this it was decided to synthesise the dibenzoates of two of the isomers to create some derivatives that would potentially be more easily crystallised.

6.2.1 Synthesis of the benzoates

The dibenzoates of derivative **222** isomer A and isomer B were synthesised through an esterification reaction with benzoyl chloride to give the desired dibenzoates in 45% and 76% yield respectively. Crystallisation of these derivatives was more successful, and high quality crystals were obtained for the dibenzoates of both isomers A and B.



222
A or B

226

227

Figure 47 Synthesis of dibenzoates.

6.2.2 Crystal structure

A crystal structure was obtained for the dibenzoate of isomer B. X-ray crystallography was carried out by Professor Chiara Massera from the University of Parma (details can be found in section 11.3 pg. 164). Unfortunately a crystal structure could not be obtained for the dibenzoate of isomer A. From the crystal structure (**Figure 48**) it can be seen that the benzylic oxygen and the nitrophenyl group are in a *trans* orientation. Therefore isomer B can be assigned to a *trans* conformation (**227**) and it can be assumed that isomer A will have a *cis* conformation

(**226**). Since the ^{1}H NMR spectra of isomers A and B are consistent for all of the derivatives it can be assumed that isomer A always corresponds to the *cis* derivative and isomer B always corresponds to the *trans* derivative.

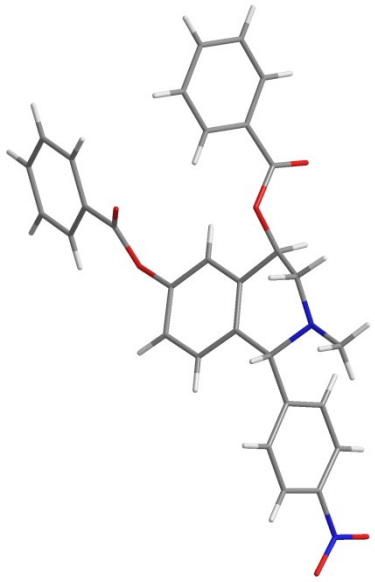


Figure 48 Crystal structure of the dibenzoate of isomer B.

With the stereochemistry of isomers A and B now assigned with reasonable confidence it is possible to relate the observed ^{1}H NMR spectra to the structures. Since for isomer A two doublets of doublets were observed which represent the coupling pattern between the two methylene protons in position 3 and the methine proton in position 4. For isomer B this was observed as a doublet of doublets and a triplet. It can be assumed that the ring structures for isomers A and B have different conformations, which cause the dihedral angles between these protons to be different accounting for the difference in coupling patterns.

6.2.3 Computational studies

As a crystal structure could not be obtained for isomer A, computational studies were used in order to confirm the structure of isomer A, as well as to better understand the conformational differences between isomers A and B. Computational studies were undertaken to calculate the energy minimised structures for each isomer.

Computational studies were carried out by Professor Andrew Rohl from Curtin University, details can be found in experimental section 11.4. The ^{1}H NMR spectra were also predicted from these energy minimised structures in order to compare them with the experimental NMR spectra and confirm the correct conformation. These calculations were also carried out by Professor Rohl, and details can be found in experimental section 11.4 pg. 165. The structures of both isomers were optimised, and the NMR chemical shifts and ^{1}H-^{1}H coupling constants were calculated. **Figure 49** below shows a representation of the crystal structure of **227** and the dihedral angles between the methine proton Hc and both of the methylene protons Ha and Hb of the isoquinoline scaffold. **Figure 50** shows the energy optimised structure of **222** isomer B and the same dihedral angles between the methine proton and both of the methylene protons of the isoquinoline scaffold. Both of these structures represent the trans isomer and from the images it is possible to see that both derivatives have the same conformation. The dihedral angles measured for the crystal structure and for the energy minimised structure are very similar. This is expected as both structures should have the same conformation. This similarity adds validity to the energy minimised structure for isomer B. The ^{1}H NMR spectrum of **222** isomer B showed the signals for the two methylene protons as a doublet of doublets (J = 10.4, 5.5 Hz) and a triplet (J = 10.4 Hz), see **Figure 46** pg.111. This observation can be explained in terms of the dihedral angles between these protons. The doublet of doublets can be explained by the coupling of methylene proton Hb to methylene proton Ha as well as to methine proton Hc. Since these two couplings would be expected to have significantly different coupling constants, ~9-13Hz for Ha-Hb (range for normal geminal coupling) and ~2-6 Hz for Hb-Hc (according to the Karplus relationship), observation of a well defined doublet of doublets would be expected. However, due to the dihedral angle between methylene proton Ha and methine proton Hc the coupling constant would be expected to be ~9-13 Hz (according to the Karplus relationship) which is the same for the coupling between Ha and Hb. This could cause overlap of the signals which explains why this proton is observed as a triplet. In the ^{1}H NMR of the benzoate of isomer B **227** (see **Figure 51**) the signal representing Ha is seen as a doublet of doublets, not a triplet. The J values are no longer the same but are similar enough to cause the doublet of doublets to almost merge into a triplet.

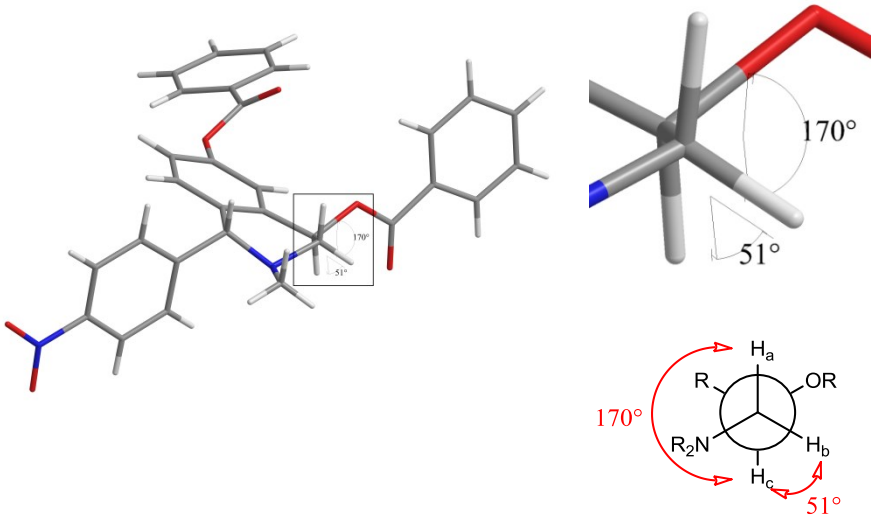


Figure 49 Dihedral angles for **227** (i.e. isomer B) obtained from the crystal structure.

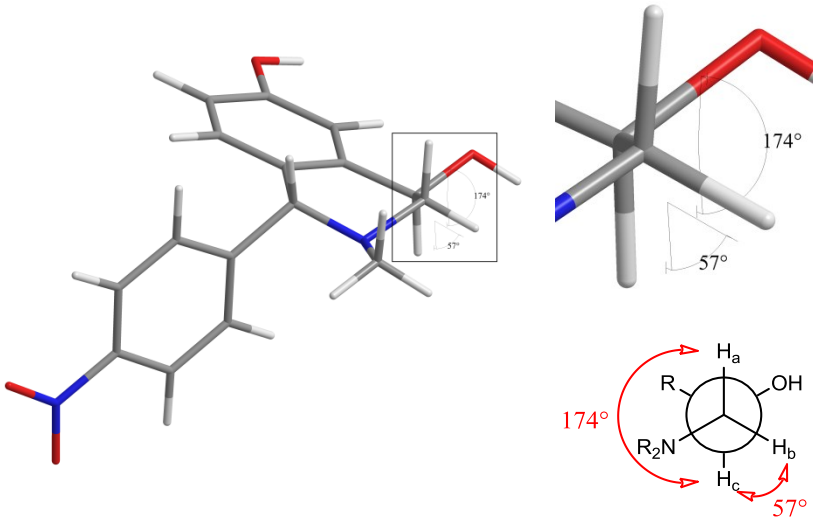


Figure 50 Dihedral angles for **222** isomer B, obtained from the energy minimised structure.

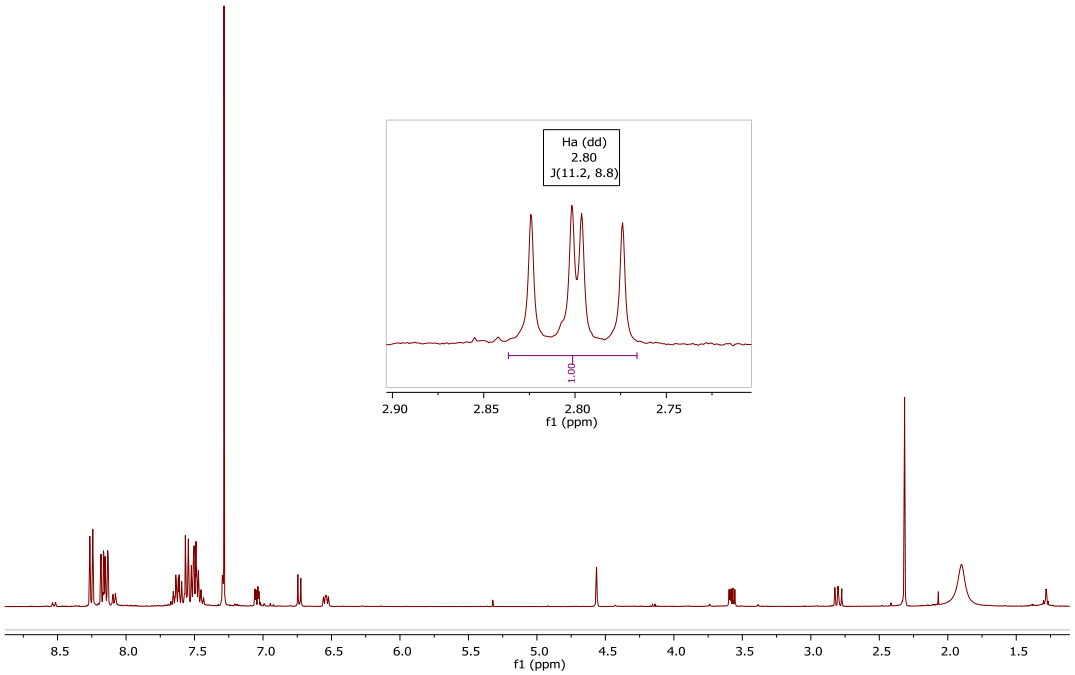


Figure 51 ^{1}H NMR spectrum of **227**.

Figure 52 below shows the energy minimised structure of **222** isomer A and the dihedral angles between the two methylene protons Ha and Hb and the methine proton Hc. This is the *cis* isomer and from the image it can be seen that it has a similar conformation to isomer B above, and consequently the dihedral angles are also similar to that of isomer B reported above. The ^{1}H NMR spectrum for **222** isomer A showed the signals for the methylene protons as two doublets of doublets (J = 12.1, 3.9 Hz and J = 12.1, 3.5 Hz) both with very similar coupling constants. This observation does not fit with the structure below. If isomer A had this conformation, the ^{1}H NMR spectrum should look similar to isomer B however it does not (see **Figure 46**, pg. 111).

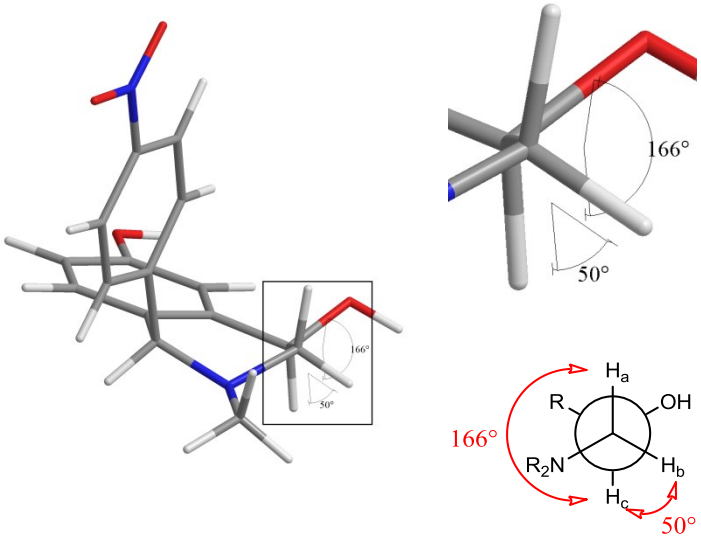
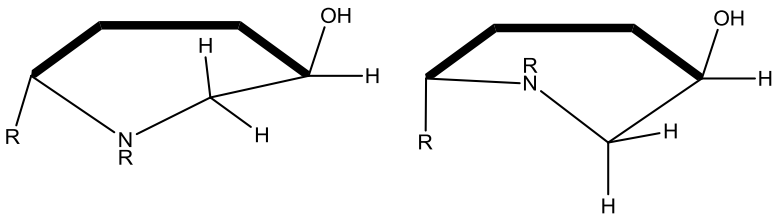


Figure 52 Dihedral angles for **222** isomer A obtained from energy minimised conformation 1.

Looking at the observed ^{1}H NMR spectrum for isomer A the dihedral angles between Ha and Hc are expected to be similar to that between Hc and Hb. This would give rise to two almost identical doublets of doublets in the spectrum. Looking at the structure of isomer A this would occur if the saturated isoquinoline ring was twisted in such a way that nitrogen atom was pointing in an upwards direction, (see **Figure 53 conformation 2**) relative to the plane of the molecule rather than down, (see **Figure 53 conformation 1**) as is represented above. With this in mind another energy minimised structure was calculated this time starting with the ring in this other conformation.



Conformation 1 **Conformation 2**

Figure 53 Two conformations of the saturated ring of isomer A, where the bold bond indicate the planar part of the ring.

Figure 54 below shows the energy minimised structure of **222** isomer A in the second conformation (i.e. with the nitrogen atom pointing up relative to the plane of the molecule). In this conformation the calculated dihedral angles between the two

protons Ha and Hc, and Hb and Hc are very similar. This fits with what would be expected from the signals in the ^{1}H NMR spectrum. In this conformation the second dihedral angle Ha-Hc is much smaller than in the first conformation, a much smaller coupling constant ~2-6 Hz would therefore be expected, which is in agreement with the spectrum. The two signals would also be expected to be almost identical which is what is observed. From this information it seems reasonable to assign the conformation of isomer A to the structure represented in **Figure 54**.

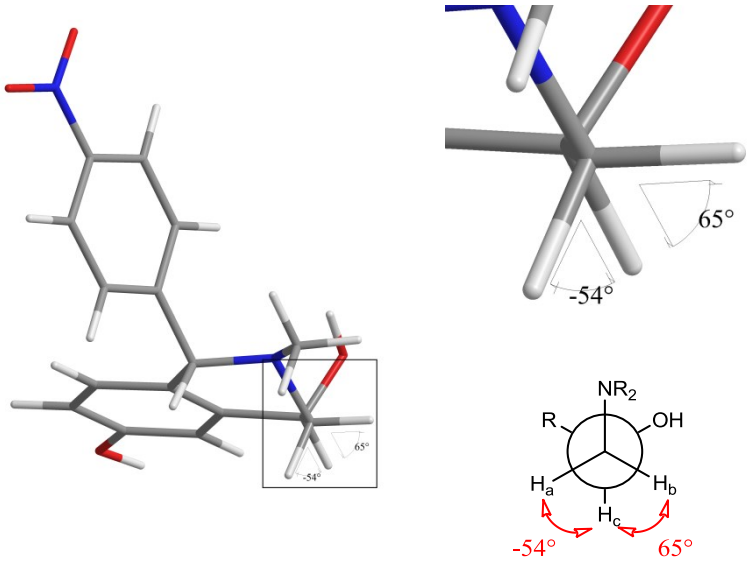
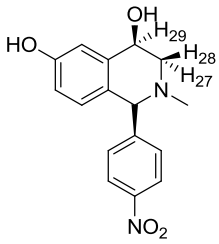


Figure 54 Dihedral angles for **222** isomer A, obtained from energy minimised conformation 2.

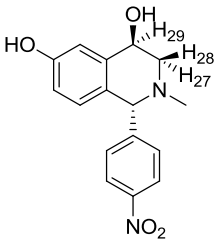
The energies of the two conformations were also calculated, and the second conformation was determined to have a lower energy than the first adding more evidence that this is the correct conformation. As another confirmation that isomers A and B had been assigned to the correct conformations the ^{1}H NMR spectra were calculated and a comparison made to the experimental spectra. **Table 27** shows a summary of the experimental and calculated ^{1}H NMR data for the methylene and methine protons discussed above for both isomers A and B. The experimental spectra were obtained using DMSO-*d6* as a solvent, while the computational spectra were determined for $CDCl_3$ solutions. Looking first at the chemical shift values for isomer B it can be seen that they fit reasonbly well with the experimental data, giving an indication that this is a reasonable model. In terms of coupling constants the experimental and calculated values are very similar, the coupling between H27 and

H28 is very different from H27-29 giving rise to the doublet of doublets seen in the experimental spectrum. Whereas the coupling between H28 and H29 is calculated to be very close to that of H27-28 which explains why a triplet is seen in the ^{1}H NMR specrtum. Looking at the chemical shifts for isomer A, both of the sets of calculated data (for conformation 1 and 2 see above) seem to fit reasonably well with the experimental data. However, looking at the coupling constants it can be seen that those calculated for the first conformation do not fit so well with the experimental data, the coupling constants are much larger than those determined experimentally. The coupling constants calculated for the second conformation fit a lot better with the experimental data, they are a little lower than those dertermined experimentally, however H27-H29 and H28-29 are much more similar which would give rise to two more similar looking signals in the spectrum which is indeed observed. Therefore conformation 2 again seems to be the best fit, and can be confidently assigned as the correct conformation of isomer A.

Table 27 Experimental and calculated ^{1}H NMR data for selected protons.



222A



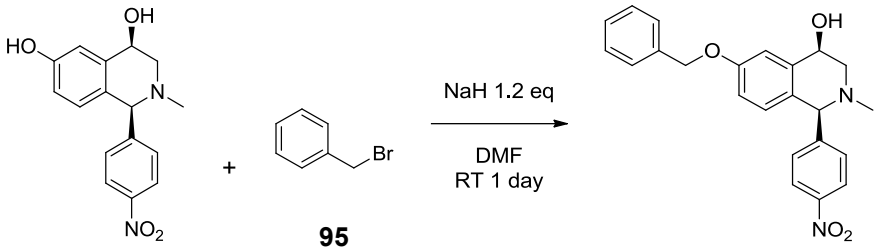
222B

Chemical shifts (ppm)						
	Exp	**Calc 1**	**Calc 2**		**Exp**	**Calc**
H27	2.65	2.41	2.78	**H27**	3.13	2.80
H28	2.92	2.71	2.88	**H28**	2.38	2.61
H29	4.51	4.76	4.16	**H29**	4.83	4.89
Coupling constants (Hz)						
	Exp	**Calc 1**	**Calc 2**		**Exp**	**Calc**
H27-28	12.1	-11.3	-11.2	**H27-28**	10.4	10.2
H27-29	3.5	6.3	1.8	**H27-29**	5.5	5.0
H28-29	3.9	9.5	2.6	**H28-29**	10.4	9.8

Where exp is experimental data and calc is calculated data. Calc 1 represents data from conformation 1 of isomer A (see **Figure 52**) and calc 2 represents data from conformation 2 of isomer A (see **Figure 54**). All experimental NMR data was obtained using DMSO-*d6* as the solvent. All calculated data was obtained using $CDCl_3$ as the solvent.

6.3 Substitution of the phenol

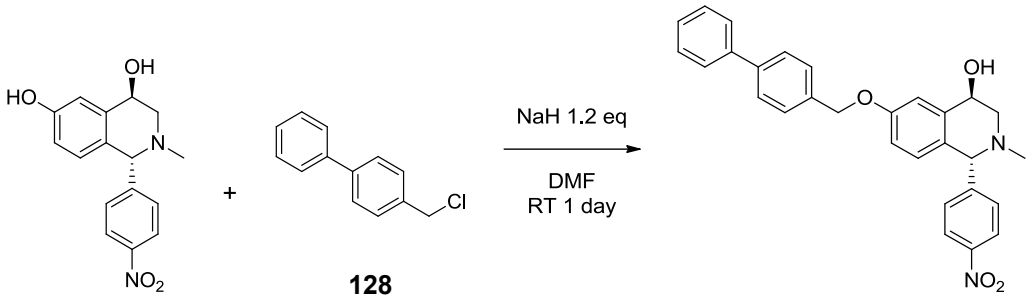
The phenol of two of the above derivatives was substituted to give the ether products in order to provide some information on how having substituents at both the phenolic position and on carbon 1 would affect anti-HAT activity. The two derivatives used were the nitrophenyl and the undecyl derivatives. The substitution reaction was carried out as described previously using either a benzyl or biphenylmethyl group as the alkylating agent. In the case of the nitrophenyl derivatives isomer A was used to give the benzyl ether in 69% yield (**Scheme 48**), while isomer B was used to give the biphenylmethyl derivative in 44% yield (**Scheme 49**). The reason that the benzyl and biphenylmethyl derivatives of only either isomer A or B, and not of both isomers, were synthesised was simply due to the fact that only low quantities of the starting material were readily available. Therefore to save time only one derivative of each isomer was made, with the rationale that when the biological results were obtained if they were interesting then the other derivatives could be synthesised. Formation of the ether was confirmed through ^{1}H NMR spectroscopy by the slight downfield shift of the signals for the aromatic protons on the isoquinoline scaffold and the new signal due to the alkyl group introduced.



222
Isomer A

228
69%

Scheme 48 Benzyl substitution of **222** isomer A.



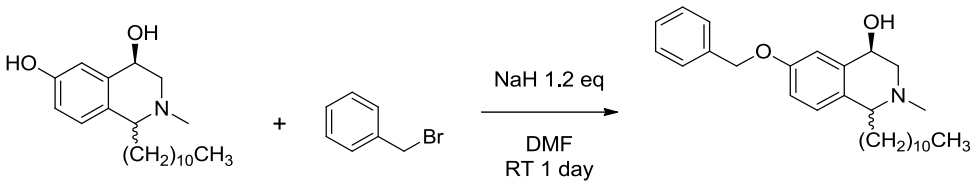
222
Isomer B

128

229
44%

Scheme 49 Biphenylmethyl substitution of **222** isomer B.

In the case of the undecyl derivative, as isomers A and B could not be separated, a mixture of the two isomers was used in the substitution reaction to give the two desired ethers in moderate yields (see **Scheme 50** and **Scheme 51**). Formation of the ether was confirmed through ^{1}H NMR spectroscopy by the slight downfield shift of the signals for the aromatic protons of the isoquinoline scaffold.

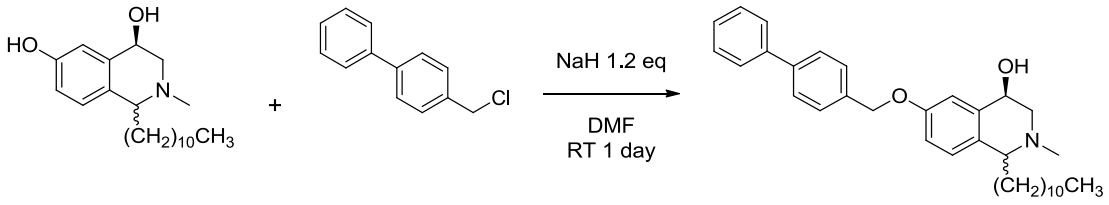


225

95

230
22%

Scheme 50 Benzyl substitution of **225**.



225

128

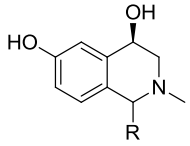
231
54%

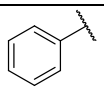
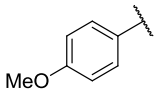
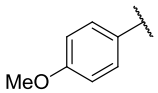
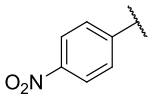
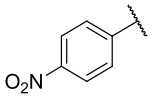
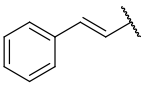
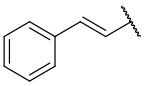
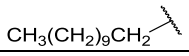
Scheme 51 Biphenylmethyl substitution of **225**.

6.4 Antitrypanosomal activity

The above cyclised derivatives and the phenolic substituted derivatives were evaluated for their activity against *T. b. rhodesiense* and mammalian cells *in vitro* (see **Table 28** and **Table 29**). The cyclised derivatives **220** to **222**, and **224**, showed no activity towards *T. b. rhodesiense*. Interestingly however, the derivatives cyclised with cinnamaldehyde (**223**) showed some activity with no significant difference in activity between isomers A and B, and also no observed cytotoxicity. The undecyl derivative **225** showed quite good activity against *T. b. rhodesiense* with lower than expected cytotoxicity, giving a selectivity index of ~60. It would be expected that a derivative such as this with a long alkyl chain would show significant cytotoxicity due to its potential to disrupt cell walls, however derivative **225** only showed moderate cytotoxicity and had a good selectivity index.

Table 28 *In vitro* activity of cyclised derivatives.



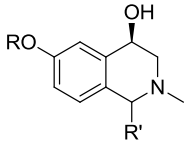
No.	R	IC_{50} *T. b. rhodesiense*[a] *(μM)*	Cytotoxicity[b] IC_{50} (μM)	Selectivity Index[c] (SI)
220A		>100	>100	
220B		>100	>100	
221A		>100	>100	
221B		>100	>100	
222A		>50	>50	
222B		>50	>50	
223A		17.5 ± 1.3	>50	2.9
223B		16.9 ± 0.9	>50	3.0
224A		>100	>100	
225		0.39 ± 0.04	24.3 ± 2.9	62.3

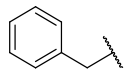
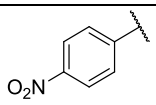
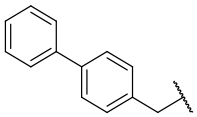
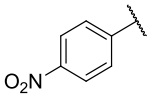
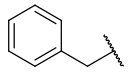
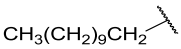
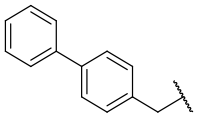
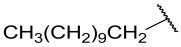
[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

The phenolic substituted derivatives **228-231** (**Table 29**) all showed some anti-HAT activity however they also showed a significant increase in cytotoxicity as compared

to their unsubstituted counterparts (**222** and **225**). For the nitrophenyl derivatives **228** and **229,** both showed almost identical activity, although from previous results it would have been expected that the biphenylmethyl derivative would be more active than the benzyl. For the phenolic substituted undecyl derivatives (**230** and **231)** the benzyl substituted derivative (**230**) showed almost identical activity to the unsubstituted derivate (**225**) with a significant increase in cytotoxicity. Interestingly the biphenylmethyl derivative, which would be expected to be more active from previous trends, showed less activity against *T. b. rhodesiense* than the unsubstituted version (**225**).

Table 29 *In vitro* activity of phenolic substituted derivatives of **222** and **225**.



No.	R	R'	IC_{50} *T. b. rhodesiense*[a] *(µM)*	Cytotoxicity[b] IC_{50} (µM)	Selectivity Index[c] (SI)
228			19.2 ± 0.6	26.8 ± 4.1	1.4
229			19.4 ± 1.0	37.6 ± 4.1	1.9
230			0.32 ± 0.01	3.2 ± 0.2	10.0
231			2.5 ± 0.2	3.6 ±0.7	1.4

[a]IC_{50} on *T. b. rhodesiense* (STIB-900) cells. [b]Cytotoxicity on VERO cells. [c]The selectivity index (SI) is defined as the ratio of IC_{50}-Vero/IC_{50}-*T. b. rhodesiense*. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls Ellipticine was used as a positive control for cytotoxcicity (see appendix A).

7 Stereochemistry of the benzylic alcohol

The core isoquinoline scaffold contains a chiral benzylic alcohol which is in the *R* configuration, it is synthesised from enantiopure (*R*)-phenylephrine. However, it cannot be assumed that the benzylic alcohol has retained the same stereochemistry throughout all the transformations of the core scaffold discussed in previous chapters. In order to confirm if the derivatives have retained the same stereochemistry, or determine if racemisation has occurred, a combination of chiral HPLC and optical rotation were used. Chiral HPLC chromatograms and specific rotations were obtained for a selection of derivatives. The derivatives selected include examples from each of the main transformations performed on the core scaffold, substitution of the phenol (**129 and 101**), Suzuki coupling (**133**), and substitution of the benzylic alcohol (**167**), as well as the two benzoates **180** and **181**. It can be assumed that the benzylic alcohol will behave the same every time under any given set of reaction conditions, and hence it seemed reasonable to analyse only one derivative from each group. Firstly a suitable chiral HPLC method needed to be developed that was able to achieve separation of two enantiomers of this kind (i.e. the *R* and *S* configurations of the benzylic alcohol in the core scaffold). Since derivatives **180** and **181** have the opposite stereochemistry they provided a perfect means of doing this. Equal amounts of derivatives **180** and **181** were mixed together and showed baseline separation (see **Figure 55**) when analysed via chiral HPLC using an amylose column and an isocratic method (see experimental section for details). This type of column was used simply because it was on hand, and fortuitously gave acceptable results. The ability to obtain baseline separation of these two enantiomers gave evidence that using this column and method would be suitable for the analysis of other similar derivatives.

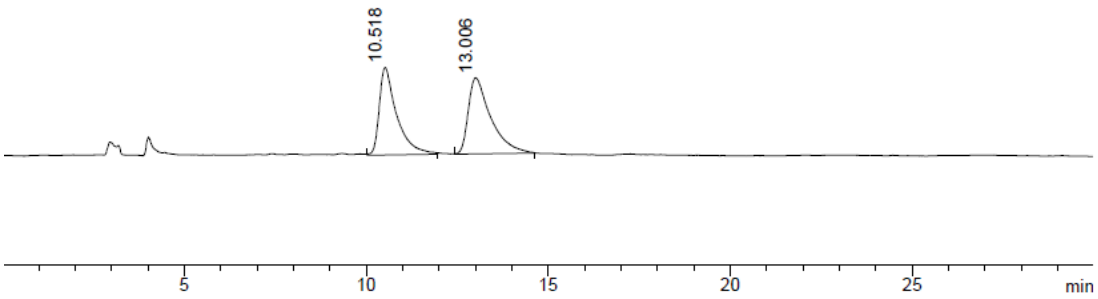


Figure 55 Chiral HPLC chromatogram of an equal mixture of derivatives **180** and **181**.

Derivatives **180** and **181** were also analysed by chiral HPLC separately, the chromatograms obtained can be seen in **Figure 56**. From the chromatograms it can be seen that in both cases there is one large and one small peak, hence each of the derivatives contains a very small amount of the other enantiomer. The enantiomeric excess was calculated to be 95%, and 98% for derivatives **180** and **181** respectively.

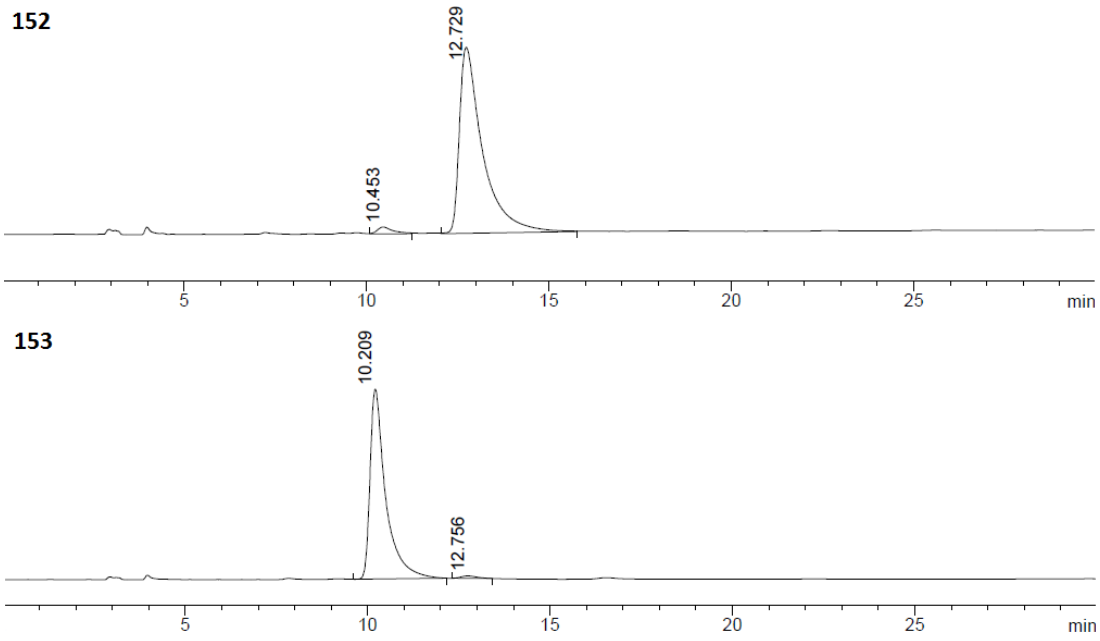
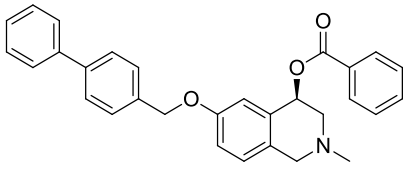
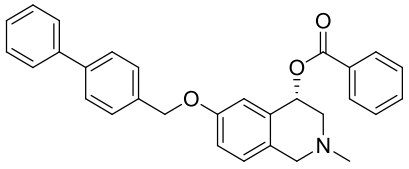


Figure 56 Chiral HPLC chromatograms of derivatives **180** and **181**.

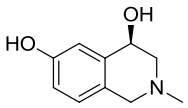
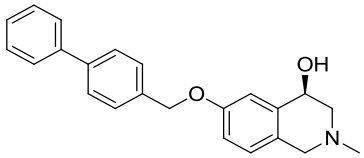
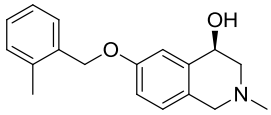
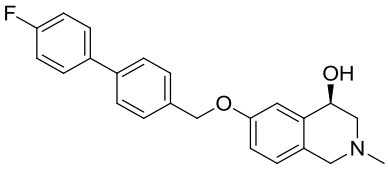
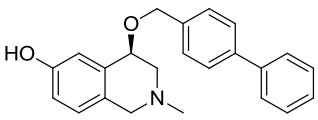
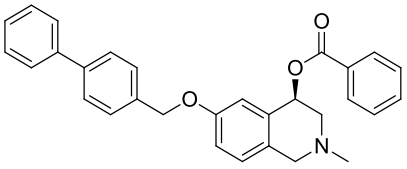
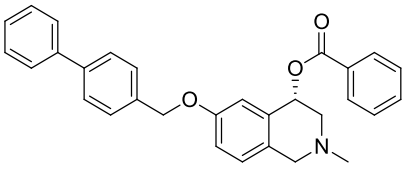
The specific rotation of both derivatives were also measured (see **Table 30**), and found to be approximately opposite, as is expected.

Table 30 Optical rotation of derivatives **180** and **181**.

Structure	Specific rotation
 **180**	$[\alpha]_D$ +29.8° (c 1.00, CH_2Cl_2)
 **181**	$[\alpha]_D$ -37.4° (c 1.01, CH_2Cl_2)

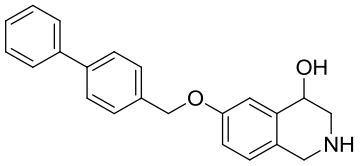
The other derivatives mentioned above were therefore analysed by chiral HPLC. A summary of the results can be seen in **Table 31**. In all but one case only one peak was observed, suggesting that each of the derivatives contained only one enantiomer. The exception to this was derivative **101** which showed two overlapping peaks in the HPLC chromatogram. The optical rotation of this derivative was also approximately zero (-0.9°), and had become negative when it is expected that it would be positive agreeing with all of the other derivatives. This derivative was resynthesised and the optical rotation of the freshly prepared sample found to be +2.9°. This result suggested that the benzylic alcohol may be susceptible to racemisation over long periods of time. Unfortunately the freshly prepared sample could not be analysed by chiral HPLC due to limited access to the instrument. The optical rotations of the other derivatives (see **Table 31**) were non-zero values, providing further evidence that racemisation had not occurred.

Table 31 Specific rotation and chiral HPLC for selected derivatives.

Structure	Specific rotation	Chiral HPLC summary
 **86**	$[\alpha]_D$ +41.0° (*c* 1.00, CH_3OH)	One peak (6.68 min)
 **129**	$[\alpha]_D$ +11.5° (*c* 1.00, CH_2Cl_2)	One peak (12.56 min)
 **101**	*$[\alpha]_D$ -0.93° (*c* 1.07, CH_2Cl_2)	Two overlapping peaks (~7.19 min)
 **133**	$[\alpha]_D$ +7.9° (*c* 0.98, CH_2Cl_2)	One peak (13.85 min)
 **167**	$[\alpha]_D$ +11.2° (*c* 1.05, CH_2Cl_2)	One peak (11.36 min)
 **180**	$[\alpha]_D$ +29.8° (*c* 1.00, CH_2Cl_2)	One peak (12.73 min)
 **181**	$[\alpha]_D$ -37.4° (*c* 1.01, CH_2Cl_2)	One peak (10.21 min)

*This derivative was resynthesised and the optical rotation remeasured at +2.9°(c 1.03, CH_2Cl_2).

The other derivatives analysed by chiral HPLC are significantly more polar than enantiomers **180** and **181** for which baseline separation was obtained. There was some concern if these derivatives were stereochemically pure, due to the difference in polarity they may not be separable via this method and only one peak would be observed. In order to test if this concern was valid a more polar derivative that was known to be racemic was analysed by chiral HPLC. Derivative **211** (see **Figure 57**) is racemic since it was synthesised initially from racemic nor-phenylephrine, it also contains a secondary amine making it much more polar. **Figure 57** shows the chiral HPLC chromatogram of derivative **211**. From the chromatogram it can be seen that there is a broad peak at about 15.5 min. Close inspection of this peak suggests two overlapping peaks, showing that separation of the two enantiomers in this case is not perfect but it is still possible to see that there are two enantiomers present. Since the other derivatives analysed by chiral HPLC are less polar than derivative **211** and some evidence of separation was obtained for enantiomers of this derivative, this gives more confidence that if the derivatives were in fact racemic some evidence would be seen in the chiral HPLC chromatogram. The specific rotation for this derivative was measured at +1.5°. This is a very low value and confirms the racemic nature of the compound.



211
$[\alpha]_D$ 1.5 (*c* 1.01, CH_3OH)

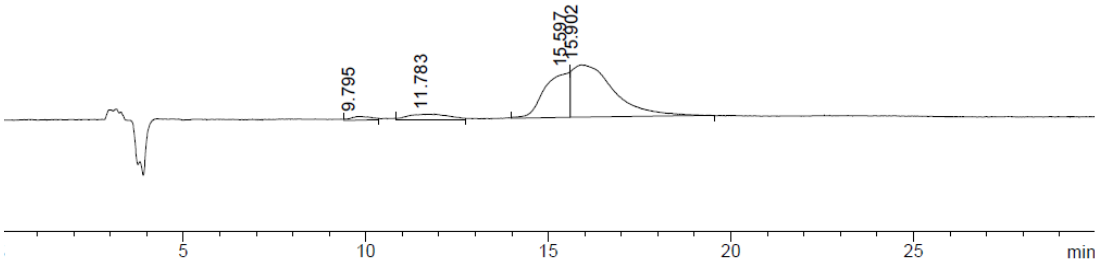
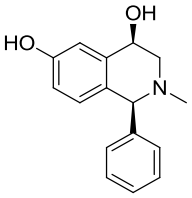
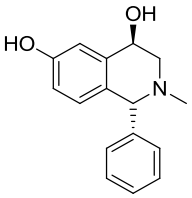


Figure 57 Chiral HPLC chromatogram of derivative **211**.

The optical rotations of cyclised derivative **220** isomer A and B were also obtained as well as chiral HPLC data. Due to the fact that this derivative has two chiral centres

the specific rotations would not be expected to be opposite, but they would be expected to be significantly different. This is in agreement with the measured rotations (see **Table 32**). A summary of the chiral HPLC chromatograms for each of these isomers can also be seen in **Table 32**. Both isomers showed only one peak on the HPLC chromatogram, and they both elute at significantly different times. This provides another confirmation that these two isomers are stereochemically pure in addition to those discussed in section 1.1, and that the cyclisation reaction does not cause racemisation of the benzylic alcohol.

Table 32 Specific rotation and chiral HPLC for derivative **220** isomers A and B.

Structure	Specific rotation	Chiral HPLC summary
 **220A**	$[\alpha]_D$ +174.6° (*c* 0.59, CH_3OH)	One peak (5.99 min)
 **220B**	$[\alpha]_D$ -59.7° (*c* 0.72, CH_3OH)	One peak (4.92 min)

Taking the chiral HPLC and optical rotation results into account it can be concluded that the benzylic alcohol retains its stereochemistry when subjected to the reaction conditions described, however it is susceptible to racemisation if left for long periods of time.

8 Summary of antitrypanosomal activity, and discussion of logD

8.1 Summary of antitrypanosomal activity and SAR development

Throughout this work 90 new compounds were synthesised based on the core scaffold below (see **Figure 58**) and evaluated *in vitro* for their activity against *T. b. rhodesiense* and mammalian cells. From this, a structure activity relationship was developed. **Figure 58** shows a summary of the structure activity relationship, which is described in more detail below.

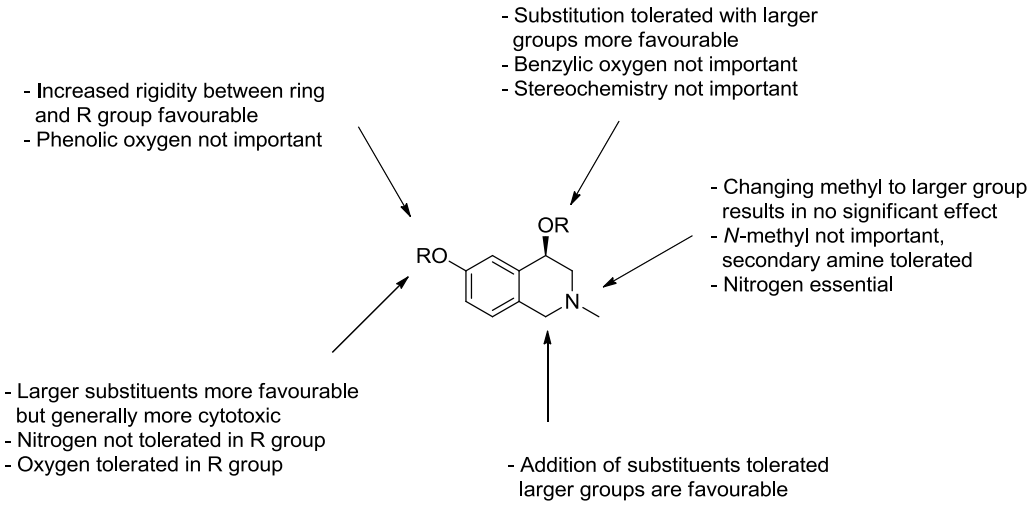
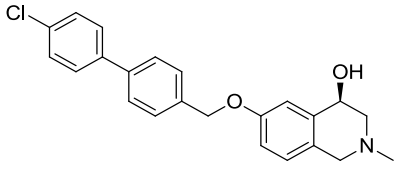


Figure 58 SAR summary.

Alkylation of the phenol generally resulted in increased activity against *T. b. rhodesiense*, with larger groups tending to be more active. However, this was generally accompanied by an increase in cytotoxicity. Having a nitrogen atom in the alkylating group resulted in a significant decrease in activity while oxygen seemed to have no effect. This suggests the possibility of a positively charged residue in the active site which would have unfavourable interactions with a nitrogen atom that would be charged at physiological pH. Derivatives substituted at the phenol with a biphenylmethyl group were generally the most active, however they were also

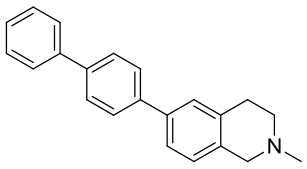
significantly cytotoxic. An exception to this is derivative **132,** with a *p*-chloro biphenylmethyl group on the phenol, which showed increased activity against *T. b. rhodesiense* with similar cytotoxicity resulting in a selectivity index of ~85.



132
IC_{50} = 0.28 ± 0.01 μM
Cytotoxicity = 24.1 ± 4.3 μM
SI = 86.1

Figure 59 Derivative **132** and its biological activity.

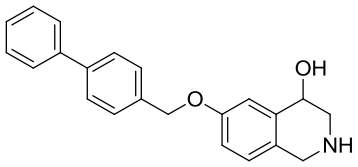
Alkylation at the benzylic alcohol resulted in moderate activity for larger groups such as cyclohexylethyl and biphenylmethyl with no observed cytotoxicity. Substitution of both the benzylic alcohol and the phenol did not result in any significant increase in activity as compared to derivatives only substituted at the phenol. Removing the benzylic alcohol completely did not have any significant effect on activity, while inverting the stereochemistry resulted in no change in activity. This suggests that the benzylic alcohol is not important to anti-HAT activity. Increasing the rigidity of the groups attached to the aromatic portion of the scaffold resulted in significantly increased activity. Where substitution directly onto the aromatic ring at position 6 resulted in derivatives with tenfold increased activity as compared to the same derivative substituted at the phenol, with derivative **191** showing activity against *T. b. rhodesiense* in the submicromolar range (0.3 ± 0.1 μM), and having a selectivity index of 57.8.



191
IC_{50} = 0.27 ± 0.01 μM
Cytotoxicity = 15.6 ± 0.3
SI = 57.8

Figure 60 Derivative **191** and its biological activity.

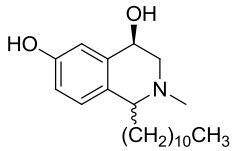
Alkylation of the nitrogen atom resulted in no significant increase in activity as compared to *N*-methyl derivatives. Removing the *N*-methyl group to give a secondary amine showed comparable results to the corresponding *N*-methyl derivatives. An exception to this was derivative **211** which showed a tenfold increase in activity as compared to its *N*-methyl counterpart. This was accompanied by no change in the cytotoxicity resulting in good selectivity for *T. b. rhodesiense* over mammalian cells (SI=83.2). Removal of the nitrogen atom from the scaffold resulted in a loss of activity, confirming its importance.



211
IC_{50} = 0.25 ± 0.02 μM
Cytotoxicity = 20.8 ± 0.8 μM
SI = 83.2

Figure 61 Derivative **211** and its biological activity.

Adding substituents at position 1 in most cases did not have any effect. However, adding a cinnamyl group gave derivatives with moderate activity while adding an undecyl group (derivative **225**) increased the activity dramatically with activity against *T. b. rhodesiense* in the sub micromolar range and lower than expected cytotoxicity giving a selectivity index of ~60. Substitution at the phenol and position 1 gave conflicting results. Derivatives with a *p*-nitrophenyl group at position 1, when substituted at the phenol, resulted in an increase in activity. Substitution at the phenol of the derivative with an undecyl group at position 1 did not result in any increased activity against *T. b. rhodesiense* for the benzyl derivative but resulted in a decrease in activity for the biphenyl derivative.



225
IC_{50} = 0.39 ± 0.04 μM
Cytotoxicity = 24.3 ± 2.9 μM
SI = 62.3

Figure 62 Derivative **225** and its biological activity.

8.2 Calculation and discussion of logD

The logD values (where D is the distribution coefficient) of all of the derivatives were calculated[181] at physiological pH and used as another way of analysing the biological data. The logD value describes the lipophilicity of a molecule and is the extent of the affinity for organic over aqueous phases and takes into account all species present at a given pH.[182] The distribution coefficient was used as opposed to the partition coefficient (i.e. logP) as the majority of the derivatives in this work contain ionisable groups and so logD is a better estimate of the lipophilicity than logP which only takes into account the neutral form. For derivatives which do not contain ionisable groups, the logD value is equal to the logP value. The graph below (**Figure 63**) shows the calculated logD values plotted against the IC_{50} values for *T. b. rhodesiense* of all derivatives with IC_{50} values of less than 5 μM, logD values of all derivatives are given in Appendix A. The graph shows that most of the derivatives are clustered together with IC_{50} values between 2 and 3 μM and logD values between 2 and 6. However, there is also another smaller group of derivatives which are circled. These are the more interesting derivatives as they all show IC_{50} values below 0.5 μM and logD values less than 5. From Lipinski's rule of 5 compounds are most likely to have good absorption if the logP/logD value is less than 5.[183,184] See **Figure 64** below for structures of the 5 derivatives circled.

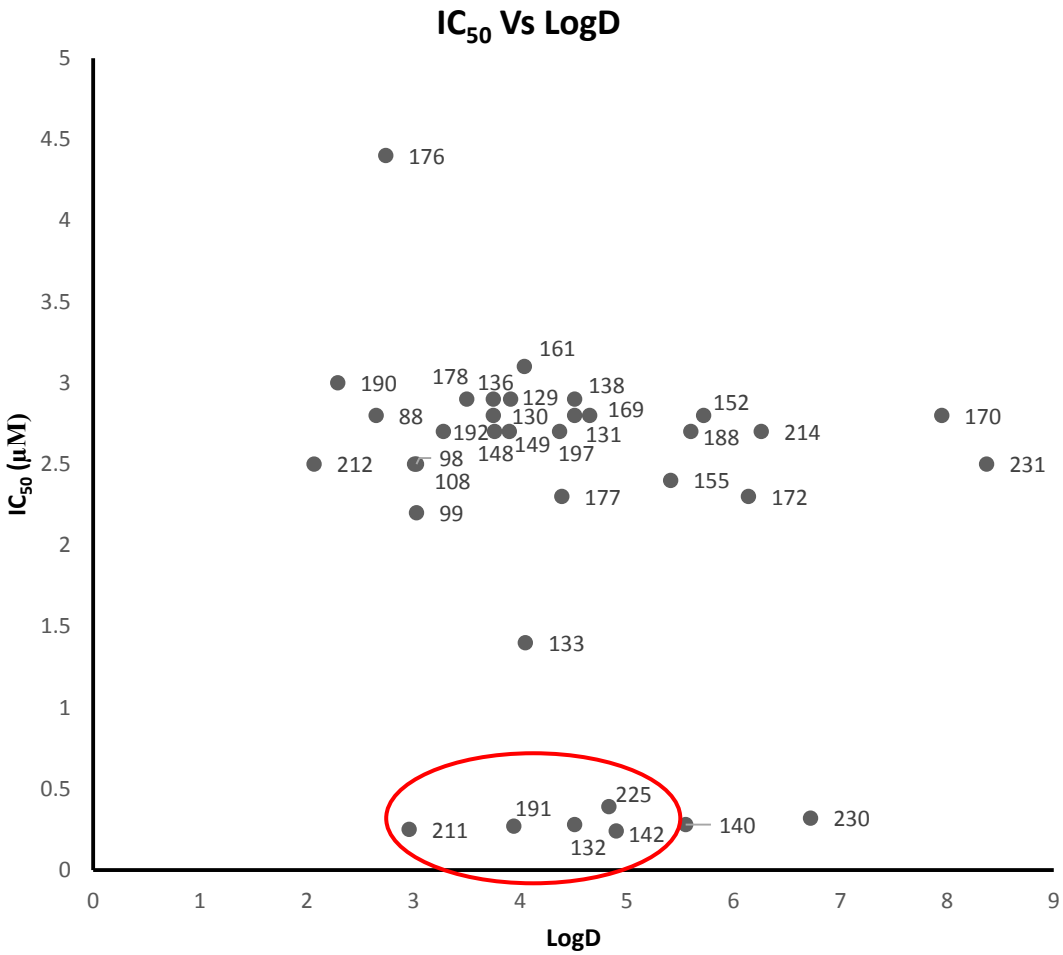
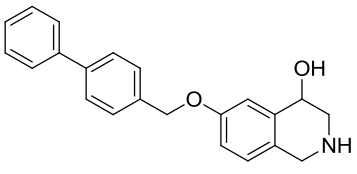
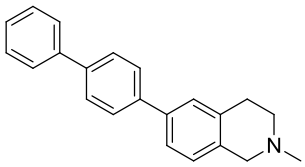


Figure 63 Plot of calculated logD values vs IC_{50} of *T. b. rhodesiense*.

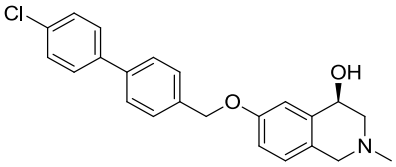
These five derivatives (**Figure 64**) all show good activity against *T. b. rhodesiense* and from the calculated logD values it can be expected that they will have good absorption. All of the compounds below also show good selectivity and provide good leads for further optimisation of this scaffold.



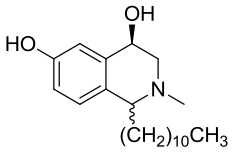
211
IC_{50} = 0.25 ± 0.02 μM
Cytotoxicity = 20.8 ± 0.8 μM
SI = 83.2
logD = 2.96



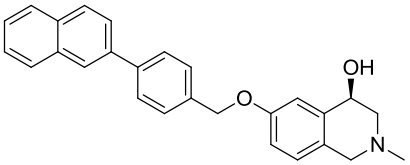
191
IC_{50} = 0.27 ± 0.01 μM
Cytotoxicity = 15.6 ± 0.3 μM
SI = 57.8
logD = 3.94



132
IC_{50} = 0.28 ± 0.01 μM
Cytotoxicity = 24.1 ± 4.3 μM
SI = 86.1
logD = 4.51



225
IC_{50} = 0.39 ± 0.04 μM
Cytotoxicity = 24.3 ± 2.9 μM
SI = 62.3
logD = 4.83



142
IC_{50} = 0.24 ± 0.01 μM
Cytotoxicity = 0.31 ± 0.01 μM
SI = 1.3
logD = 4.90

Figure 64 Five derivatives circled in **Figure 63**.

8.3 ADME properties

The five compounds above were submitted to SwissADME,[185] in order to evaluate their ADME properties. None of the compounds were found to show any motifs that are of concern in terms of metabolic stability. SwissADME analyses molecules based on both the PAINS[186] and Brenk[187] models. Additionally all of the compounds were predicted to be able to passively permeate through the blood-brain barrier, this was predicted using the BOILED-Egg model[188] inside of SwissADME. These results are only predictions and as such not conclusive. However, the results suggest that these molecules will be metabolically stable and are also capable of crossing the blood-brain barrier, making them good candidates for further optimisation and testing.

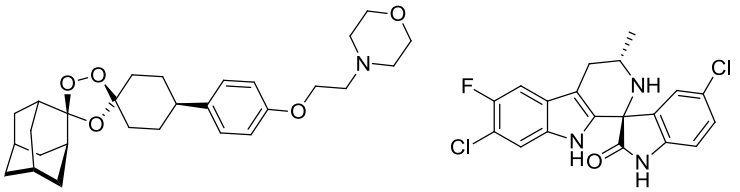
9 Potential antimalarials

Compounds showing activity against *T. brucei* are often found to show activity against the causative agent of Malaria, and vice versa.[46,63,74,98,115,189] For this reason, as well as ready access to antimalarial testing, all of the compounds synthesised in this study were also analysed for their antimalarial activity.

9.1 Malaria

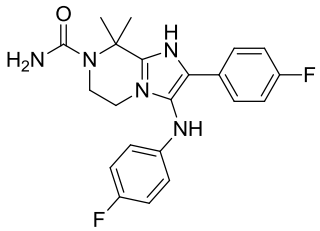
Malaria is a parasitic disease which is caused by infection of red blood cells by parasites belonging to the genus *Plasmodium*, which is spread from person to person via the bite of female mosquitoes. In 2015, it was estimated that the number of cases of malaria was 214 million resulting in 438,000 deaths. There are five species of *plasmodium* which cause malaria. Of these, *Plasmodium falciparum,* occurring mainly in Africa, is the most prevalent and is responsible for the most deaths.[190] Initial symptoms of malaria are nonspecific and include headache, muscle and joint ache fatigue, followed by fever and vomiting.[191] When prompt treatment is administered full recovery is expected, however if treatment is delayed progression to severe malaria will occur which usually takes days but can occur within hours. Severe malaria is fatal in the majority of cases.[192] Artemisinin combination therapies (ACTs) are used to treat Malaria. ACTs are a combination of a derivative of the natural product artemisinin and a quinoline or aminoalcohol partner drug. The artemisinin derivative clears parasites from the blood while the main role of the partner drug is to provide protection against development of resistance to the artemisinin derivatives. There are currently five ACTs recommended for the treatment of Malaria.[192,193] Resistance in recent years to many of the current antimalarial drugs means new drugs are urgently needed.[194] This has led to a huge amount of research being undertaken into new antimalarial lead compounds.[193,195–197] There are currently a number of new molecules undergoing different stage clinical trials for malaria treatment.[198] Four of the most promising new molecules currently undergoing clinical trials are a novel trioxolane OZ439 **232**,[199] spiroindolone

KAE609 **233**,[200–202] imidazolopiperazine KAF156 **234**,[203] and triazolopyrimidine DSM265 **235**[204] (see **Figure 65**).

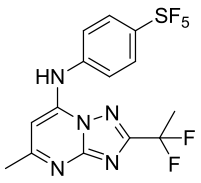


232
OZ439

233
KAE609



234
KAF156



235
DSM265

Figure 65 New molecules undergoing different stage clinical trials for malaria treatment.

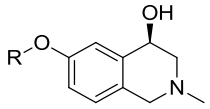
9.2 Antimalarial activity of derivatives substituted at the phenol

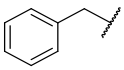
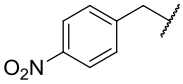
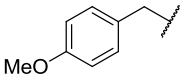
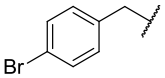
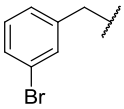
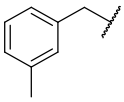
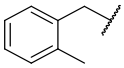
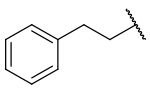
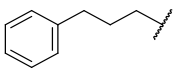
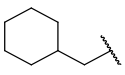
All of the derivatives synthesised were also evaluated for their *in vitro* activity against two strains of *P. falciparum*; TM4/8.2 (a wild-type drug sensitive strain), and K1CB1 (a multidrug resistant strain).

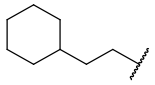
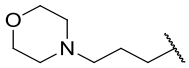
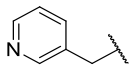
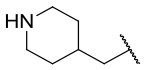
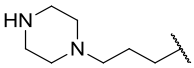
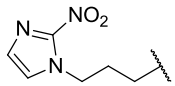
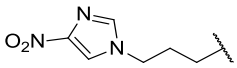
9.2.1 Benzyl substituents, cyclohexyl substituents, and *N*-heterocycles

Derivatives of isoquinoline **86** showed some activity against both strains of *P. falciparum* when substituted at the phenol. The benzyl substituted derivative **87** showed activity in the micromolar range against both strains, with slightly better activity against wildtype *P. falciparum*. Adding an electron withdrawing nitro group to the benzyl ring (**96)** increases the activity against both strains of *P. falciparum* with IC_{50} values for both in the low micromolar range. Substitution of the phenol with a methoxy (**97**), bromo (**98** and **99**), or methyl (**100** and **101**) substituted benzyl group resulted in comparable or slightly reduced activity as compared to the unsubstituted benzyl derivative. Increasing the chain length between the phenolic oxygen and the phenyl group to two carbons in length (**103**) did not improve the activity against *P. falciparum*. Interestingly increasing the chain length to three carbons (**105**) improved the activity against the multidrug resistant strain by twentyfold as compared to benzyl substituted derivative **87**, while the activity against the wildtype strain was unchanged. The two cyclohexyl derivatives (**88** and **108**) showed some activity, but again they were comparable or less active than the benzyl substituted derivative. The derivatives functionalised with an *N*-heterocycle (**111** to **127**) were mostly inactive. Exceptions being the pyridine derivative **112,** which showed mild activity, and nitroimidazole derivative **126**, which interestingly showed good activity while contrastingly nitroimidazole derivative **127** was inactive.

Table 33 *In vitro* activity against *P. falciparum* of phenol substituted derivatives.



R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
H	>100	>100	>100
86 	5.2 ± 1.0	15.1 ± 3.9	>100
87 	1.6 ± 0.7	3.0 ± 0.3	>50
96 	7.3 ± 1.4	14.9 ± 2.6	>50
97 	14.4 ± 3.6	5.4 ± 1.2	37.0 ± 6.0
98 	12.2 ± 1.6	5.2 ± 0.8	60.3 ± 34.8
99 	13.7 ± 1.0	10.3 ± 2.2	>50
100 	27.8 ± 3.1	11.0 ± 2.6	>100
101 	23.8 ± 1.3	14.9 ±2.6	>50
103 	4.3 ± 0.4	0.7 ± 0.1	>50
105 	19.8 ± 1.3	77.9 ± 14.1	65.6 ± 2.3
88			

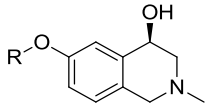
R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **108**	16.9 ± 1.8	6.6 ± 1.5	>50
 **111**	>50	>50	>50
 **112**	25.0 ± 3.3	21.7 ± 6.4	>50
 **118**	>100	>100	>100
 **119**	59.0 ± 9.4	>100	>100
 **126**	5.0 ± 1.7	13.7 ± 6.5	>50
 **127**	>50	>50	>50

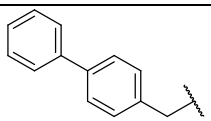
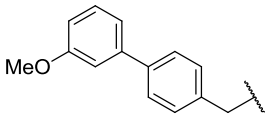
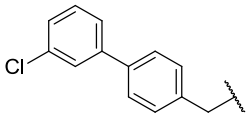
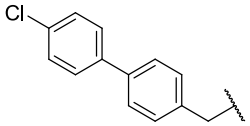
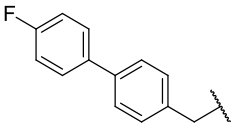
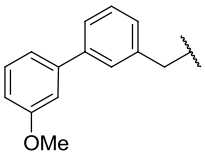
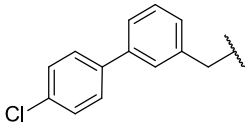
9.2.2 Biphenyl and diphenyl ether substituents

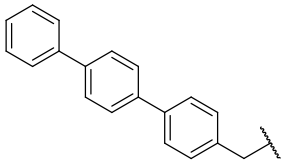
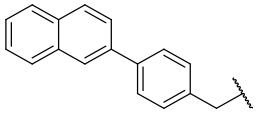
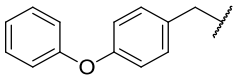
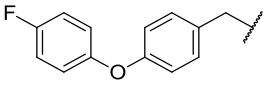
Derivatives of isoquinoline **86** substituted at the phenol with larger biphenyl and diaryl ether groups also showed some activity against both strains of *P. falciparum*. Contrastingly to the *T. b. rhodesiense* activities, derivative **129** substituted at the phenol with a biphenyl methyl group showed decreased activity as compared to the benzyl substituted derivative **87**. All of the substituted biphenyl derivatives (**130** to **133**) showed similar activity, while methoxy substituted and chloro substituted derivatives **136** and **132** showed slightly increased activity. The *p*-terphenyl derivative **140** showed good activity in the low micromolar range against both strains of *P. falciparum*, however it is highly cytotoxic, while the naphthyl derivative **142** showed comparable activity to the biphenyl derivatives. Both of the diaryl ether derivatives **148** and **149** showed good activity against both strains. Derivative **148** was approximately fivefold more active against the wildtype strain than the multi

drug resistant strain. Derivative **149** showed comparable activity for both strains with an IC_{50} of ~3 μM.

Table 34 *In vitro* activity against *P. falciparum* of phenol substituted derivatives.



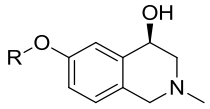
R	IC_{50} *P. falciparum* Wildtype (μM)	IC_{50} *P. falciparum* Multi drug resistant (μM)	Cytotoxicity (μM)
 **129**	24.5 ± 0.3	21.3 ± 2.9	23.0 ± 2.1
 **130**	17.6 ± 1.1	17.0 ± 2.6	10.8 ± 4.2
 **131**	17.5 ± 4.6	18.3 ± 1.4	25.5 ± 3.0
 **132**	7.4 ± 0.5	17.6 ± 0.8	24.1 ± 4.3
 **133**	20.9 ± 2.4	20.1 ± 0.9	33.8 ± 16.7
 **136**	7.0 ± 0.8	6.3 ± 1.8	24.3 ± 3.8
 **138**	12.8 ± 4.1	7.8 ± 3.3	27.3 ± 2.6

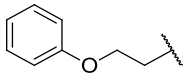
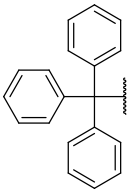
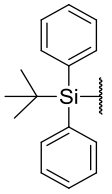
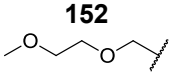
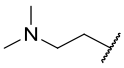
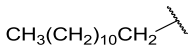
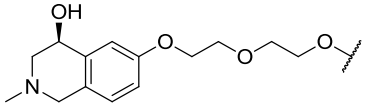
R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **140**	3.7 ± 0.2	3.6 ± 0.9	0.28 ± 0.04
 **142**	7.4 ± 1.1	7.5 ± 1.0	0.31 ± 0.01
 **148**	3.6 ± 1.0	16.2 ± 5.6	3.4 ± 0.8
 **149**	2.7 ± 1.0	2.9 ± 1.5	5.6 ± 0.1

9.2.3 Other phenolic substituents

In terms of other phenolic substituents, TBDPS substituted derivative **152** showed good activity against both strains of *P. falciparum* with IC_{50} values of ~3 µM, which is comparable to the activity of this derivative against *T. b. rhodesiense*. Dodecyl derivative **155** showed only mild activity against both strains, and was not selective for *P. falciparum* over mammalian cells.

Table 35 *In vitro* activity against *P. falciparum* of phenol substituted derivatives.

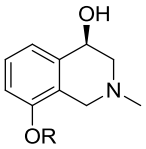


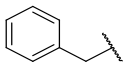
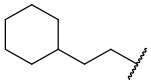
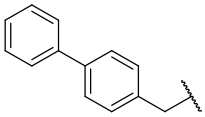
R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **150**	52.2 ± 1.1	23.9 ± 2.1	>100
 **151**	41.5 ± 5.9	43.1 ± 5.0	87.9 ± 7.1
 **152**	2.7 ± 1.5	3.2 ± 0.5	19.1 ± 0.6
 **153**	>50	>50	>50
 **154**	>50	>50	>50
 **155**	19.8 ± 1.6	19.4 ± 4.4	18.3 ± 3.7
 **157**	66.0 ± 0.9	77.9 ± 14.1	>100

9.2.4 Derivatives of isoquinoline 90

Derivatives of isoquinoline **90** substituted at the phenol with a cyclohexylethyl **160** or biphenylmethyl group **161** showed activity against both strains of *P. falciparum*. The cyclohexyl derivative **160** showed good activity against the multi drug resistant strain with an IC_{50} value of ~3 µM.

Table 36 *In vitro* activity against *P. falciparum* of phenol substituted derivatives of **90**.



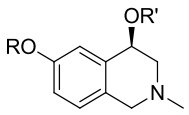
R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **158**	>100	>100	>100
 **159**	72.0 ± 13.6	19.9 ± 3.2	>100
 **160**	20.2 ± 3.2	3.2 ± 0.9	62.7 ± 9.1
 **161**	21.2 ± 4.3	18.8 ± 6.0	>50

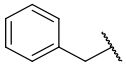
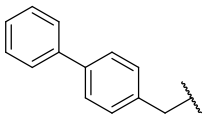
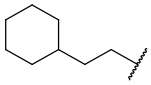
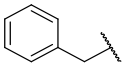
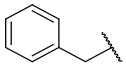
9.3 Antimalarial activity of derivatives modified at the benzylic alcohol

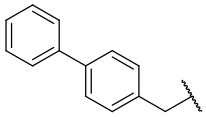
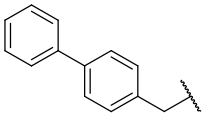
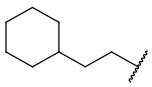
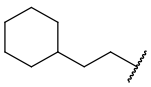
9.3.1 Substitution of the benzylic alcohol

Derivatives substituted at the benzylic alcohol with a methyl (**162)** or benzyl group (**166**) were inactive against *P. falciparum*. However, substitution with a biphenylmethyl group (**167)** gave a derivative with good activity against the wildtype strain of *P. falciparum* and mild activity against the multi drug resistant strain. The cyclohexylethyl derivative **168** showed mild activity against both strains. Disubstituted derivatives **169** to **172**, derivatives substituted at both the phenol and benzylic alcohol, showed mild activity against both strains of *P. falciparum*, however they were also significantly cytotoxic.

Table 37 *In vitro* activity against *P. falciparum* of benzylic alcohol substituted derivatives.



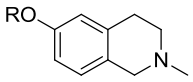
No.	R	R'	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
162	H		>100	>100	>100
166	H		>50	>50	>50
167	H		2.2 ± 0.2	27.1 ± 8.1	>50
168	H		19.6 ± 1.6	28.7 ± 13.1	>50
169			19.4 ± 4.5	17.1 ± 4.3	23.5 ± 1.4

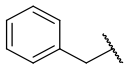
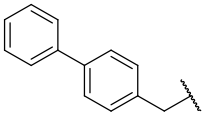
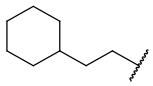
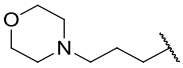
No.	R	R'	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
170			>10	>10	>10
172			6.7 ± 1.6	12.8 ± 0.9	23.6 ± 1.5

9.3.2 Removal of the benzylic alcohol and substitution of the phenol

Derivatives substituted at the phenol with the benzylic alcohol removed showed mild activity. The benzyl substituted derivative **176** was significantly less active against *P. falciparum* than the corresponding derivative with the benzyl alcohol intact (**87**). However, cyclohexylethyl derivative **178** showed comparable activity to its corresponding derivative with the benzyl alcohol still intact (**108**). These conflicting results are not sufficient to determine if the benzylic alcohol is important in *P. falciparum* inhibition.

Table 38 *In vitro* activity against *P. falciparum* of derivatives with the benzylic alcohol removed.

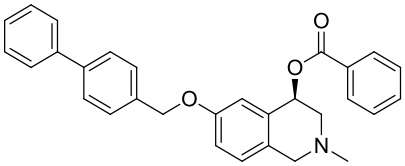
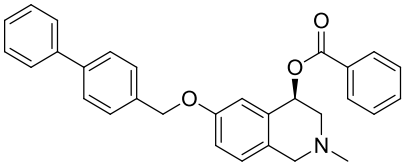
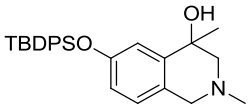


R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
H **175**	>100	>100	>100
 **176**	57.9 ± 8.4	26.7 ± 3.6	>100
 **177**	>20	>20	16.5 ± 2.8
 **178**	13.5 ± 2.8	14.0 ± 3.8	25.0 ± 3.9
 **179**	>50	>50	>50

9.3.3 Changing the stereochemistry and Grignard product

Derivatives **180** and **181** showed almost identical activity against *P. falciparum*, suggesting the stereochemistry of the benzylic alcohol is not important to *P. falciparum* inhibition. However, both of these derivatives showed good activity in the low micromolar range against both strains of *P. falciparum*, although they are both significantly cytotoxic. Derivative **188** also showed good activity against both strains of *P. falciparum* with lower cytotoxicity.

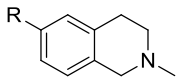
Table 39 *In vitro* activity against *P. falciparum* of derivatives **180**, **181**, and **188**.

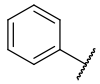
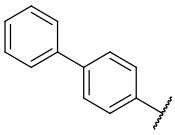
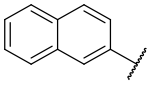
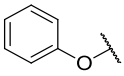
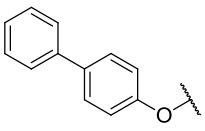
Derivative	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **180**	3.0 ± 0.7	2.3 ± 0.6	10.5 ± 4.1
 **181**	2.8 ± 0.5	2.8 ± 0.4	12.9 ± 2.3
 **188**	4.3 ± 0.4	3.3 ± 0.6	22.2 ± 1.1

9.4 Antimalarial activity of derivatives modified at position 6

Derivatives substituted directly at the aromatic ring at position 6 (**190** to **192**) showed mild activity. Derivative **191** has improved activity as compared to the phenol substituted biphenylmethyl derivative **129**, however it is not evident from these results if the increase in rigidity of these compounds is having an effect on the inhibition of *P. falciparum*. The aryl ether derivatives **195** and **197** did not show any significant activity against *P. falciparum*.

Table 40 *In vitro* activity against *P. falciparum* of derivatives modified at position 6.



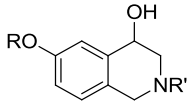
R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **190**	26.5 ± 2.9	30.9 ± 13.0	>50
 **191**	5.7 ± 1.8	10.1 ± 2.0	15.6 ± 0.3
 **192**	21.6 ± 1.2	21.4 ± 1.4	24.1 ± 2.2
 **195**	>100	>100	>100
 **197**	41.4 ± 11.6	41.2 ± 6.3	22.3 ± 0.44

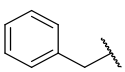
9.5 Antimalarial activity of derivatives modified at the nitrogen atom

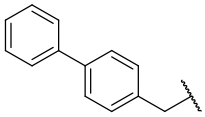
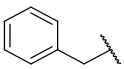
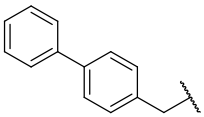
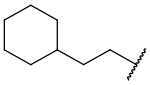
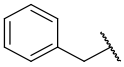
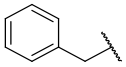
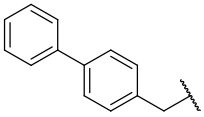
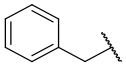
9.5.1 Substitution of the nitrogen atom

Derivatives substituted at the nitrogen atom with larger groups showed some activity, with biphenyl substituted derivative **205** showing mild activity against both strains of *P. falciparum*. However, derivatives substituted at the nitrogen atom with smaller groups such as ethyl and propyl derivatives **202** and **203** were inactive, while substitution with a somewhat larger benzyl group (**204**) showed very mild activity to the multi drug resistant strain. Derivatives of the secondary amine substituted at the phenol (**210** to **212**) showed mild activity, however there is no improvement in activity as compared to derivatives with an *N*-methyl group in the scaffold. Derivatives **213** and **214** which are substituted at both the phenol and the nitrogen atom showed good activity against both strains of *P. falciparum* with IC_{50} values of ~4 μM and reasonable selectivity over mammalian cells.

Table 41 *In vitro* activity against *P. falciparum* of derivatives modified at the nitrogen atom.



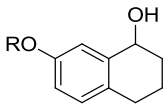
No.	R	R'	IC_{50} *P. falciparum* Wildtype (μM)	IC_{50} *P. falciparum* Multi drug resistant (μM)	Cytotoxicity (μM)
200	H	H	>100	>100	>100
202	H		>100	>100	>100
203	H		>100	>100	>100
204	H		>50	40.2 ± 6.3	>100

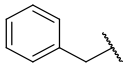
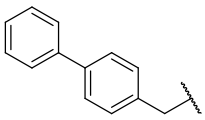
No.	R	R'	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
205	H		19.0 ± 2.4	13.7 ± 1.7	>50
210		H	27.9 ± 10.1	18.3 ± 3.5	>50
211		H	7.7 ± 0.4	14.4 ± 2.3	20.8 ± 0.8
212		H	19.8 ± 0.9	4.8 ± 1.7	>50
213			3.7 ± 0.3	3.5 ± 0.1	31.8 ± 6.7
214			3.9 ± 0.4	3.4 ± 0.3	14.8 ± 5.5

9.5.2 Derivatives without a nitrogen atom

Derivatives without a nitrogen atom in the core scaffold showed no activity against *P. falciparum*, except derivative **217** which showed good activity against wildtype *P. falciparum* and no activity against multidrug resistant *P. falciparum*. This result is inconsistent with what has been seen from other derivatives tested against *P. falciparum,* and therefore is questionable and requires further testing to confirm the result.

Table 42 *In vitro* activity against *P. falciparum* of derivatives without a nitrogen atom.

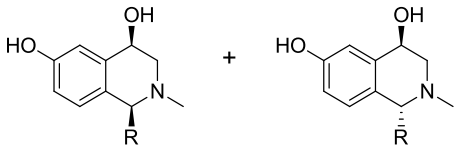


R	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
H **217**	3.3 ± 0.22	>100	>100
 **218**	>100	>100	39.0 ± 10.4
 **219**	>100	>100	>100

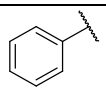
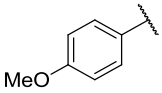
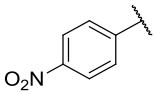
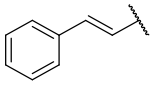
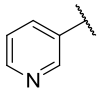
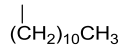
9.6 Antimalarial activity of derivatives modified at position 1

Derivatives substituted at position 1 showed similar trends in activity against *P. falciparum* as compared to activity against *T. b. rhodesiense*, with most derivatives showing no activity. However, both isomers of cinnamyl derivative **223** showed mild activity against both strains of *P. falciparum,* with good selectivity over mammalian cells. The undecyl derivatives **225** showed good activity against both strains of *P. falciparum* with reasonable selectivity over mammalian cells.

Table 43 *In vitro* activity against *P. falciparum* of derivatives substituted at position 1.



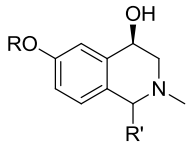
A **B**

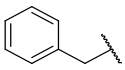
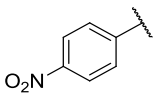
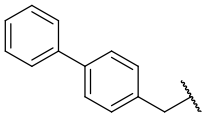
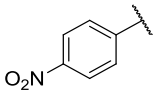
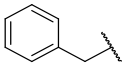
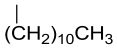
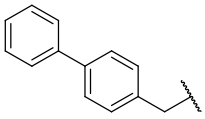
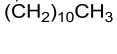
R	Isomer	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
 **220**	A	>100	60.6 ± 25.9	>100
	B	>100	73.8 ± 7.2	>100
 **221**	A	>100	>100	>100
	B	>100	>100	>100
 **222**	A	>50	>50	>50
	B	>50	>50	>50
 **223**	A	24.2 ± 0.7	19.7 ± 2.0	>50
	B	12.0 ± 1.4	19.7 ± 1.8	>50
 **224**	A	>100	>100	>100
 **225**	A+B	5.2 ± 2.4	3.1 ± 0.9	24.3 ± 2.9

9.6.1 Substitution of the phenol

Derivatives with a nitrophenyl group at position 1 and substituted at the phenol (**228** and **229**) showed activity against both strains of *P. falciparum* with better activity against the wildtype strain than the multi drug resistant strain. Derivatives substituted at position 1 with an undecyl group and substituted at the phenol (**230** and **231**) showed good activity against both strains of *P. falciparum*, however there was no selectivity over mammalian cells.

Table 44 *In vitro* activity against *P. falciparum* of derivatives substituted at position 1 and the phenol.



No.	R	R'	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)
228 A			4.9 ± 1.2	22.3 ± 5.0	26.8 ± 4.1
229 B			9.9 ± 1.3	22.1 ± 3.7	37.6 ± 4.1
230 A+B			2.8 ± 0.2	2.1 ± 0.7	3.2 ± 0.2
231 A+B			16.6 ± 4.9	2.9 ± 0.8	3.6 ±0.7

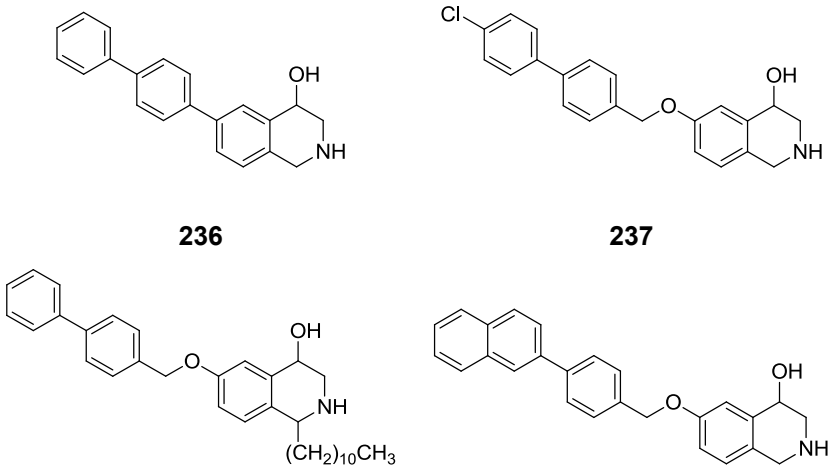
In conclusion, the derivatives above show potential to be developed into antimalarial compounds, with many derivatives showing good inhibition of both wildtype and multidrug resistant *P. falciparum* in the low micromolar range and with good

selectivity over mammalian cells. The most promising derivatives are *p*-nitrobenzyl substituted phenol derivative **96** which showed activity against wildtype *P. falciparum* and multidrug resistant *P. falciparum* with IC_{50} values of 1.6 ± 0.7 μM and 3.0 ± 0.3 μM respectively, and phenylpropyl phenol substituted derivative **105** which showed activity against wildtype *P. falciparum* and multidrug resistant *P. falciparum* with IC_{50} values of 4.3 ±0.4 μM and 0.7 ± 0.1 μM respectively. From this study there is insufficient data to develop an accurate SAR for this scaffold against *P. falciparum*. Further studies would be required to achieve this.

10 Future work and conclusion

10.1 Future work

The five derivatives mentioned above (**Figure 64**) provide good leads for further optimisation of this scaffold. Looking at these derivatives, the most obvious path is to start by synthesising derivatives of compounds **191**, **132**, **225**, and **142** without the *N*-methyl group to give a secondary amine similar to compound **211,** which would give derivatives **236** to **239** (see **Figure 66**). From the activities of the above derivatives and looking at the SAR it would be expected that doing this would give derivatives with more potent activity against *T. b. rhodesiense*.



236 **237**

238 **239**

Figure 66 Four most obvious derivatives to synthesise in the future.

From this study a number of areas that could be advantageous to explore in the future have been identified. These are discussed below. It was reported previously that phenolic substituents containing nitrogen atoms were generally not tolerated, however oxygen atoms were tolerated. This suggests the possibility of an unfavourable interaction between the nitrogen atom which would be charged at physiological pH and a positively charged residue in the active site. Therefore exploration of derivatives with a negatively charged residue, such as a carboxylic

acid, attached to the scaffold at the phenolic position could prove to be interesting. Another area to be explored more thoroughly in the future is the oxidation of the benzylic alcohol. Oxidation of the benzylic alcohol to give the ketone was achieved, although isolation of a pure product was not. The ketone would provide access to many different ways of functionalising the core scaffold, and indeed it was shown that Grignard chemistry is possible. Optimisation of reaction conditions as well as isolation and purification methods are needed to satisfactorily synthesise the ketone and isolate it with reasonable purity. Both the Oppenauer and Jones oxidation methods showed potential and should be revisited. Inversion of the stereochemistry of the benzylic alcohol has been described, synthesis of both the *R* and *S* benzoates was achieved. It was shown that the benzylic alcohol plays little or no part in anti-HAT activity and there was no difference in activity between the *R* and *S* benzoates suggesting that the stereochemistry of the benzylic alcohol was not important. However, hydrolysis of both of the benzoates to give the *R* and *S* benzylic alcohols would provide another confirmation of the lack of importance of the stereochemistry of the benzylic alcohol. Of the derivatives substituted at position 1 of the isoquinoline scaffold only those substituted with larger groups, such as a cinnamyl and undecyl group, showed any anti-HAT activity. It would be interesting to explore the addition of different derivatives at this position and evaluate if addition of some larger aromatic groups for example would improve the anti-HAT activity. Substitution of the phenol of the cinnamyl derivative would also be interesting to explore. Establishing collaborations in order to try and determine the target of these types of molecules and how they work in a mechanistic sense would also be very valuable to the progression of this work in the future.

10.2 Testing at other labs

All of the biological results reported in this thesis were obtained by the BIOTEC Medical Molecular Biology Research Unit in Thailand. However, biological testing of some compounds was also carried out by two other labs. Details and results can be found in Appendix B.

10.3 Conclusion

In conclusion, over 90 compounds were synthesised based around a phenylephrine derived tetrahydroisoquinoline scaffold. These compounds were evaluated for their activity against *T. b. rhodesiense* and two strains of *P. falciparum*, as well as their cytotoxicity to mammalian cells. From this study a structure activity relationship was developed between *T. b. rhodesiense* and this tetrahydroisoquinoline scaffold. Five derivatives, with sub micromolar activity against *T. b. rhodesiense* and good selectivity against mammalian cells, were identified as being promising leads for further optimisation. This scaffold was also shown to have potential to be explored as an antimalarial compound, with two derivatives identified with good activity against *P. falciparum* and selectivity over mammalian cells.

11 Experimental

11.1 General methods

All reactions were conducted under a positive pressure of nitrogen. (4*R*)-4,6-Dihydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**86**) was obtained from Epichem Pty Ltd. All other materials were obtained from commercial sources unless otherwise stated. Dry solvents were prepared according to Armarego and Chai.[205] Compounds were purified via column chromatography on Davisil silica gel 40-63 μm. Melting points were determined using an Electrothermal 1A9100 digital melting point apparatus. NMR spectra were recorded on a Bruker AVANCEIII 400 MHz spectrometer (^{1}H NMR 400 MHz, ^{13}C NMR 100 MHz). All NMR spectra were referenced to residual proton solvent signal. Multiplicity was assigned as follows: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet m = multiplet. High resolution mass spectrometry (HRMS) ESI measurements were recorded in positive ionisation mode on a LQT orbitrap XL instrument at Curtin University. Elemental analysis was carried out at Curtin University. Optical rotations were measured using a Rudolph research analytical autopol I polarimeter. Chiral HPLC was performed on a Phenomenex Lux Amylose-2 column, 150mm x 4.6mm, 5 micron, and the flow rate was 0.6mL/min with a 5uL injection. The conditions were isocratic, run with 30% isopropyl alcohol containing 0.1% diethylamine and 70% hexane. Microwave reactions were carried out using a Biotage Initiator EXP machine. All exact masses were calculated using chemdraw, the exact mass is calculated bases on the most common isotope for each element.

Workup Method 1: The reaction mixture was concentrated under reduced pressure, diluted with 5% sodium bicarbonate solution, and extracted three times with ethyl acetate. The ethyl acetate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford the crude product.

Workup Method 2: The reaction mixture was concentrated under reduced pressure, diluted with 5% sodium bicarbonate solution, and extracted three times with 10% isopropyl alcohol in ethyl acetate.

Workup Method 3: The reaction mixture was diluted with ethyl acetate and washed with water. The ethyl acetate fraction was dried over magnesium sulfate, and concentrated under reduced pressure to afford the crude product.

11.2 Biological Methods

Biological testing was carried out by Sumalee Kamchonwongpaisan, Jutharat Pengon, and Roonglawan Rattanajak from BIOTEC Medical Molecular Biology Research Unit, National Science and Technology Development Agency, 113 Thailand Science Park, Phahonyothin Road, Khlong Nueng, Khlong Luang, Pathum Thani 12120, Thailand. A series of standard antifolates (pyrimethamine, cycloguanil, and WR99210, were used as positive controls for *T. b. rhodesiense* and *P. falciparum* testing. Ellipticine was used as a positive control for cytotoxicity.

11.2.1 Trypanosome culture and testing compounds *in vitro*

Trypanosome brucei rhodesiense (STB900) was maintained continuously in MEM/EBSS medium supplemented with 3 g/L sodium bicarbonate, 4.5 g/L glucose, 25 mM HEPES, pH 7.3, 0.05 mM bathocuproinedisulfonic acid disodium salt, 1.5 mM L-cysteine, 1 mM hypoxanthine, 0.16 mM thymidine, 1 mM sodium pyruvate, 0.2 mM 2-mercaptoethanol, 1% MEM non-essential amino acid, and 15% heated fetal bovine serum, in a 5% CO_2 incubator. To assay anti-*T. b. rhodesiense* activity, a modified reported protocol[206] was used. Briefly, 2 x 10^4 trypanosome cells in 175 μL culture media /well were incubated with 25 μL of varying concentrations of each compound in a 96-well plate under the same culture condition. The compounds were dissolved in DMSO and the final concentration of DMSO in each well was 0.1% which causes no effect on parasite viability. Following 72-hour incubation, 20 μL Alamar Blue (a resazurin solution) was added in each well. The reaction was further incubated at 37°C, 5% CO_2 for 3 hours to allow irreversible reduction of resazurin

(violet colour) to resorufin (pink colour) by viable trypanosome cells. The fluorescence signals were measured by a spectrofluorometer at ex530/em585 nm. The results were read as concentration of each compound that exhibit 50% growth inhibition (IC_{50}) from the dose-response curve established from the fluorescence signals at each concentration of compounds.

11.2.2 Parasite Culture and Antimalarial Testing *in Vitro*.

Two *P. falciparum* strains, TM4/8.2 (wild-type drug sensitive strain) and K1CB1 (multidrug resistant strain) were used in this study. These were generous gifts from S. Thaithong, Department of Biology, Faculty of Science, Chulalongkorn University. The parasites were maintained continuously in human erythrocytes at 37°C under 3% CO_2 in RPMI 1640 culture media (Gibco, USA) supplemented with 25 mM HEPES (Sigma), pH 7.4, 2 g/L $NaHCO_3$ and 10% human serum. *In vitro* antimalarial activity was determined by using the [^{3}H] hypoxanthine incorporation method. 1.5% cell suspension of parasitised erythrocytes with 1% parasitemia (200 μL) in each well was incubated with varying concentration of compound (25 μL) under the same culture conditions for 24 h. Parasite survival was determined by [^{3}H] hypoxanthine incorporation assay. Briefly, 25 μL of 0.5 μCi [^{3}H] hypoxanthine was added to each well, and the mixture was further incubated for 18-20 h. Then the cells were lysed with water and the parasite DNA was harvested onto 96-well microplates with built-in glass fiber filters (Unifilter TM plates, Packard, USA). The filters in the plates were air-dried, and then 22 μL of liquid scintillation fluid (Microscint, Packard) was added. The radioactivity on the filters was then measured using a microplate scintillation counter (TopCount, Packard, USA). The IC_{50} of each compound was determined from dose-response curve.[207]

11.2.3 Cytotoxicity testing by sulforhodamine B (SRB) colorimetric assay.

African green monkey kidney fibroblast (Vero cells) and human epidermoid carcinoma (KB) cells were obtained from the bioassay laboratory, BIOTEC, NSTDA. Vero cells were maintained continuously in MEM/EBSS medium

supplemented with 10% heated fetal bovine serum, 2.2 g/L sodium bicarbonate, and 100 mM sodium pyruvate. KB cells were maintained continuously in DMEM/low glucose medium supplemented with 10% heated fetal bovine serum, 3.7 g/L sodium bicarbonate, and 1% non-essential amino acid. Cytotoxicity was determined by sulforhodamine B (SRB) assay. Briefly, 1.9 x 10^4 cells were incubated with test compounds at 37°C, 5% CO_2 for 72 hours. Then, the cells were fixed with 10% trichloroacetic acid at 4°C for 45 minutes, washed with water and dried at room temperature overnight. Then the plate was stained with 0.057% (W/V) sulforhodamine B, washed 4 times with 1% (V/V) acetic acid, and left dry at room temperature overnight. Finally, 10X tris-base was added to each well to dissolve protein-bound dye. The optical density was determined by spectrophotometer at wavelength 510 nm. The IC_{50} value of each compound was determined from the dose-response curve.[208]

11.3 X-ray Crystallography

The crystal structure of compound **227** was determined by X-ray diffraction methods. Intensity data and cell parameters were recorded at 100(2) K at the ELETTRA Synchrotron Light Source (CNR Trieste, strada statale 14, Area Science Park, 34149, Basovizza, Trieste, Italy). The raw frame data were processed using the program package CrysAlisPro 1.171.38.41.[209] The structure was solved by Direct Methods using the SIR97 program[210] and refined on F_o^2 by full-matrix least-squares procedures, using the SHELXL-2014/7 program [211] in the WinGX suite v.2014.1.[212,213] All non-hydrogen atoms were refined with anisotropic atomic displacements. The hydrogen atoms were included in the refinement at idealized geometry (C-H 0.95 Å) and refined "riding" on the corresponding parent atoms. The weighting scheme used in the last cycle of refinement was $w = 1/ [\sigma^2 F_o^2 + (0.1020P)^2 + 0.0528P]$, where $P = (F_o^2 + 2F_c^2)/3$. Crystal data and experimental details for data collection and structure refinement are reported in Appendix C.

11.4 Computational methods

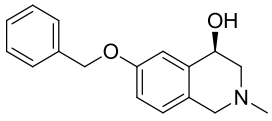
Computational studies were carried out by Professor Andrew Rohl at Curtin University. The NMR chemical shifts and ^{1}H-^{1}H coupling constants were computed using the Gaussian 09 software,[214] utilising the recommended procedure of Bally and Rablen.[215] Each structure/conformation was optimised at the B3LYP/6-31G(d) level in the gas phase. The isotropic magnetic shieldings, *m*, were calculated at this geometry at the WP04/cc-pVDZ level using the Gauge-Independent Atomic Orbital (GIAO) method in a chloroform implicit solvent. Chemical shifts were calculated by:

$$\delta = (31.844 - m) / 1.0205$$

^{1}H-^{1}H Fermi contact terms were calculated at the B3LYP/6-31G(d,p)u+1s[H] level and these were multiplied by 0.9155 to yield the proton-proton coupling constants.

11.5 Substitution of the phenol

11.5.1 (*R*)-6-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (87)



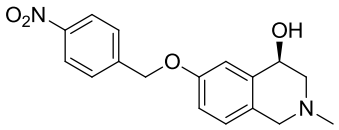
87

The isoquinoline hydrochloride **86** (0.502 g, 2.30 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.204 g, 5.10 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes. Benzyl bromide (305 μL, 2.60 mmol) was added and the reaction mixture stirred at room temperature for a further 24 hrs. The reaction was quenched with methanol (2 mL) and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a pale orange gummy solid (0.363 g, 56%). ^{1}H NMR ($CDCl_3$) δ 7.46-7.43 (2 H, m), 7.41-7.36 (2 H, m), 7.34-7.30 (1 H, m), 7.04 (1 H, d, *J* = 2.8 Hz), 6.87 (1 H, dd, *J* = 8.4, 2.8 Hz), 6.80 (1 H, d, *J* = 8.4), 5.08 (2 H, s), 4.52 (1 H, t, *J* =

2.8 Hz), 3.12 (1 H, d, *J* = 14.4 Hz), 3.02 (1 H, d, *J* = 14.4), 2.93 (1 H, ddd, *J* = 11.8, 2.8, 1.0 Hz), 2.44 (1 H, dd, *J* = 11.8, 2.8 Hz), 2.29 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.7, 137.4, 137.2, 128.7, 128.1, 127.6, 127.5, 127.2, 115.6, 114.4, 70.2, 67.3, 60.5, 57.1, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1489; Found 270.1489.

Also isolated was the disubstituted product (**169**) as a pale orange gummy solid (0.140 g, 18%). ^{1}H NMR ($CDCl_3$) δ 7.46 -7.27 (10 H, m), 7.01 (1 H, d, *J* = 2.6 Hz), 6.98 (1 H, d, *J* = 8.4 Hz), 6.87 (1 H, dd, *J* = 8.4, 2.6 Hz), 5.08- 4.95 (2 H, m), 4.78-4.57 (3 H, m), 3.60 (1 H, d, *J* = 14.6 Hz), 3.48 (1 H, d, *J* = 14.6 Hz), 2.89 (1 H, ddd, *J* = 11.6, 4.7, 0.9 Hz), 2.79 (1 H, dd, *J* = 11.6, 6.0 Hz), 2.48 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.4, 138.7, 137.1, 135.4, 128.6, 128.4, 127.9, 127.9, 127.6, 127.5, 127.1, 115.1, 113.9, 73.6, 70.9, 70.1, 57.4, 57.2, 46.2 (note some peaks coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{26}NO_2$ 360.1958; Found 360.1951.

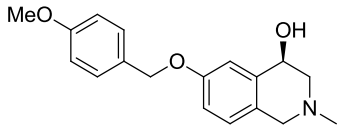
11.5.2 (*R*)-2-Methyl-6-((4-nitrobenzyl)oxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (96)



96

The isoquinoline hydrochloride **86** (0.505 g, 2.34 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.247 g, 6.18 mmol) and 4-nitrobenzyl bromide (0.553 g, 2.56 mmol) as described for **87** and then subjected to workup method 1. The resulting orange solid was purified by column chromatography (15% methanol in ethyl acetate) to afford the desired product as a pale yellow solid (0.425 g, 58%). m.p. 155.0 - 160°C; ^{1}H NMR ($CDCl_3$) δ 8.25-8.22 (2 H, m), 7.62-7.58 (2 H, m), 7.01 (1 H, d, *J* = 2.8 Hz), 6.91 (1 H, d, *J* = 8.4 Hz), 8.86 (1 H, dd, *J* = 8.4, 2.8 Hz), 5.17 (2 H, s), 4.54 (1 H, t, *J* = 2.8 Hz), 3.41 (1 H, d, *J* = 14.8 Hz), 3.15 (1 H, d, *J* = 14.8 Hz), 2.94 (1 H, ddd, *J* = 11.6, 2.8, 1.0 Hz), 2.52 (1 H, dd, *J* = 11.6, 2.8), 2.37 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.1, 147.7, 144.7, 137.7, 127.72, 127.69, 124.0, 115.6, 114.4, 68.9, 67.3, 60.4, 57.2, 46.1 (note some peaks coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_4$ 315.1339; Found 315.1338.

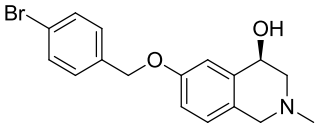
11.5.3 (*R*)-6-((4-Methoxybenzyl)oxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (97)



97

The isoquinoline hydrochloride **86** (0.430 g, 2.73 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.240 g, 6.08 mol) and 1-(chloromethyl)-4-methoxybenzene **240** (0.500 g, 2.31 mmol) as described for **87** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (40% methanol in ethyl acetate) to afford the desired product as an orange gummy solid (0.20 g, 29%). ^{1}H NMR ($CDCl_3$) δ 7.37-7.34 (2 H, m), 7.02 (1 H, d, *J* = 2.4 Hz), 6.93-6.89 (2 H, m), 6.85 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.77 (1 H, d, *J* = 8.4 Hz), 4.99 (2 H, s), 4.52 (1 H, t, *J* = 2.6 Hz), 3.80 (3 H, s), 3.05 (1 H, d, *J* = 14.6 Hz), 2.99 (1 H, d, *J* = 14.6 Hz), 2.93 (1 H, dd, *J* = 11.8, 2.6 Hz), 2.43 (1 H, dd, *J* = 12.0, 2.6 Hz), 2.28 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 159.5, 157.5, 137.2, 129.2, 129.1, 127.6, 127.0, 115.6, 114.2, 114.1, 69.9, 67.0, 60.5, 56.7, 55.4, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{22}NO_3$ 300.1594; Found 300.1595. See pg. 240 for details on the synthesis of 1-(chloromethyl)-4-methoxybenzene **240**.

11.5.4 (*R*)-6-((4-Bromobenzyl)oxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (98)

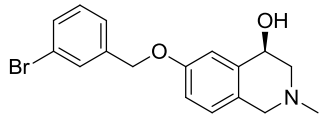


98

The isoquinoline hydrochloride **86** (1.04 g, 4.83 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.430 g, 10.6 mmol) and 4-bromobenzyl bromide (1.33 g, 5.31 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (10% methanol in dichloromethane) to afford the desired product as

a brown solid (1.01 g, 60%). m.p. 127 - 129°C; ^{1}H NMR ($CDCl_3$) δ 7.52-7.49 (2 H, m), 7.32-7.29 (2 H, m), 7.00 (1 H, d, *J* = 2.6 Hz), 6.88 (1 H, d, *J* = 8.5 Hz), 6.84 (1 H, dd, *J* = 8.5, 2.6 Hz), 5.02 (2 H, s), 4.54 (1 H, t, *J* = 2.8 Hz), 3.43 (1 H, d, *J* = 14.5 Hz), 3.15 (1 H, d, *J* = 14.5 Hz), 2.93 (1 H, ddd, *J* = 11.7, 2.8, 1.2 Hz), 2.51 (1 H, dd, *J* = 11.7, 2.8 Hz), 2.38 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.4, 137.6, 136.2, 131.9, 129.2, 127.6, 127.6, 122.0, 115.6, 114.4, 69.4, 67.4, 60.5, 57.2, 46.2; Anal. Calcd for $C_{17}H_{18}BrNO_2$: C, 58.63; H, 5.21; N 4.02. Found: C, 58.44; H, 4.97; N, 3.93.

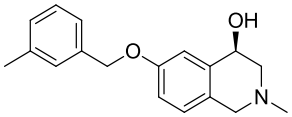
11.5.5 (*R*)-6-((3-Bromobenzyl)oxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (99)



99

The isoquinoline hydrochloride **86** (1.00 g, 4.64 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.420 g, 10.4 mmol) and 3-bromobenzyl bromide (1.260 g, 5.100 mmol) as described for **87** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (2% methanol, 1% triethylamine in dichloromethane) to afford the desired product as a waxy orange solid (1.07 g, 66%). m.p. 64 - 75°C; ^{1}H NMR ($CDCl_3$) δ 7.60 (1 H, t, *J* = 1.5 Hz), 7.49-7.47 (1 H, m), 7.35 (1 H, dd, *J* = 7.8, 0.5 Hz), 7.23 (1 H, d, *J* = 7.8 Hz), 7.00 (1 H, d, *J* = 2.6 Hz), 6.85 (1 H, dd, *J* = 8.4, 2.6 Hz), 6.79 (1 H, d, *J* = 8.4 Hz), 5.04 (2 H, s), 4.50 (1 H, t, *J* = 2.7 Hz), 3.06 (1 H, d, *J* = 14.7 Hz), 3.00 (1 H, d, *J* = 14.7 Hz), 2.92 (1 H, dd, *J* = 11.8, 1.8 Hz), 2.42 (1 H, dd, *J* = 11.8, 2.7 Hz), 2.27 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.3, 139.6, 137.5, 131.1, 130.4, 130.3, 127.7, 127.6, 126.0, 122.8, 115.6, 114.3, 69.2, 67.2, 60.5, 57.0, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}NO_2Br$ 348.0594; Found 348.0576.

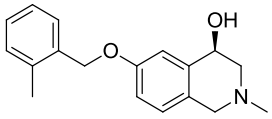
11.5.6 (*R*)-2-Methyl-6-((3-methylbenzyl)oxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (100)



100

The isoquinoline hydrochloride **86** (0.505 g, 2.34 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.230 g, 5.80 mmol) and 3-methylbenzyl chloride **241** (0.372 g, 2.65 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (10% methanol in ethyl acetate) to afford the desired product as a colourless gummy solid (0.285 g, 43%). ^{1}H NMR ($CDCl_3$) δ 7.29-7.22 (3 H, m), 7.15-7.12 (1 H, m), 7.05 (1 H, d, *J* = 2.8 Hz), 6.87 (1 H, dd, *J* = 8.4, 2.8 Hz), 6.75 (1 H, d, *J* = 8.4 Hz), 5.04 (2 H, s), 4.51 (1 H, t, *J* = 3.0 Hz), 2.95 (2 H, s), 2.92 (1 H, dd, *J* = 12.0, 3.0 Hz), 2.40 (1 H, dd, *J* = 12.0, 3.0 Hz), 2.38 (3 H, s), 2.24 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.5, 138.3, 137.2, 137.0, 128.8, 128.5, 128.2, 127.6, 127.0, 124.6, 115.5, 114.2, 70.1, 66.9, 60.5, 56.6, 46.0, 21.5; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{22}NO_2$ 284.1645; Found 284.1637. See pg. 241 for details on the synthesis of 3-methylbenzyl chloride **241**.

11.5.7 (*R*)-2-Methyl-6-((2-methylbenzyl)oxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (101)

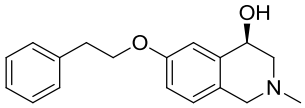


101

The isoquinoline hydrochloride **86** (0.101 g, 0.460 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.040 g, 1.0 mmol) and 2-methylbenzyl chloride (67 μL, 0.51 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a

colourless gummy solid which slowly crystallised (0.085 g, 65%). m.p. 122 - 124°C; ^{1}H NMR ($CDCl_3$) δ 7.43-7.41 (1 H, m), 7.28-7.20 (3 H, m), 7.09 (1 H, d, *J* = 2.4 Hz), 6.72 (1 H, dd, *J* = 8.4, 2.4), 6.88 (1 H, d, *J* = 8.4), 5.07 (2 H, s), 4.58 (1 H, t, *J* = 2.4 Hz), 3.31 (1 H, d, *J* = 14.6 Hz), 3.12 (1 H, d, *J* = 14.6 Hz), 2.98 (1 H, dd, *J* = 11.8, 2.4 Hz), 2.51 (1 H, dd, *J* = 11.8, 2.4 Hz), 2.41 (3 H, s), 2.38 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.8, 137.4, 136.8, 135.0, 130.5, 128.7, 128.4, 127.6, 127.1, 126.1, 115.6, 114.2, 68.8, 67.3, 60.5, 57.0, 46.1, 19.0; Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N 4.94. Found: C, 76.20; H, 7.35; N, 4.76; $[\alpha]_D$ +2.9°(c 1.03, CH_2Cl_2).

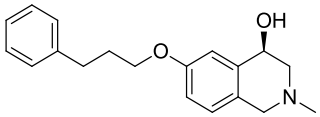
11.5.8 (*R*)-2-Methyl-6-phenethoxy-1,2,3,4-tetrahydroisoquinolin-4-ol (103)



103

The isoquinoline hydrochloride **86** (0.506 g, 2.34 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.245 g, 6.35 mmol) and phenylethyl tosylate **102** (0.722 g, 2.61 mmol) as described for **87** and then subjected to workup method 1. The resulting pale orange solid was then recrystallised from petroleum spirits 60-80 to afford the desired product as a white solid (0.268 g, 40%). m.p. 90 - 91°C; ^{1}H NMR ($CDCl_3$) δ 7.34-7.21 (5 H, m), 6.95 (1 H, d, *J* = 2.4 Hz), 6.88 (1 H, d, *J* = 8.4 Hz), 6.80 (1 H, dd, *J* = 8.4, 2.4 Hz), 4.54 (1 H, t, *J* = 2.8 Hz), 4.21-4.15 (2 H, m), 3.44 (1 H, d, *J* = 14.4), 3.17 (1 H, d, *J* = 14.4 Hz), 3.10 (2 H, t, *J* = 7.0 Hz), 2.96 (1 H, ddd, *J* = 12.4, 2.8, 1.2 Hz), 2.53 (1 H, dd, *J* = 12.4, 2.8 Hz), 2.40 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.8, 138.4, 137.3, 129.1, 128.6, 127.5, 126.7, 126.6, 115.4, 114.1, 68.9, 67.3, 60.5, 57.1, 46.1, 35.9; Anal. Calcd for $C_{18}H_{21}NO_3$: C, 76.29; H, 7.47; N 4.94. Found: C, 76.14; H, 7.57; N, 4.86. See pg. 43 for details on the synthesis of phenylethyl tosylate **102**.

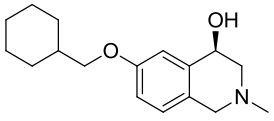
11.5.9 (*R*)-2-Methyl-6-(3-phenylpropoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (105)



105

The isoquinoline hydrochloride **86** (0.102 g, 0.470 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.041 g, 0.47 mmol) and 3-bromopropylbenzene (76 μL, 0.51 mmol) as described for **87** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography 5% methanol in dichloromethane) to afford the desired product as a pale orange gummy solid (0.081 g, 58%). ^{1}H NMR ($CDCl_3$) δ 7.32-7.28 (2 H, m), 7.24-7.18 (3 H, m), 6.95 (1 H, d, *J* = 2.0 Hz), 6.83 (1 H, d, *J* = 8.4 Hz), 6.80 (1 H, dd, *J* = 8.4, 2.4 Hz), 4.53 (1 H, t, *J* = 2.8 Hz), 3.97 (2 H, t, *J* = 6.2 Hz), 3.16 (1 H, d, *J* = 14.4 Hz), 3.05 (1 H, d, *J* = 14.4), 2.94 (1 H, dd, *J* = 12.0, 2.8 Hz), 2.82 (2 H, t, *J* = 7.6 Hz), 2.46 (1 H, dd, *J* = 12.0, 2.8 Hz), 2.32 (3 H, s), 2.15-2.08 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 157.9, 141.6, 137.3, 128.6, 128.5, 127.5, 126.8, 126.0, 115.3, 113.9, 67.2, 67.1, 60.5, 56.9, 46.1, 32.2, 30.9; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{24}NO_2$ 298.1807; Found 298.1800.

11.5.10 (*R*)-6-(Cyclohexylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (88)

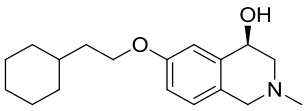


88

The isoquinoline hydrochloride **86** (0.215 g, 1.00 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.088 g, 2.2 mmol) and cyclohexylmethyl bromide (0.15 mL, 1.1 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a

colourless gummy solid which slowly crystallised to give a white solid (0.135 g, 49%). m.p. 94 - 96 °C; ^{1}H NMR ($CDCl_3$) δ 6.93 (1 H, d, *J* = 2.6 Hz), 6.90 (1 H, d, *J* = 8.4 Hz), 6.79 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.55 (1 H, t, *J* = 2.8 Hz), 3.78-3.72 (2 H, m), 3.49 (1 H, d, *J* = 14.5 Hz), 3.17 (1 H, d, *J* = 14.5 Hz), 2.93 (1 H, ddd, *J* = 11.7, 2.8, 1.3 Hz), 2.52 (1 H, dd, *J* = 11.7, 2.8 Hz), 2.40 (3 H, s), 1.89-1.83 (2 H, m), 1.79-1.66 (4 H, m), 1.35-1.18 (3 H, m), 1.09-0.99 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 158.3, 137.4, 127.4, 126.8, 115.4, 113.9, 73.8, 67.6, 60.6, 57.3, 46.2, 37.9, 30.1, 26.7, 26.0; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{26}NO_2$ 276.1958; Found 276.1955.

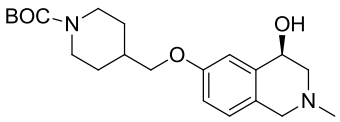
11.5.11 (*R*)-6-(2-Cyclohexylethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (108)



108

The isoquinoline hydrochloride **86** (0.202 g, 0.940 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.092 g, 2.3 mmol) and 2-cyclohexylethyl tosylate 107 (0.289 g, 1.02 mmol) as described for **87** and then subjected to workup method 1. The resulting white solid was purified by recrystallisation (petroleum spirits 60-80) to afford the desired product as a white crystalline solid (0.157 g, 58%). m.p. 108 - 110°C; ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, d, *J* = 2.8 Hz), 6.87 (1 H, d, *J* = 8.6 Hz), 6.79 (1 H, dd, *J* = 8.6, 2.8 Hz), 4.55 (1 H, t, *J* = 2.8 Hz), 3.99 (2 H, t, *J* = 6.8 Hz), 3.39 (1 H, d, *J* = 14.4 Hz), 3.15 (1 H, d, *J* = 14.4 Hz), 2.97 (1 H, ddd, *J* = 11.8, 2.8, 1.1 Hz), 2.52 (1 H, dd, *J* = 11.8, 2.8 Hz), 2.39 (3 H, s), 1.79-1.65 (7 H, m), 1.55-1.45 (1 H, m), 1.23-1.11 (3 H, m), 1.02-0.92 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 158.1, 137.2, 127.5, 126.4, 115.4, 113.9, 67.3, 66.2, 60.5, 57.1, 46.1, 36.8, 34.7, 33.5, 33.4, 26.7; Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N 4.84. Found: C, 74.74; H, 9.70; N, 4.83. See pg. 238 for details on the synthesis of 2-cyclohexylethyl tosylate 107.

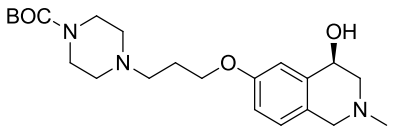
11.5.12 (*R*)-*tert*-Butyl 4-(((4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)methyl)piperidine-1-carboxylate (109)



109

The isoquinoline hydrochloride **86** (0.500 g, 2.54 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.204 g, 5.10 mmol) and *tert*-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate **243** (0.746 g, 2.54 mmol) as described for **87** and then subjected to workup method 2. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.276 g, 32%). ^{1}H NMR ($CDCl_3$) δ 6.94 (1 H, d, *J* = 2.6 Hz), 6.90 (1 H, d, *J* = 8.4 Hz), 6.78 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.58 (1 H, br. s.), 4.26 - 4.01 (2 H, m), 3.79 (2 H, dd, *J* = 6.5, 2.1 Hz), 3.54 (1 H, d, *J* = 14.5 Hz), 3.23 (1 H, d, *J* = 14.5 Hz), 2.99 (1 H, dd, *J* = 11.8, 2.4 Hz), 2.74 (2 H, t, *J* = 12.2 Hz), 2.58 (1 H, dd, *J* = 11.8, 2.4 Hz), 2.43 (3 H, s), 2.01 - 1.87 (1 H, m), 1.83-1.78 (2 H, m), 1.46 (9 H, s), 1.32 - 1.17 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 158.1, 155.0, 137.2, 127.4, 126.0, 115.5, 114.0, 79.5, 72.6, 67.1, 60.4, 57.1, 45.9, 36.3, 29.8, 29.0, 28.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{33}N_2O_4$ 377.2435; Found 377.2423. See pg.241 for details on the synthesis of *tert*-butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate **243**.

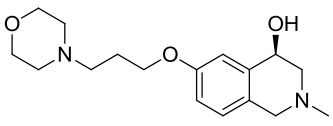
11.5.13 (*R*)-*tert*-Butyl 4-(3-((4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)propyl)piperazine-1-carboxylate (110)



110

The isoquinoline hydrochloride **86** (0.502 g, 5.10 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.204 g, 5.10 mmol) and *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate 115 (0.670 g, 2.55 mmol) as described for **87** and then subjected to workup method 2. The resulting brown gummy solid was purified by column chromatography (10% methanol, 1% triethylamine in dichloromethane) to afford the desired product as an orange gummy solid (0.724 g, 76%). ^{1}H NMR ($CDCl_3$) δ 6.93 (1 H, d, *J* = 2.6 Hz), 6.84 (1 H, d, *J* = 8.6 Hz), 6.77 (1 H, dd, *J* = 8.6, 2.6 Hz), 4.52 (1 H, t, *J* = 2.8 Hz), 4.00 (2 H, t, *J* = 6.4 Hz), 3.46 - 3.36 (4 H, m), 3.28 (1 H, d, *J* = 14.5 Hz), 3.09 (1 H, d, *J* = 14.5 Hz), 2.91 (1 H, dd, *J* = 11.7, 2.1 Hz), 2.56 - 2.44 (3 H, m), 2.39 (4 H, t, *J* = 5.1 Hz), 2.34 (3 H, s), 2.04 - 1.88 (2 H, m), 1.45 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 157.9, 154.9, 137.4, 127.4, 126.9, 115.3, 113.9, 79.7, 67.4, 66.3, 66.0, 60.5, 57.2, 55.3, 53.2, 46.1, 28.6, 26.8. See pg. 239 for details on the synthesis of *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate **115**.

11.5.14 (*R*)-2-Methyl-6-(3-morpholinopropoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (111)

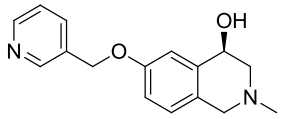


111

The isoquinoline hydrochloride **86** (0.203 g, 0.940 mmol) was treated with potassium *tert*-butoxide (0.217 g, 1.95 mmol), sodium iodide (0.300 g, 2.00 mmol), and 4-(3-chloropropyl)morpholine **117** (0.168 g, 1.03 mmol) as described for **87** and then

subjected to workup method 2. Attempted purification by column chromatography was unsuccessful. The resulting orange gummy solid was purified by dissolving in a mixture of hot ethyl acetate and petroleum spirits 40-60, decanting off the solvent and concentrating under reduced pressure to afford a pale yellow gummy solid (0.049 g, 17%). ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, d, *J* = 2.6 Hz), 6.89 (1 H, d, *J* = 8.4 Hz), 6.79 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.56 (1 H, t, *J* = 2.6 Hz), 4.03-3.99 (2 H, m), 3.73-3.70 (4 H, m), 3.47 (1 H, d, *J* = 14.7 Hz), 3.19 (1 H, d, *J* = 14.7 Hz), 2.97 (1 H, ddd, *J* = 11.7, 3.1, 1.0 Hz), 2.54-2.50 (3 H, m), 2.47-2.44 (4 H, m), 2.42 (3 H, s), 1.99-1.92 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 157.9, 137.4, 127.4, 127.0, 115.4, 114.0, 67.5, 67.1, 66.4, 60.5, 57.3, 55.7, 53.9, 46.2, 26.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{27}N_2O_3$ 307.2016; Found 307.2005. See pg. 239 for details on the synthesis of 4-(3-chloropropyl)morpholine **117**.

11.5.15 (*R*)-2-Methyl-6-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (112)

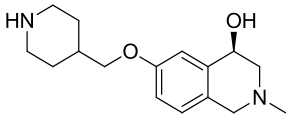


112

2-(Chloromethyl)pyridine hydrochloride (0.168 g, 1.02 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.120 g, 2.98 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 10 minutes. The isoquinoline hydrochloride **86** (0.202 g, 0.930 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with methanol (2 mL) and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a colourless gummy solid (0.146 g, 58%). ^{1}H NMR ($CDCl_3$) δ 8.65 (1 H, dt, *J* = 1.6, 0.8 Hz), 8.55 (1 H, dd, *J* = 4.9, 1.7 Hz), 7.78 - 7.73 (1 H, m), 7.30 (1 H, ddd, *J* = 7.8, 4.9, 1.0 Hz), 7.06 - 7.03 (1 H, m), 6.89 - 6.82 (2 H, m), 5.06 (2 H, s), 4.60 - 4.55 (1 H, m), 3.41 (1 H, d, *J* = 14.6 Hz), 3.21 (1 H, d, *J* = 14.6 Hz), 2.97 (1 H, ddd, *J* = 11.8, 3.3, 1.3 Hz), 2.58 (1 H, dd, *J* = 11.8, 3.2 Hz), 2.42 - 2.37 (3 H, m);

^{13}C NMR ($CDCl_3$) δ 157.6, 149.5, 149.1, 137.1, 135.5, 132.6, 127.6, 125.8, 123.7, 115.9, 114.4, 67.8, 66.5, 60.1, 56.7, 45.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_2$ 271.1441; Found 271.1443.

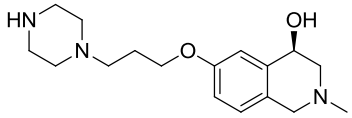
11.5.16 (*R*)-2-Methyl-6-(piperidin-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (118)



118

The BOC protected amine **109** (0.485 g, 1.29 mmol) was dissolved in a mixture of anhydrous dichloromethane and trifluoroacetic acid (2:1), stirred at room temperature for 15 minutes, and subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (15% methanol, 2% sat.ammonia, in dichloromethane) to afford the desired product as a colourless gummy solid (0.323 g, 83%). ^{1}H NMR (D_2O) δ 7.25 (1 H, d, *J* = 8.4 Hz), 7.14 - 7.08 (2 H, m), 5.13 - 5.05 (1 H, m), 4.59 (1 H, d, *J* = 15.4 Hz), 4.28 (1 H, d, *J* = 15.4 Hz), 4.04 (2 H, d, *J* = 6.3 Hz), 3.78 - 3.70 (1 H, m), 3.64 - 3.56 (1 H, m), 3.56 - 3.43 (2 H, m), 3.13-3.04 (5 H, m), 2.29 - 2.17 (1 H, m), 2.17 - 2.05 (2 H, m), 1.71 - 1.52 (2 H, m); ^{13}C NMR (D_2O) δ 163.1, 162.8, 158.3, 127.9, 117.8, 114.9, 71.9, 63.5, 54.4, 43.6, 43.3, 33.0, 25.1 (note some peaks coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_2$ 277.1911; Found 277.1910.

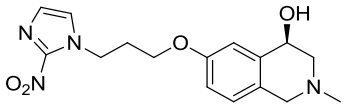
11.5.17 (*R*)-*tert*-Butyl 4-(3-((4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)propyl)piperazine-1-carboxylate (119)



119

The BOC protected amine **110** (0.100 g, 0.250 mmol) was deprotected as described for **118**, and subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (15% methanol 1% triethylamine in dichloromethane) to afford the desired product as a pale orange gummy solid (0.033 g, 44%). ^{1}H NMR ($CDCl_3$) δ 6.96 - 6.89 (2 H, m), 6.78 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.61 (1 H, t, *J* = 3.0 Hz), 3.99 (2 H, td, *J* = 6.1, 2.6 Hz), 3.61 (1 H, d, *J* = 14.7 Hz), 3.26 (1 H, d, *J* = 14.7 Hz), 3.14 - 3.06 (4 H, m), 2.99 (1 H, dd, *J* = 11.8, 2.2 Hz), 2.72 - 2.62 (4 H, m), 2.62 - 2.52 (3 H, m), 2.45 (3 H, s), 1.91 (2 H, quin, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 157.9, 137.4, 127.4, 127.0, 115.3, 114.0, 67.4, 66.4, 60.5, 57.4, 55.6, 53.6, 46.2, 45.6, 26.7; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{28}N_3O_2$ 306.2176; Found 306.2176.

11.5.18 (*R*)-2-Methyl-6-(3-(2-nitro-1*H*-imidazol-1-yl)propoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (126)

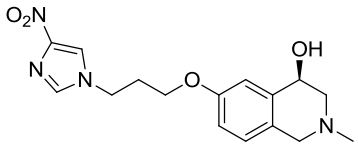


126

The isoquinoline hydrochloride **86** (0.086 g, 0.400 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.035 g, 0.880 mmol), and 1-(3-chloropropyl)-2-nitro-1*H*-imidazole **122** (0.095 g, 0.500 mmol) as described for **87** and then subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a yellow gummy solid (0.014 g,

11%). ^{1}H NMR (DMSO-d_6) δ 7.65 (1 H, d, J = 1.0 Hz), 7.17 (1 H, d, J = 1.0 Hz), 6.98 - 6.90 (2 H, m), 6.71 (1 H, s), 5.22 (1 H, d, J = 6.9 Hz), 4.57 (3 H, t, J = 6.9 Hz), 3.99 - 3.88 (2 H, m), 3.48 (1 H, s), 3.27 (1 H, s), 2.89 - 2.79 (1 H, m), 2.31 (3 H, s), 2.28 - 2.20 (3 H, m); ^{13}C NMR (DMSO-d_6) δ 156.7, 139.5, 127.9, 127.8, 127.1, 126.5, 113.5, 112.4, 65.7, 64.6, 60.5, 57.1, 46.9, 45.7, 29.3 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}N_4O_4$ 333.1557; Found 333.1573. See pg. 242 for details on the synthesis of 1-(3-chloropropyl)-2-nitro-1*H*-imidazole122.

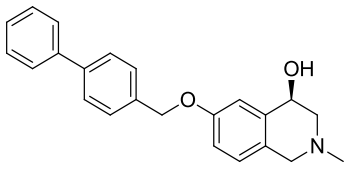
11.5.19 (*R*)-2-Methyl-6-(3-(4-nitro-1*H*-imidazol-1-yl)propoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (127)



127

The isoquinoline hydrochloride **86** (0.151 g, 0.700 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.061 g, 1.5 mmol), 1-(3-chloropropyl)-4-nitro-1*H*-imidazole **125** (0.155 g, 0.820 mmol), and sodium iodide (0.251 g, 1.67 mmol) as described for **87** and then subjected to workup method 2. The resulting brown gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a colourless gummy solid (0.085 g, 37%). ^{1}H NMR (DMSO-d_6) δ 8.46 (1 H, d, J = 1.5 Hz), 7.88 (1 H, d, J = 1.5 Hz), 6.98 (1 H, d, J = 2.6 Hz), 6.95 (1 H, d, J = 8.4 Hz), 6.72 (1 H, dd, J = 8.4, 2.6 Hz), 5.25 (1 H, d, J = 6.9 Hz), 4.63 - 4.52 (1 H, m), 4.25 (2 H, t, J = 7.0 Hz), 3.96 - 3.86 (2 H, m), 3.52 (1 H, d, J = 14.7 Hz), 3.32 - 3.28 (1 H, m), 2.86 (1 H, ddt, J = 11.1, 5.4, 0.6 Hz), 2.35 - 2.31 (3 H, m), 2.30 - 2.18 (3 H, m); ^{13}C NMR (DMSO-d_6) δ 156.7, 147.0, 139.4, 137.5, 127.0, 126.6, 121.7, 113.7, 112.5, 65.7, 64.5, 60.4, 57.0, 45.6, 44.8, 29.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{21}N_4O_4$ 333.1557; Found 333.1560. See pg. 243 for details on the synthesis of 1-(3-chloropropyl)-4-nitro-1*H*-imidazole **125**.

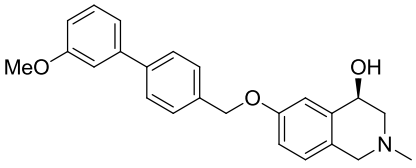
11.5.20 (*R*)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (129)



129

The isoquinoline hydrochloride **86** (0.201 g, 0.930 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.091 g, 2.3 mmol) and 4-(chloromethyl)-1,1'-biphenyl **128** (0.205 g, 1.01 mmol) as described for **87** and then subjected to workup method 1. The resulting brown solid was purified by column chromatography (50:50 ethyl acetate: petroleum spirits 40-60 then 25% methanol in ethyl acetate) to afford the desired product as a white solid (0.173 g, 54%). m.p. 159 - 161°C; ^{1}H NMR ($CDCl_3$) δ 7.63-7.58 (4 H, m), 7.51-7.49 (2 H, m), 7.46-7.42 (2 H, m), 7.37-7.33 (1 H, m), 7.08 (1 H, d, *J* = 2.4 Hz), 6.94 (1 H, d, *J* = 8.4 Hz), 6.91 (1 H, dd, *J* = 8.4, 2.4 Hz), 5.11 (2 H, s), 4.62 (1 H, t, *J* = 2.8 Hz), 3.66 (1 H, d, *J* = 14.4 Hz), 3.30 (1 H, d, *J* = 14.4 Hz), 3.06 (1 H, ddd, *J* = 12.0, 2.8, 1.0 Hz), 2.65 (1 H, dd, *J* = 12.0, 2.8 Hz), 2.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.9, 141.1, 140.9, 137.1, 136.1, 128.9, 128.1, 127.5, 127.3, 126.2, 115.9, 114.5, 70.0, 67.0, 60.4, 57.0, 45.8 (note some signals coincident); Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N 4.05. Found: C, 79.62; H, 6.58; N, 3.91; $[\alpha]_D$ +11.5° (*c* 1.00, CH_2Cl_2). See pg. 240 for details on the synthesis of 4-(chloromethyl)-1,1'-biphenyl **128**.

11.5.21 (*R*)-6-((3'-Methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (130)

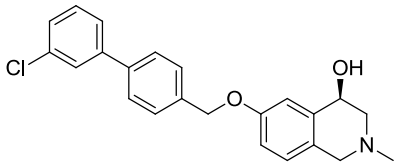


130

Bromophenyl ether **98** (0.103 g, 0.300 mmol) was combined with 3-methoxyphenylboronic acid (0.037 g, 0.42 mmol), potassium carbonate (0.169 g,

1.20 mmol), dioxane (0.8 mL), and water (0.8 mL). This mixture was degassed by bubbling with nitrogen gas for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.0027 g, 0.0023 mmol) was added and the reaction mixture was heated to 160°C for 13 minutes in a microwave reactor, and subjected to workup method 3. The resulting orange gummy solid was purified by column chromatography (0-10% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.021 g, 19%). ^{1}H NMR ($CDCl_3$) δ 7.62-7.59 (2 H, m), 7.50 (2 H, d, *J* = 8.0 Hz), 7.36 (1 H, t, *J* = 8.0 Hz), 7.19-7.17 (1 H, m), 7.13-7.12 (1 H, m), 7.06 (1 H, d, *J* = 2.5 Hz), 6.95-6.88 (3 H, m), 5.11 (2 H, s), 4.57 (1 H, t, *J* = 3.0 Hz), 3.87 (3 H, s), 3.54 (1 H, d, *J* = 14.6 Hz), 3.19 (1 H, d, *J* = 14.6 Hz), 2.95 (1 H, ddd, *J* = 11.7, 3.0, 1.2 Hz), 2.54 (1 H, dd, *J* = 11.7, 3.0 Hz), 2.41 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 160.1, 157.7, 142.5, 141.0, 137.5, 136.4, 129.9, 128.1, 127.6, 127.5, 127.4, 119.8, 115.7, 114.4, 113.1, 112.9, 70.0, 67.5, 60.5, 57.3, 55.5, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{26}NO_3$ 376.1907; Found 376.1898.

11.5.22 (*R*)-6-((3'-Chloro-[1,1'-biphenyl]-4-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (131)

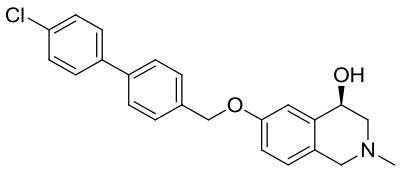


131

Bromophenyl ether **98** (0.102 g, 0.290 mmol) was treated with 3-chlorophenylboronic acid (0.054 g, 0.34 mmol), potassium carbonate (0.160 g, 1.15 mmol), dioxane (4 mL), and water (2 mL). The mixture was degassed by bubbling with nitrogen for 15 minutes. Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.0035 g, 0.0043 mmol) was added and the reaction mixture heated at reflux for 6 hrs, then subjected to workup method 3. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a pale yellow solid (0.093 g, 84 %). m.p. 108.5 - 110.1°C; ^{1}H NMR ($CDCl_3$) δ 7.61 - 7.56 (3 H, m), 7.53 - 7.49 (2 H, m), 7.46 (1 H, dt, *J* = 7.5, 1.5 Hz), 7.40 - 7.34 (1 H,

m), 7.34 - 7.30 (1 H, m), 7.05 (1 H, d, *J* = 2.4 Hz), 6.93 (1 H, d, *J* = 8.6 Hz), 6.89 (1 H, dd, *J* = 8.6, 2.4 Hz), 5.11 (2 H, s), 4.59 - 4.54 (1 H, m), 3.51 (1 H, d, *J* = 14.7 Hz), 3.18 (1 H, d, *J* = 14.7 Hz), 2.99 - 2.89 (1 H, m), 2.53 (1 H, dd, *J* = 11.7, 3.0 Hz), 2.41 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.6, 142.8, 139.6, 137.5, 136.9, 134.8, 130.2, 128.2, 127.6, 127.5, 127.5, 127.4, 125.4, 115.7, 114.4, 69.8, 67.5, 60.5, 57.3, 46.2 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{23}ClNO_2$ 380.1412; Found 380.1412.

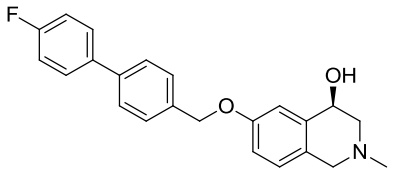
11.5.23 (*R*)-6-((4'-Chloro-[1,1'-biphenyl]-4-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (132)



132

Bromophenyl ether **98** (0.103 g, 0.300 mmol) was combined with 4-chlorophenylboronic acid (0.054 g, 0.340 mmol), potassium carbonate (0.170 g, 1.23 mmol), dioxane (1.0 mL), and water (1.0 mL). This mixture was degassed by bubbling with nitrogen gas for 10 minutes. [1,1′-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (0.0031 g, 0.0043 mmol) was added and the reaction mixture was heated to 140°C for 30 minutes in a microwave reactor, and subjected to workup method 3. The resulting orange gummy solid was purified by column chromatography (0-10% methanol in dichloromethane) to afford the desired product as an orange solid (0.072 g, 64%). m.p. 138 - 146°C; ^{1}H NMR ($CDCl_3$) δ 7.58 - 7.55 (2 H, m), 7.53 - 7.49 (4 H, m), 7.42 - 7.40 (2 H, m), 7.05 (1 H, d, *J* = 2.6 Hz), 6.95 (1 H, d, *J* = 8.4 Hz), 6.89 (1 H, dd, *J* = 8.4, 2.6 Hz), 5.11 (2 H, s), 4.57 (1 H, br. s.), 3.58 (1 H, d, *J* = 14.7 Hz), 3.21 (1 H, d, *J* = 14.7 Hz), 2.95 (1 H, ddd, *J* = 11.8, 3.0, 1.0 Hz), 2.55 (1 H, dd, *J* = 11.8, 3.0 Hz), 2.42 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.6, 139.8, 139.4, 137.6, 136.6, 133.7, 129.1, 128.5, 128.2, 127.6, 127.5, 127.3, 115.7, 114.4, 69.9, 67.5, 60.5, 57.3, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{23}NO_2Cl$ 380.1412; Found 380.1401.

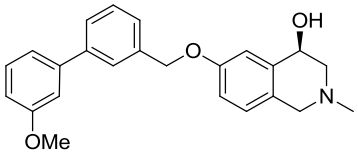
11.5.24 (*R*)-6-((4'-fluoro-[1,1'-biphenyl]-4-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (133)



133

Bromophenyl ether **98** (0.098 g, 0.29 mmol) was treated with 4-fluorophenylboronic acid (0.049 g, 0.34 mmol), potassium carbonate (0.158 g, 1.15 mmol), and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.0040 g, 0.0049 mmol) as described for **131**136, and subjected to workup method 3. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a brown solid (0.079 g, 75 %). m.p. 117.9 - 120.9 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 - 7.45 (6 H, m), 7.17 - 7.05 (3 H, m), 6.95 - 6.86 (2 H, m), 5.15 - 5.01 (2 H, m), 4.63 (1 H, t, *J* = 2.8 Hz), 3.62 (1 H, d, *J* = 14.6 Hz), 3.31 (1 H, d, *J* = 14.6 Hz), 3.08 (1 H, dd, *J* = 11.8, 2.1 Hz), 2.67 (1 H, dd, *J* = 11.8, 2.8 Hz), 2.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 162.6 (d, $^{1}J_{CF}$ = 245.1 Hz), 157.7, 140.0, 137.0, 136.9 (d, $^{4}J_{CF}$ = 3.1 Hz), 136.0, 128.7 (d, $^{3}J_{CF}$ = 8.0 Hz), 128.0, 127.4, 127.2, 126.1, 115.73, 115.67 (d, $^{2}J_{CF}$ = 21.4 Hz), 114.3, 69.8, 66.7, 60.2, 56.7, 45.7; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{23}FNO_2$ 364.1707; Found 364.1707; $[\alpha]_D$ +7.9° (*c* 0.98, CH_2Cl_2).

11.5.25 (*R*)-6-((3'-Methoxy-[1,1'-biphenyl]-3-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (136)

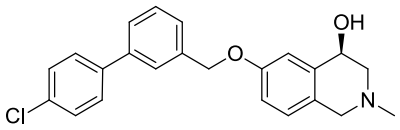


136

Bromophenyl ether **99** (0.105 g, 0.300 mmol) was treated with 3-methoxyphenylboronic acid (0.054 g, 0.36 mmol), potassium carbonate (0.173 g, 1.25 mmol) and, bis(diphenylphosphino)ferrocene]-dichloropalladium (II) (0.0038 g,

0.0047 mmol) as described for **131**. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.055 g, 49%). ^{1}H NMR ($CDCl_3$) δ 7.66 (1 H, s), 7.55 (1 H, dt, *J* = 7.2, 2.0 Hz), 7.46 (1 H, d, *J* = 7.2 Hz), 7.44 - 7.40 (1 H, m), 7.36 (1 H, t, *J* = 8.1 Hz), 7.21 - 7.17 (1 H, m), 7.15 - 7.11 (1 H, m), 7.07 (1 H, d, *J* = 2.0 Hz), 6.93 - 6.84 (3 H, m), 5.13 (2 H, s), 4.55 (1 H, t, *J* = 2.8 Hz), 3.87 (3 H, s), 3.39 (1 H, d, *J* = 14.5 Hz), 3.12 (1 H, d, *J* = 14.5 Hz), 2.95 (1 H, dd, *J* = 11.8, 2.8 Hz), 2.50 (1 H, dd, *J* = 11.8, 2.8 Hz), 2.37 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 160.0, 157.9, 142.4, 141.5, 137.4, 136.8, 129.8, 129.0, 127.3, 126.9, 126.6, 126.3, 119.7, 115.9, 114.4, 112.9, 112.9, 70.1, 66.6, 60.1, 56.7, 55.3, 45.4 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{27}NO_3$ 376.1907; Found 376.1908.

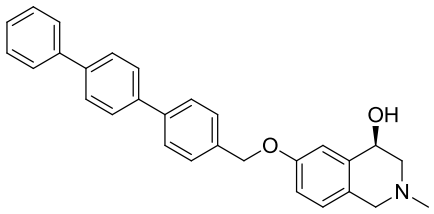
11.5.26 (*R*)-6-((4'-Chloro-[1,1'-biphenyl]-3-yl)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (138)



138

Bromophenyl ether **99** (0.099 g, 0.28 mmol) was combined with 4-chlorophenylboronic acid (0.055 g, 0.35 mmol), potassium carbonate (0.159 g, 1.15 mmol, and bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.0036 g, 0.0044 mmol) as described for **131**, and subjected to workup method 3. The resulting orange gummy solid was purified by column chromatography (0-10% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.070 g, 66%). ^{1}H NMR ($CDCl_3$) δ 7.62 (1 H, s), 7.55 - 7.38 (7 H, m), 7.06 (1 H, d, *J* = 2.1 Hz), 6.95 - 6.87 (2 H, m), 5.12 (2 H, s), 4.56 (1 H, t, *J* = 2.9 Hz), 3.51 (1 H, d, *J* = 14.5 Hz), 3.18 (1 H, d, *J* = 14.5 Hz), 2.95 (1 H, ddd, *J* = 11.8, 2.9, 1.0 Hz), 2.54 (1 H, dd, *J* = 11.8, 2.9 Hz), 2.40 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.6, 140.5, 139.5, 137.9, 137.5, 133.7, 129.3, 129.1, 128.6, 127.6, 127.4, 126.8, 126.7, 126.2, 115.6, 114.4, 70.1, 67.4, 60.5, 57.2, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{23}NO_2Cl$ 380.1412; Found 380.140.

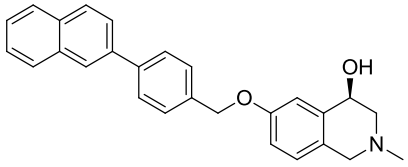
11.5.27 (*R*)-6-([1,1':4',1''-Terphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (140)



140

Bromophenyl ether **98** (0.100 g, 0.290 mmol) was combined with 4-biphenylboronic acid (0.071 g, 0.35 mmol), potassium carbonate (0.164 g, 1.19 mmol), triphenylphosphine (0.0057 g, 0.020 mmol), dioxane (4.0 mL), and water (4.0 mL). This mixture was degassed by bubbling with nitrogen for 15 minutes. Palladium acetate (0.005 g, 0.02 mmol) was added and the reaction mixture heated to reflux for 6 hrs, and subjected to workup method 3. The resulting cream coloured solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a cream coloured solid (0.45 g, 37%). m.p.182 - 184.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 - 7.62 (8 H, m), 7.55 - 7.50 (2 H, m), 7.49 - 7.43 (2 H, m), 7.41 - 7.37 (1 H, m), 7.07 (1 H, d, *J* = 2.6 Hz), 6.98 (1 H, d, *J* = 8.4 Hz), 6.91 (1 H, dd, *J* = 8.4, 2.6 Hz), 5.12 (2 H, dd, *J* = 1.6, 0.5 Hz), 4.59 (1 H, br. s.), 3.70 (1 H, d, *J* = 14.5 Hz), 3.26 (1 H, d, *J* = 14.5 Hz), 2.96 (1 H, ddd, *J* = 11.8, 3.3, 1.2 Hz), 2.58 (1 H, dd, *J* = 11.8, 2.6 Hz), 2.46 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.7, 140.8, 140.6, 140.4, 139.8, 137.6, 136.3, 129.0, 128.2, 127.7, 127.6, 127.52, 127.50, 127.47, 127.4, 127.20 115.7, 114.4, 70.0, 67.6, 60.5, 57.5, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{28}NO_2$ 422.2120; Found 422.2115.

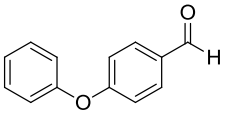
11.5.28 (*R*)-2-Methyl-6-((4-(naphthalen-2-yl)benzyl)oxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (142)



142

Bromophenyl ether **98** (0.100 g, 0.290 mmol) was treated with 2-napthylboronic acid (0.060 g, 0.35 mmol), potassium carbonate (0.160 g, 1.16 mmol), triphenylphosphine (0.0056 g, 0.020 mmol), and palladium acetate (0.0053 g, 0.020 mmol) as described for **140**, and subjected to workup method 3. The resulting orange solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a white solid (0.084 g, 73%). m.p. 160.5 - 163 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 - 8.02 (1 H, m), 7.95 - 7.83 (3 H, m), 7.78 - 7.72 (3 H, m), 7.58 - 7.45 (4 H, m), 7.08 (1 H, d, *J* = 2.3 Hz), 6.97 - 6.89 (2 H, m), 5.19 - 5.08 (2 H, m), 4.58 (1 H, t, *J* = 3.0 Hz), 3.56 (1 H, d, *J* = 14.7 Hz), 3.21 (1 H, d, *J* = 14.7 Hz), 2.96 (1 H, ddd, *J* = 11.8, 3.1, 1.3 Hz), 2.55 (1 H, dd, *J* = 11.8, 2.9 Hz), 2.43 - 2.38 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 157.7, 141.0, 138.3, 137.5, 136.3, 133.8, 132.8, 128.6, 128.4, 128.2, 127.79, 127.76, 127.5, 127.4, 126.5, 126.1, 125.9, 125.6, 115.7, 114.4, 70.0, 67.5, 60.5, 57.3, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{26}NO_2$ 396.1964; Found 396.1959.

11.5.29 4-Phenoxybenzaldehyde (145a)

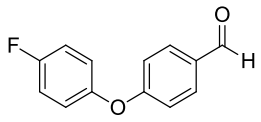


145a

4-Hydroxybenzaldehyde (0.501 g, 4.10 mmol), phenylboronic acid (0.447 g, 3.67 mmol), copper(II) acetate monohydrate (0.732 g, 3.67 mmol), and triethylamine (2.60 mL, 18.4 mol) were dissolved in anhydrous dichloromethane. 4Å molecular sieves were added and the reaction mixture stirred at room temperature open to the air for 24 hrs. The reaction mixture was filtered and concentrated under reduced

pressure. The resulting black gummy solid was purified by column chromatography (10% ethyl acetate in petroleum spirit 40-60) to afford the desired product as a pale yellow gummy solid (0.194 g, 27%). ^{1}H NMR ($CDCl_3$) δ 9.93 (1 H, s), 7.89 - 7.82 (2 H, m), 7.46 - 7.40 (2 H, m), 7.26 - 7.21 (1 H, m), 7.12 - 7.05 (4 H, m).

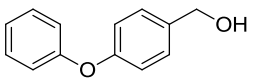
11.5.30 4-(4-Fluorophenoxy)benzaldehyde (145b)



145b

4-Hydroxybenzaldehyde (0.500 g, 4.10 mmol) was treated with 4-fluorophenylboronic acid (0.515 g, 4.10 mmol), copper(II) acetate monohydrate (0.820 g, 4.10 mmol), and triethylamine (2.90 mL, 20.5 mol) as described for **145a**. The resulting green gummy solid was purified by column chromatography (10% ethyl acetate in petroleum spirit 40-60) to afford the desired product as a colourless gummy solid which slowly crystallised (0.161 g, 18%). ^{1}H NMR ($CDCl_3$) δ 9.93 (1 H, s), 7.89 - 7.82 (2 H, m), 7.16 - 7.01 (6 H, m).

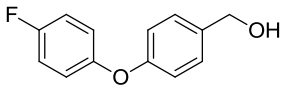
11.5.31 (4-Phenoxyphenyl)methanol (146a)



146a

Aldehyde **145a** (0.194 g, 0.920 mmol) was dissolved in methanol. Sodium borohydride (0.040 g, 1.1 mmol) was added and the reaction mixture stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, diluted with water, and extracted three times with ethyl acetate. The ethyl acetate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting colourless oil (0.180 g, 92%) was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.38 - 7.31 (4 H, m), 7.15 - 7.09 (1 H, m), 7.05 - 6.99 (4 H, m), 4.68 (2 H, s).

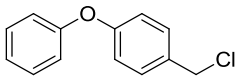
11.5.32 (4-(4-Fluorophenoxy)phenyl)methanol (146b)



146b

Aldehyde **145b** (0.160 g, 0.740 mmol) was treated with sodium borohydride (0.029 g, 0.77 mmol) as described for **146a**. The resulting colourless oil (0.180 g, >95%) was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.37 - 7.31 (2 H, m), 7.07 - 6.94 (6 H, m), 4.67 (2 H, s).

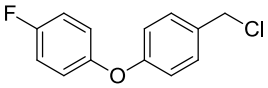
11.5.33 1-(Chloromethyl)-4-phenoxybenzene (147a)



147a

Alcohol **146a** (0.180 g, 0.850 mmol) was treated with methanesulfonyl chloride (79 μL, 1.0 mmol), and triethylamine (181 μL, 1.30 mmol) as described for **243**. The resulting colourless oil (0.190 g, >95%) was determined to be the alkyl chloride and was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.39 - 7.33 (4 H, m), 7.17 - 7.10 (1 H, m), 7.06 - 6.96 (4 H, m), 4.60 (2 H, s).

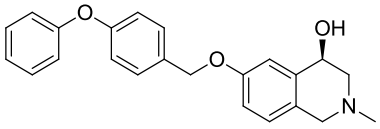
11.5.34 1-(Chloromethyl)-4-(4-fluorophenoxy)benzene (147b)



147b

Alcohol **146b** (0.166 g, 0.760 mmol) was treated with methanesulfonyl chloride (70 μL, 0.91 mmol), and triethylamine (159 μL, 1.14 mmol) as described for **243**. The resulting pale yellow oil (0.152 g, 85%) was determined to be the alkyl chloride and was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.36 - 7.32 (2 H, m), 7.07 - 6.96 (4 H, m), 6.96 - 6.90 (2 H, m), 4.58 (2 H, s).

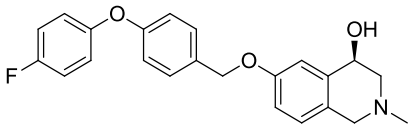
11.5.35 (*R*)-2-Methyl-6-((4-phenoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (148)



148

The isoquinoline hydrochloride **86** (0.170 g, 0.790 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.071 g, 1.7 mmol), diphenyl ether **147a** (0.190 g, 0.870 mmol), and sodium iodide (0.244 g, 1.63 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a pale pink gummy solid (0.106 g, 37%). ^{1}H NMR ($CDCl_3$) δ 7.44 - 7.30 (4 H, m), 7.19 - 7.09 (1 H, m), 7.06 - 6.99 (4 H, m), 6.98 - 6.94 (1 H, m), 6.94 - 6.91 (1 H, m), 6.90 - 6.87 (1 H, m), 5.08 - 4.99 (2 H, m), 4.60 - 4.53 (1 H, m), 3.48 (1 H, dd, *J* = 14.6, 0.4 Hz), 3.18 (1 H, d, *J* = 14.6 Hz), 3.00 - 2.92 (1 H, m), 2.50 - 2.56 (1 H, m), 2.41 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.7, 157.3, 157.2, 137.5, 131.9, 129.9, 129.4, 127.6, 127.4, 123.5, 119.1, 119.0, 115.7, 114.3, 69.8, 67.5, 60.5, 57.2, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{24}NO_3$ 362.1751; Found 362.1752.

11.5.36 (*R*)-6-((4-(4-Fluorophenoxy)benzyl)oxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (149)

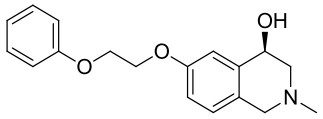


149

The isoquinoline hydrochloride **86** (0.114 g, 0.530 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.048 g, 1.2 mmol), diphenyl ether **147b** (0.137 g, 0.580 mmol), and sodium iodide (0.160 g, 1.06 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.133 g, 66%). ^{1}H NMR ($CDCl_3$) δ

7.42 - 7.37 (2 H, m), 7.07 - 6.96 (7 H, m), 6.89 (2 H, t, J = 1.6 Hz), 5.03 (2 H, s), 4.60 - 4.53 (1 H, m), 3.41 (1 H, dt, J = 14.6, 0.6 Hz), 3.19 - 3.12 (1 H, m), 2.98 (1 H, ddd, J = 11.8, 3.0, 1.0 Hz), 2.53 (1 H, dd, J = 11.8, 3.1 Hz), 2.43 - 2.37 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 159.0 (d, $^{1}J_{CF}$ = 240.6 Hz), 157.7, 157.6, 152.8 (d, $^{4}J_{CF}$ = 2.6 Hz), 137.4, 131.8, 129.4, 127.6, 127.3, 120.8 (d, $^{3}J_{CF}$ = 8.1 Hz), 118.4, 116.4 (d, $^{2}J_{CF}$ = 23.0 Hz), 115.7, 114.3, 69.8, 67.3, 60.5, 57.2, 46.1; HRMS *m/z*: [M+H]+ Calcd for $C_{23}H_{23}FNO_3$ 380.1656; Found 380.1659.

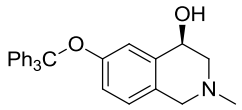
11.5.37 (*R*)-2-Methyl-6-(2-phenoxyethoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (150)



150

The isoquinoline hydrochloride **86** (0.495 g, 2.30 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.230 g, 5.80 mmol) and 2-phenoxyethyl tosylate **245** (0.753 g, 2.58 mmol) as described for **87** and then subjected to workup method 1. The resulting light brown solid was purified by column chromatography (10% methanol in ethyl acetate) to afford the desired product as an off-white solid (0.444 g, 65%) which was further purified by recrystallisation (ethyl acetate: petroleum spirits 60-80) to afford a white solid (0.352 g, 51%). m.p. 123 - 125°C; ^{1}H NMR ($CDCl_3$) δ 7.32 - 7.26 (2 H, m), 7.01 (1 H, d, J = 2.4 Hz), 6.99 - 6.94 (3 H, m), 6.91 (1 H, d, J = 8.4 Hz), 6.86 (1 H, dd, J = 8.4, 2.4 Hz), 4.57 (1 H, t, J = 2.8 Hz), 4.33 (4 H, s), 3.44 (1 H, d, J = 14.6 Hz), 3.18 (1 H, d, J = 14.6), 2.96 (1 H, dd, J = 11.8, 2.8 Hz), 2.54 (1 H, dd, J = 11.8, 2.8 Hz), 2.40 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 158.8, 157.6, 137.4, 129.6, 127.6, 127.2, 121.3, 115.7, 114.9, 114.2, 67.3, 66.9, 66.6, 60.5, 57.1, 46.1; Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N 4.68. Found: C, 72.12; H, 7.01; N, 4.66. See pg. 244 for details on the synthesis of 2-phenoxyethyl tosylate **245**.

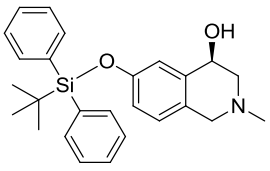
11.5.38 (*R*)-2-Methyl-6-(trityloxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (151)



151

The isoquinoline hydrochloride **86** (0.286 g, 1.33 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.117 g, 2.90 mmol) and trityl chloride (0.408 g, 1.46 mmol) as described for **87** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol, 1% triethylamine in ethyl acetate) to afford the desired product as a colourless gummy solid (0.242 g, 46%). This was then recrystallised from petroleum spirits 60-80 to afford a white solid (0.111 g, 21%). m.p. 84 - 89 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 - 7.43 (6 H, m), 7.30 - 7.18 (9 H, m), 6.73 (1 H, br.s), 6.54 - 6.53 (2 H, m), 4.32 (1 H, br. s.), 3.27 (1 H, d, *J* = 14.8 Hz), 3.01 (1 H, d, *J* = 14.8 Hz), 2.81 (1 H, ddd, *J* = 11.8, 3.1, 1.0 Hz), 2.40 (1 H, dd, *J* = 11.8, 2.9 Hz), 2.33 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 155.0, 144.3, 136.4, 129.1, 127.9, 127.7, 127.3, 126.3, 121.3, 120.6, 90.5, 67.1, 60.4, 57.3, 46.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{28}NO_2$ 422.2115; Found 422.2112.

11.5.39 (*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (152)

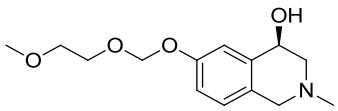


152

The isoquinoline hydrochloride **86** (1.01 g, 4.67 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.410 g, 10.2 mmol) and *tert*-butylchlorodiphenylsilane (1.33 mL, 5.10 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired

product as a pale yellow solid (1.56 g, 80%). m.p. 115 - 120°C; ^{1}H NMR ($CDCl_3$) δ 7.76 - 7.65 (4 H, m), 7.46 - 7.30 (6 H, m), 6.89 (1 H, d, *J* = 2.1 Hz), 6.59 - 6.51 (2 H, m), 4.43 - 4.34 (1 H, m), 3.19 (1 H, d, *J* = 14.7 Hz), 3.00 (1 H, d, *J* = 14.7 Hz), 2.88 - 2.84 (1 H, m), 2.41 (1 H, dd, *J* = 12.0, 2.8 Hz), 2.30 (3 H, s), 1.07 - 1.15 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 154.3, 137.2, 135.7, 135.7, 130.0, 127.9, 127.4, 127.1, 120.0, 119.4, 67.1, 60.4, 57.1, 46.2, 26.7, 19.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{32}SiNO_2$ 418.2197; Found 418.2198.

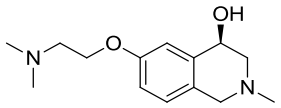
11.5.40 (*R*)-6-((2-Methoxyethoxy)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (153)



153

The isoquinoline hydrochloride **86** (1.00 g, 4.64 mmol) as treated with sodium hydride (60% dispersion in mineral oil, 0.410 g, 10.3 mmol) and 2-methoxyethoxymethyl chloride (585 μL, 5.12 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a brown oil (0.756 g, 61%). ^{1}H NMR ($CDCl_3$) δ 7.13 (1 H, d, *J* = 2.5 Hz), 6.95 (1 H, dd, *J* = 8.5, 2.5 Hz), 6.90 (1 H, d, *J* = 8.5 Hz), 5.30 - 5.21 (2 H, m), 4.62 - 4.55 (1 H, m), 3.85 - 3.79 (2 H, m), 3.59 - 3.54 (2 H, m), 3.53 - 3.46 (1 H, m), 3.40 - 3.34 (3 H, m), 3.23 (1 H, d, *J* = 14.7 Hz), 3.06 - 2.97 (1 H, m), 2.64 - 2.55 (1 H, m), 2.44 (3 H, s); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{22}NO_4$ 268.1543; Found 268.1546.

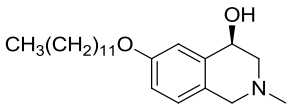
11.5.41 (*R*)-6-(2-(Dimethylamino)ethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (154)



154

The isoquinoline hydrochloride **86** (0.202 g, 0.93 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.119 g, 2.98 mmol) and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0.149 g, 1.02 mmol) as described for **112** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a yellow gummy solid (0.120 g, 52%). ^{1}H NMR ($CDCl_3$) δ 6.95 (1 H, d, *J* = 2.5 Hz), 6.89 (1 H, d, *J* = 8.3 Hz), 6.82 (1 H, dd, *J* = 8.3, 2.5 Hz), 4.55 (1 H, t, *J* = 3.2 Hz), 4.08 (2 H, t, *J* = 5.6 Hz), 3.46 (1 H, d, *J* = 14.6 Hz), 3.17 (1 H, d, *J* = 14.6 Hz), 2.93 (1 H, dd, *J* = 11.6, 3.0 Hz), 2.77 (2 H, t, *J* = 5.6 Hz), 2.53 (1 H, dd, *J* = 11.6, 3.0 Hz), 2.39 (3 H, s), 2.38 - 2.35 (6 H, m); ^{13}C NMR ($CDCl_3$) δ 157.7, 137.4, 127.4, 127.1, 115.5, 113.9, 67.4, 66.0, 60.5, 58.4, 57.2, 46.1, 45.9; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{23}N_2O_2$ 251.1754; Found 271.1756.

11.5.42 (*R*)-6-(Dodecyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (155)

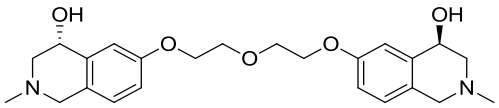


155

The isoquinoline hydrochloride **86** (0.200 g, 0.930 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.082 g, 2.05 mmol) and 1-bromododecane (212 μL, 0.880 mmol) as described for **87** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a brown solid (0.215 g, 74%) m.p. 52.5 - 53.9°C; ^{1}H NMR ($CDCl_3$) δ 6.94 (1 H, d, *J* = 2.6 Hz), 6.91 (1 H,

d, *J* = 8.4 Hz), 6.80 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.58 - 4.54 (1 H, m), 3.98 - 3.90 (2 H, m), 3.55 (1 H, d, *J* = 14.5 Hz), 3.20 (1 H, d, *J* = 14.5 Hz), 2.96 (1 H, ddd, *J* = 11.5, 3.1, 1.3 Hz), 2.57 - 2.51 (1 H, m), 2.42 (3 H, s), 1.82 - 1.71 (2 H, m), 1.50 - 1.39 (2 H, m), 1.31 - 1.23 (16 H, m), 0.93 - 0.80 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 158.0, 137.3, 127.5, 126.7, 115.4, 113.8, 68.3, 67.4, 60.6, 57.1, 46.2, 32.1, 29.8, 29.8, 29.7, 29.7, 29.54, 29.49, 29.4, 26.2, 22.8, 14.3; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{38}NO_2$ 348.2897; Found 348.2902.

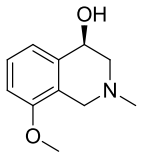
11.5.43 (4*R*,4'*R*)-6,6'-((Oxybis(ethane-2,1-diyl))bis(oxy))bis(2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol) (157)



157

Isoquinoline hydrochloride **86** (0.202 g, 0.940 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.076 g, 1.9 mmol) in anhydrous dimethylformamide (20 mL), and the reaction mixture stirred at room temperature for 30 minutes. Diethylene glycol bis(*p*-toluenesulfonate) (0.182 g, 0.440 mmol) was added and the reaction mixture stirred for a further 2 weeks at room temperature. The reaction was quenched with methanol (2 mL), and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (10% methanol in dichloromethane) to afford the desired product as a white solid (0.090 g, 48%). m.p. 111 - 112.8 °C; ^{1}H NMR ($CDCl_3$) δ 6.89 (2 H, d, *J* = 2.5 Hz), 6.87 - 6.84 (2 H, m), 6.82 - 6.78 (2 H, m), 4.52 (2 H, t, *J* = 3.1 Hz), 4.20 - 4.09 (4 H, m), 3.98 - 3.88 (4 H, m), 3.40 (2 H, d, *J* = 14.5 Hz), 3.17 (2 H, d, *J* = 14.5 Hz), 2.91 (2 H, ddd, *J* = 11.8, 3.1, 0.8 Hz), 2.54 (2 H, dd, *J* = 11.8, 3.1 Hz), 2.39 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 157.7, 137.3, 127.4, 126.9, 115.4, 114.3, 70.1, 67.8, 67.0, 60.6, 57.2, 46.0; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O_5$ 429.2384; Found 429.2387.

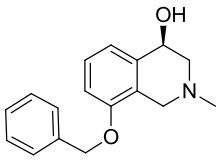
11.5.44 (*R*)-8-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (158)



158

Isoquinoline hydrochloride **90** (0.200 g, 0.930 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.085 g, 2.1 mmol) and iodomethane (64 µL, 1.0 mmol) as described for **87**, and subjected to workup method 2. The resulting yellow gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid which slowly crystallised (0.051 g, 30%). m.p. 115.5 - 117.6 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (1 H, t, *J* = 7.9 Hz), 7.05 (1 H, d, *J* = 7.4 Hz), 6.77 (1 H, dd, *J* = 8.1, 0.7 Hz), 4.62 (1 H, t, *J* = 2.9 Hz), 3.87 (1 H, d, *J* = 16.0 Hz), 3.82 (3 H, s), 3.16 (1 H, d, *J* = 16.0 Hz), 3.01 (1 H, ddd, *J* = 11.7, 2.9, 1.2 Hz), 2.61 (1 H, dd, *J* = 11.7, 2.9 Hz), 2.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 155.6, 137.1, 127.8, 122.5, 121.4, 109.1, 66.8, 59.7, 55.5, 52.7, 45.9; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{16}NO_2$194.1176; Found 194.1175.

11.5.45 (*R*)-8-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (159)

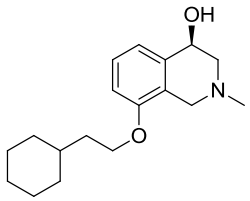


159

Isoquinoline **90** hydrochloride (0.202 g, 0.940 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.084 g, 2.1 mmol) and benzyl bromide (122 µL, 1.02 mmol) as described for **87**, and subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a pale yellow gummy solid (0.171 g, 68%). ^{1}H NMR ($CDCl_3$) δ 7.40 - 7.39 (4 H, m), 7.36 - 7.31 (1 H, m),

7.20 (1 H, t, *J* = 7.9 Hz), 7.07 (1 H, d, *J* = 7.4 Hz), 6.80 (1 H, dd, *J* = 8.1, 0.7 Hz), 5.05 (2 H, s), 4.62 (1 H, t, *J* = 3.0 Hz), 3.86 (1 H, d, *J* = 16.2 Hz), 3.18 (1 H, d, *J* = 16.2 Hz), 2.98 (1 H, ddd, *J* = 11.7, 3.0, 1.1 Hz), 2.59 (1 H, dd, *J* = 11.7, 3.0 Hz), 2.49 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 154.7, 137.6, 137.2, 128.7, 128.0, 127.5, 127.3, 123.7, 121.7, 110.3, 69.9, 67.0, 59.9, 52.9, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1489; Found 270.1489.

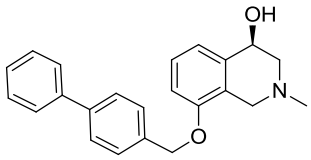
11.5.46 (*R*)-8-(2-Cyclohexylethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (160)



160

Isoquinoline hydrochloride **90** (0.198 g, 0.920 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.084 g, 2.1 mmol) and 2-cyclohexylethyl tosylate **107** (0.291 g, 1.03 mmol) as described for **87**, and subjected to workup method 1. The resulting yellow solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a white solid (0.131 g, 50%). m.p. 85.5 - 86.8 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 - 7.16 (1 H, m), 7.02 (1 H, d, *J* = 7.8 Hz), 6.74 (1 H, dd, *J* = 7.8, 0.7 Hz), 4.61 (1 H, t, *J* = 2.8 Hz), 3.99 (2 H, t, *J* = 6.7 Hz), 3.84 (1 H, d, *J* = 16.2 Hz), 3.13 (1 H, d, *J* = 16.2 Hz), 2.99 (1 H, ddd, *J* = 11.7, 2.8, 1.2 Hz), 2.59 (1 H, dd, *J* = 11.7, 2.8 Hz), 2.54 - 2.49 (3 H, m), 1.81- 1.60 (7 H, m), 1.48 (1 H, s), 1.33 - 1.10 (3 H, m), 1.05 - 0. 91 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 155.1, 137.3, 127.5, 123.3, 121.1, 109.8, 67.1, 66.2, 59.9, 52.9, 46.1, 36.7, 34.9, 33.5, 26.7, 26.4; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2$ 290.2115; Found 290.2114. See pg. 238 for details on the synthesis of 2-cyclohexylethyl tosylate **107**.

11.5.47 (*R*)-8-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (161)

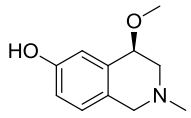


161

Isoquinoline hydrochloride **90** (0.201 m, 0.930 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.084 g, 2.1 mmol) and 4-(chloromethyl)-1,1'-biphenyl **128** (0.207 g, 1.02 mmol) as described for **87**, and subjected to workup method 1. The resulting brown solid was purified by column chromatography (2% methanol in dichloromethane) to afford the desired product as a white solid (0.145 g, 45%). m.p. 177 - 179 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 - 7.58 (4 H, m), 7.52 - 7.43 (4 H, m), 7.40 - 7.34 (1 H, m), 7.26 - 7.20 (1 H, m), 7.08 (1 H, d, *J* = 7.8 Hz), 6.86 (1 H, dd, *J* = 7.8, 0.7 Hz), 5.14 (2 H, s), 4.63 (1 H, t, *J* = 2.8 Hz), 4.00 (1 H, d, *J* = 16.2 Hz), 3.23 (1 H, d, *J* = 16.2 Hz), 2.99 (1 H, ddd, *J* = 11.6, 2.8, 1.0 Hz), 2.60 (1 H, dd, *J* = 11.6, 2.8 Hz), 2.53 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 154.8, 141.1, 140.9, 137.8, 136.2, 129.0, 127.8, 127.6, 127.5, 127.4, 127.3, 124.1, 121.7, 110.3, 69.8, 67.3, 59.9, 53.1, 46.3; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{24}NO_2$ 346.1802; Found 346.1800.

11.6 Modification of the benzylic alcohol

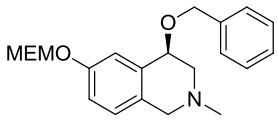
11.6.1 (*R*)-4-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (162)



162

Alcohol **152** (0.200 g, 0.480 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.105 g, 2.63 mmol) in anhydrous tetrahydrofuran (5 mL) and the reaction mixture stirred at room temperature for 30 minutes. Iodomethane (33 μL, 0.53 mmol) was added and the reaction mixture stirred for a further 2 days at room temperature. The reaction was quenched with methanol (2 mL), and subjected to workup method 2. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford an orange gummy solid (0.046 g, 50%) which was determined to be the deprotected phenol of the desired product. ^{1}H NMR ($CDCl_3$) δ 6.86 (1 H, d, *J* = 8.2 Hz), 6.79 (1 H, d, *J* = 2.6 Hz), 6.65 (1 H, dd, *J* = 8.2, 2.6 Hz), 4.33 (1 H, t, *J* = 4.9 Hz), 3.61 (1 H, d, *J* = 14.4 Hz), 3.49 - 3.40 (4 H, m), 2.87 - 2.73 (2 H, m), 2.47 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 155.0, 134.9, 127.4, 126.4, 115.8, 115.2, 75.6, 57.3, 56.9, 56.5, 46.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{16}NO_2$ 194.1181.; Found 194.1175.

11.6.2 (*R*)-4-(Benzyloxy)-6-((2-methoxyethoxy)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (163)

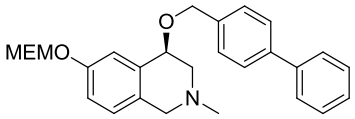


163

The MEM protected phenol **153** (0.152 g, 0.560 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.045 g, 1.1 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes.

Benzyl bromide (74 μL, 0.62 mmol) was added and the reaction mixture stirred at room temperature for 1.5 hrs, quenched with methanol (2 mL), then subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (2% methanol in dichloromethane) to afford the desired product as a yellow gummy solid (0.072 g, 36%). ^{1}H NMR (DMSO-d_6) δ 7.43 - 7.33 (4 H, m), 7.32 - 7.25 (1 H, m), 7.06 - 6.98 (2 H, m), 6.91 - 6.86 (1 H, m), 5.22 - 5.16 (2 H, m), 4.69 - 4.62 (2 H, m), 4.59 - 4.51 (1 H, m), 3.72 - 3.67 (2 H, m), 3.47 - 3.43 (2 H, m), 3.41 (2 H, s), 3.21 (3 H, s), 2.94 - 2.84 (1 H, m), 2.62 - 2.54 (1 H, m), 2.34 (3 H, s).

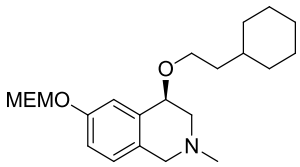
11.6.3 (*R*)-4-([1,1'-Biphenyl]-4-ylmethoxy)-6-((2-methoxyethoxy)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (164)



164

The MEM protected phenol **153** (0.200 g, 0.750 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.063 g, 1.6 mmol), 4-(chloromethyl)-1,1'-biphenyl **128** (0.170 g, 0.830 mmol) and sodium iodide (0.225 g, 1.50 mmol) as described for **163**, then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (2% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.270 g, 83%). ^{1}H NMR (DMSO-d_6) δ 7.70 - 7.60 (4 H, m), 7.51 - 7.43 (4 H, m), 7.36 (1 H, s), 7.07 (1 H, d, J = 2.6 Hz), 7.02 (1 H, d, J = 8.4 Hz), 6.90 (1 H, dd, J = 8.3, 2.6 Hz), 5.20 (2 H, d, J = 1.3 Hz), 4.71 (2 H, d, J = 3.8 Hz), 4.62 - 4.56 (1 H, m), 3.72 - 3.67 (2 H, m), 3.47 - 3.40 (4 H, m), 3.21 - 3.17 (3 H, m), 2.92 (1 H, dd, J = 11.5, 4.8 Hz), 2.61 (1 H, dd, J = 11.5, 6.3 Hz), 2.35 (3 H, s).

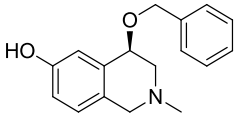
11.6.4 (*R*)-4-(2-Cyclohexylethoxy)-6-((2-methoxyethoxy)methoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (165)



165

The MEM protected phenol **153** (0.200 g, 0.750 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.060 g, 1.5 mmol), and 2-cyclohexylethyl methanesulfonate **242** (0.170 g, 0.830 mmol) as described for **163**, then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (2% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.130 g, 46%). ^{1}H NMR (DMSO-d_6) δ 7.00 (2 H, s), 6.90 - 6.85 (1 H, m), 5.20 (2 H, s), 4.45 - 4.36 (1 H, m), 3.74 - 3.67 (2 H, m), 3.66 - 3.51 (2 H, m), 3.49 - 3.42 (2 H, m), 3.41 - 3.35 (2 H, m), 3.22 (3 H, s), 2.91 - 2.80 (1 H, m), 2.46 - 2.39 (1 H, m), 2.32 (3 H, s), 1.76 - 1.56 (5 H, m), 1.48 - 1.34 (3 H, m), 1.27 - 1.06 (3 H, m), 0.95 - 0.82 (2 H, m). See pg. 241 for details on the synthesis of 2-cyclohexylethyl methanesulfonate **242**.

11.6.5 (*R*)-4-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (166)

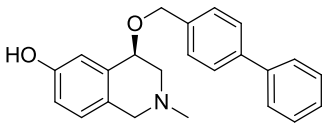


166

The MEM protected phenol **163** (0.072 g, 0.20 mmol) was dissolved in a mixture of anhydrous dichloromethane and trifluoroacetic acid (1:1), and the reaction mixture stirred at room temperature for 45 minutes, then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as an orange gummy

solid (0.027 g, 50%). ^{1}H NMR (DMSO-d_6) δ 9.18 (1 H, s), 7.42 - 7.34 (4 H, m), 7.33 - 7.26 (1 H, m), 6.87 (1 H, d, J = 8.3 Hz), 6.82 (1 H, d, J = 2.6 Hz), 6.61 (1 H, dd, J = 8.3, 2.6 Hz), 4.70 - 4.59 (2 H, m), 4.53 (1 H, t, J = 5.8 Hz), 3.36 (2 H, m), 2.90 (1 H, dd, J = 11.5, 5.0 Hz), 2.59 - 2.47 (1 H, m), 2.33 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 155.6, 139.0, 135.7, 128.3, 127.7, 127.5, 126.8, 125.7, 114.9, 114.1, 73.3, 70.0, 57.0, 56.7, 45.7; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1489; Found 270.1490.

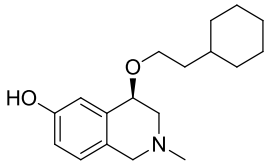
11.6.6 (*R*)-4-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (167)



167

The MEM protected phenol **164** (0.270 g, 0.620 mmol) was deprotected as described for **166** and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a cream coloured solid (0.068 g, 32%). m.p. 72 - 75°C; ^{1}H NMR (DMSO-d_6) δ 9.20 (1 H, s), 7.70 - 7.63 (4 H, m), 7.51 - 7.43 (4 H, m), 7.40 - 7.32 (1 H, m), 6.92 - 6.84 (2 H, m), 6.63 (1 H, dd, J = 8.2, 2.6 Hz), 4.74 - 4.64 (2 H, m), 4.57 (1 H, t, J = 5.6 Hz), 3.40 3.36 - (2 H, m), 2.92 (1 H, dd, J = 11.4, 4.8 Hz), 2.57 (1 H, dd, J = 11.4, 6.4 Hz), 2.35 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 155.5, 139.9, 138.2, 135.7, 128.9, 128.2, 127.4, 126.6, 126.5, 114.8, 114.0, 73.4, 69.6, 57.0, 56.7, 45.7 (note some signals conincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{24}NO_2$ 346.1802; Found 346.1806; $[\alpha]_D$ +11.2° (*c* 1.05, CH_2Cl_2).

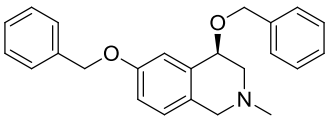
11.6.7 (*R*)-4-(2-Cyclohexylethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (168)



168

The MEM protected phenol **165** (0.130 g, 0.340 mmol) was deprotected as described for **166** and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a gummy orange solid (0.052 g, 53%). ^{1}H NMR (DMSO-d_6) δ 9.16 (1 H, s), 6.85 (1 H, d, J = 8.2 Hz), 6.76 (1 H, d, J = 2.6 Hz), 6.60 (1 H, dd, J = 8.2, 2.6 Hz), 4.40 - 4.32 (1 H, m), 3.66 - 3.48 (2 H, m), 3.40 - 3.25 (2 H + H_2O, m), 2.89 - 2.79 (1 H, m), 2.40 (1 H, dd, J = 11.2, 6.8 Hz), 2.30 (3 H, s), 1.74 - 1.56 (5 H, m), 1.47 - 1.32 (3 H, m), 1.27 - 1.06 (3 H, m), 0.95 - 0.81 (2 H, m); ^{13}C NMR (DMSO-d_6) δ 155.5, 136.0, 126.5, 125.6, 114.6, 113.9, 73.7, 66.0, 57.0, 56.9, 45.7, 37.2, 33.9, 32.8, 32.8, 26.1, 25.8; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2$ 290.2120; Found 290.2115.

11.6.8 (R)-4,6-bis(benzyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (169)

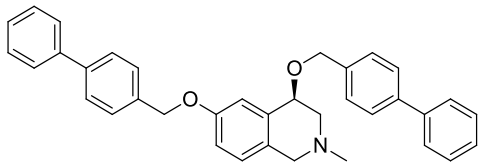


169

See section 11.5.1 pg, 165 for details. ^{1}H NMR ($CDCl_3$) δ 7.46 - 7.27 (10 H, m), 7.01 (1 H, d, J = 2.6 Hz), 6.98 (1 H, d, J = 8.4 Hz), 6.87 (1 H, dd, J = 8.4, 2.6 Hz), 5.08 - 4.95 (2 H, m), 4.78 - 4.57 (3 H, m), 3.60 (1 H, d, J = 14.6 Hz), 3.48 (1 H, d, J = 14.6 Hz), 2.89 (1 H, ddd, J = 11.6, 4.7, 0.9 Hz), 2.79 (1 H, dd, J = 11.6, 6.0 Hz), 2.48 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.4, 138.7, 137.1, 135.4, 128.6, 128.4, 127.9, 127.9,

127.6, 127.5, 127.1, 115.1, 113.9, 73.6, 70.9, 70.1, 57.4, 57.2, 46.2 (note some peaks coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{26}NO_2$ 360.1958; Found 360.1951.

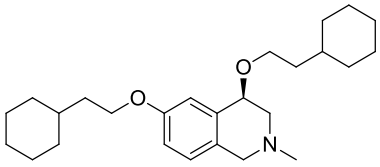
11.6.9 (*R*)-4,6-Bis([1,1'-biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (170)



170

The isoquinoline hydrochloride **86** (0.100 g, 0.460 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.058 g, 1.5 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes. 4-(Chloromethyl)-1,1'-biphenyl **128** (0.206 g, 1.02 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs, quenched with methanol (2 mL) and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a white solid (0.017 g, 7%). m.p. 162 - 164.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 - 7.56 (8 H, m), 7.50 - 7.41 (8 H, m), 7.40 - 7.32 (2 H, m), 7.05 (1 H, d, *J* = 2.5 Hz), 7.01 (1 H, d, *J* = 8.4 Hz), 6.90 (1 H, dd, *J* = 8.4, 2.5 Hz), 5.13 - 5.04 (2 H, m), 4.78 - 4.69 (2 H, m), 4.68 (1 H, t, *J* = 5.2 Hz), 3.63 (1 H, d, *J* = 14.4 Hz), 3.49 (1 H, d, *J* = 14.4 Hz), 2.91 (1 H, dd, *J* = 11.6, 4.7 Hz), 2.83 (1 H, dd, *J* = 11.6, 5.9 Hz), 2.50 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.6, 141.02, 140.96, 140.7, 137.9, 136.3, 135.6, 128.9, 128.9, 128.5, 128.1, 127.5, 127.4, 127.30, 127.27, 127.2, 115.3, 114.0, 73.8, 70.7, 70.0, 57.6, 57.4, 46.4 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{34}NO_2$ 512.2590; Found 512.2580.

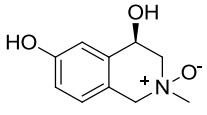
11.6.10 (*R*)-4,6-Bis(2-cyclohexylethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (172)



172

The isoquinoline hydrochloride **86** (0.100 g, 0.460 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.060 g, 1.5 mmol) and 2-cyclohexylethyl methanesulfonate **242** (0.210 g, 1.02 mmol) as described for **170** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a pale yellow gummy solid (0.026 g, 14%). ^{1}H NMR ($CDCl_3$) δ 6.96 (1 H, d, *J* = 2.7 Hz), 6.94 (1 H, d, *J* = 8.4 Hz), 6.77 (1 H, dd, *J* = 8.4, 2.7 Hz), 4.50 (1 H, t, *J* = 5.7 Hz), 4.03 - 3.94 (2 H, m), 3.78 - 3.67 (1 H, m), 3.63 (1 H, dt, *J* = 9.2, 6.7 Hz), 3.55 - 3.45 (2 H, m), 2.91 (1 H, dd, *J* = 11.3, 4.9 Hz), 2.64 (1 H, dd, *J* = 11.3, 6.4 Hz), 2.48 - 2.42 (3 H, m), 1.85 - 1.62 (12 H, m), 1.61 - 1.42 (4 H, m), 1.34 - 1.11 (6 H, m), 1.04 - 0.78 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 157.9, 136.0, 127.3, 127.0, 114.8, 113.1, 74.7, 67.3, 66.1, 57.6, 57.5, 46.4, 37.7, 36.9, 34.7, 34.7, 33.7, 33.5, 33.5, 33.4, 26.8, 26.7, 26.53, 26.51, 26.4 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{42}NO_2$ 400.3216; Found 400.3206. See pg. 241 for details on the synthesis of 2-cyclohexylethyl methanesulfonate **242**.

11.6.11 (4*R*)-4,6-Dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide (173)

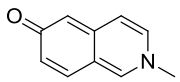


173

Hydrogen peroxide (30%, 7.0 mL, 62 mmol) was added to a solution of isoquinoline **86** as the free base (1.05 g, 5.86 mmol) in methanol (30 mL) and this was stirred at room temperature for 18 hrs. Excess peroxide was decomposed with manganese

dioxide. The manganese dioxide was removed by filtration, and the filtrate was concentrated under reduced pressure to afford a yellow solid as a mixture of diastereomers A and B (70:30) which were not separated (1.14 g, >99%). m.p. 180°C decomp.; ^{1}H NMR (D_2O, selected peaks of isomer A) δ 7.12 (1 H, d, *J* = 8.4 Hz), 7.04 (1 H, d, *J* = 2.4 Hz), 6.93 (1 H, dd, *J* = 8.4, 2.4 Hz), 4.51 (1 H, d, *J* = 15.2 Hz), 3.93 (1 H, dd, *J* = 12.8, 4.8 Hz), 3.73 (1 H, d, *J* = 12.8 Hz), 3.36 (3 H, s); ^{1}H NMR (D_2O, selected peaks of isomer B) δ 7.08 (1 H,d, *J* = 3.2 Hz), 5.20 (1 H, t, *J* = 6.8 Hz), 4.62 (1 H, d, *J* = 14.8 Hz), 4.38 (1 H, d, *J* = 14.8 Hz), 3.86 (1 H, dd, *J* = 12.4, 6.4), 3.57 (1 H, dd, *J* = 12.4, 7.6 Hz), 3.38 (3 H, s); ^{13}C NMR (D_2O, mixture of isomers A and B) δ 155.7, 155.6, 134.7, 134.3, 128.2, 128.1, 119.9, 119.4, 116.5, 116.1, 114.9, 113.6, 67.9, 67.8, 67.6, 65.1, 63.8, 58.3, 57.5 (2 isomers some signals coincident).

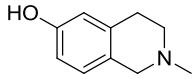
11.6.12 2-Methylisoquinolin-6(2*H*)-one (174)



174

Acetic anhydride (6.0 mL, 64 mmol) was added to a suspension of *N*-oxide **173** (1.14 g, 5.84 mmol) in ethyl acetate (50 mL), and stirred at room temperature for 2.5 days. The reaction mixture was concentrated under reduced pressure, diluted with water (20 mL) and neutralised with solid sodium bicarbonate. This mixture was then concentrated under reduced pressure, adsorbed onto silica and purified by column chromatography (15% methanol, 2% sat. ammonia, in dichloromethane) to afford the desired product as a yellow gummy solid which slowly crystallised (0.59 g, 64%). m.p. 95 - 100°C; ^{1}H NMR (DMSO-d_6) δ 8.44 (1 H, s), 7.57 - 7.47 (2 H, m), 7.05 (1 H, d, *J* = 7.1 Hz), 6.65 (1 H, dd, *J* = 9.2, 2.1 Hz), 6.17 (1 H, d, *J* = 1.8 Hz), 6.19 - 6.13 (1 H, m), 3.86 (3 H, s); ^{13}C NMR (D_2O) δ 176.7, 144.7, 140.1, 132.9, 131.8, 128.9, 120.2, 118.9, 109.7, 45.4. Spectral data was in agreement with Fourneau et al.[158]

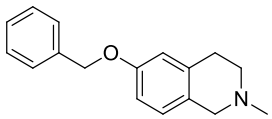
11.6.13 2-Methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (175)



175

Sodium borohydride (0.333 g, 8.68 mmol) was added to a solution of isoquinolone **174** (0.690 g, 4.34 mmol) in methanol (40 mL). This was stirred at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure, diluted with water (50 mL), and extracted with ethyl acetate (3×50 mL) The ethyl acetate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford a cream coloured solid (0.530 g, 75%) which was used without further purification. m.p. 176 - 178°C (185°C lit[158]); ^{1}H NMR ($CDCl_3$) δ 6.84 (1 H, d, *J* = 8.2 Hz), 6.55 (1 H, dd, *J* = 8.2, 2.6 Hz), 6.39 (1 H, d, *J* = 2.6 Hz), 3.52 (2 H, s), 2.77 (2 H, t, *J* = 6.0 Hz), 2.66 (2 H, t, *J* = 6.0 Hz), 2.44 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 155.1, 134.4, 127.4, 124.9, 115.1, 113.9, 57.1, 52.6, 45.6, 28.5.

11.6.14 6-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (176)

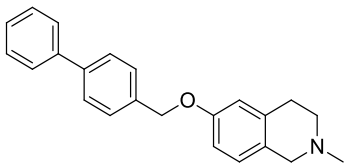


176

The isoquinoline **175** (0.100 g, 0.610 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.034 g, 0.85 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes. Benzyl bromide (80 μL, 0.67 mmol) was added and the reaction mixture stirred at room temperature for 2 days. The reaction was quenched with methanol (2 mL) and then subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.107 g, 69%). m.p. 51 - 54°C; ^{1}H NMR ($CDCl_3$) δ 7.45 - 7.28 (5 H, m), 6.93 (1 H, d, *J* = 8.4 Hz), 6.79 - 6.74 (1 H, m), 6.73 (1 H, d, *J* = 2.5 Hz), 5.03 (2 H, s), 3.53 (2 H, s), 2.90 (2 H, t, *J* = 5.9 Hz), 2.73 - 2.62

(2 H, m), 2.46 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.5, 137.1, 134.2, 128.6, 127.9, 127.5, 127.5, 125.3, 114.4, 113.3, 70.1, 56.7, 52.3, 45.1, 28.4; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO$ 254.1539; Found 254.1538.

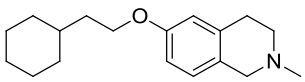
11.6.15 6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (177)



177

The isoquinoline **175** (0.101 g, 0.620 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.031 g, 0.78 mmol) and 4-(chloromethyl)-1,1'-biphenyl **128** (0.136 g, 0.670 mmol) as described for **176** and then subjected to workup method 1. The resulting cream coloured solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a white solid (0.060 g, 30%). m.p. 132 - 136°C; ^{1}H NMR ($CDCl_3$) δ 7.64 - 7.56 (4 H, m), 7.52- 7.41 (4 H, m), 7.39 - 7.31 (1 H, m), 6.96 (1 H, d, *J* = 8.4 Hz), 6.81 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.76 (1 H, d, *J* = 2.4 Hz), 5.08 (2 H, s), 3.63 (2 H, s), 3.03 - 2.90 (2 H, m), 2.81 - 2.73 (2 H, m), 2.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.4, 141.0, 141.0, 136.4, 135.01, 128.9, 128.1, 127.6, 127.5, 127.3, 127.2, 114.5, 113.1, 69.9, 57.5, 52.9, 46.1, 29.5 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{24}NO$ 330.1852; Found 330.1853.

11.6.16 6-(2-Cyclohexylethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (178)

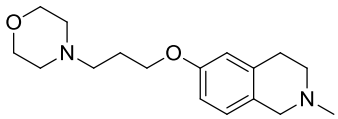


178

The isoquinoline **175** (0.100 g, 0.610 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.030 g, 0.73 mmol) and 2-cyclohexylethyl tosylate **107**

(0.190 g, 0.670 mmol) as described for **176** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.137 g, 82%). ^{1}H NMR ($CDCl_3$) δ 6.92 (1 H, d, *J* = 8.4 Hz), 6.69 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.64 (1 H, d, *J* = 2.4 Hz), 3.95 (2 H, t, *J* = 6.8 Hz), 3.58 (2 H, s), 2.92 (2 H, t, *J* = 5.9 Hz), 2.73 (2 H, t, *J* = 5.9 Hz), 2.49 (3 H, s), 1.80 - 1.58 (7 H, m), 1.54 - 1.43 (1 H, m), 1.32 - 1.08 (3 H, m), 1.01 - 0.91 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 157.8, 134.2, 127.4, 125.2, 113.9, 112.9, 66.0, 56.8, 52.5, 45.3, 36.7, 34.6, 33.3, 28.7, 26.5, 26.3; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{28}NO$ 274.2165; Found 274.2161. See pg. 238 for details on the synthesis of 2-cyclohexylethyl tosylate **107**.

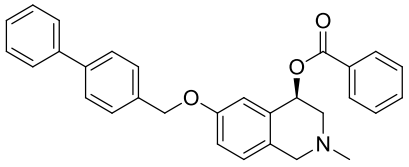
11.6.17 4-(3-((2-Methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)propyl)morpholine (179)



179

The isoquinoline **175** (0.101 g, 0.620 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.037 g, 0.93 mmol) and 4-(3-chloropropyl)morpholine **117** (0.111 g, 0.680 mmol) as described for **176** and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (10% methanol, 0.5% sat. ammonia in dichloromethane) to afford the desired product as a colourless gummy solid (0.103 g, 57%). ^{1}H NMR ($CDCl_3$) δ 6.91 (1 H, d, *J* = 8.4 Hz), 6.68 (1 H, dd, *J* = 8.4, 2.5 Hz), 6.63 (1 H, d, *J* = 2.5 Hz), 3.97 (2 H, t, *J* = 6.4 Hz), 3.74 - 3.66 (4 H, m), 3.53 (2 H, s), 2.92 - 2.85 (2 H, m), 2.68 (2 H, t, *J* = 5.9 Hz), 2.53 - 2.47 (2 H, m), 2.47 - 2.41 (7 H, m), 1.98 - 1.88 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 157.8, 134.4, 127.6, 125.5, 114.1, 113.1, 67.1, 66.2, 57.0, 55.7, 53.9, 52.6, 45.5, 28.8, 26.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{27}N_2O_2$ 291.2067; Found 291.2057.

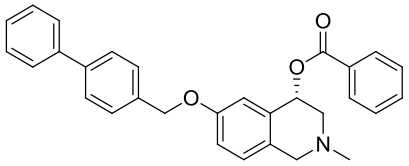
11.6.18 (*R*)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl benzoate (180)



180

Isoquinoline **129** (0.102 g, 0.290 mmol) was dissolved in anhydrous dichloromethane (10 mL). Triethylamine (80 µL, 0.58 mmol) was added followed by benzoyl chloride (51 µL, 0.44 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (10 mL) and the organic phase separated, dried over magnesium sulfate, and concentrated under reduced pressure to afford a cream coloured solid which was purified by column chromatography (2% methanol in dicloromethane) to give the desired product as a colourless gummy solid which slowly crystallised (0.106 g, 81%). m.p. 132.5 - 136.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 - 8.05 (2 H, m), 7.59 - 7.50 (5 H, m), 7.49 - 7.32 (7 H, m), 7.07 (1 H, d, *J* = 8.5 Hz), 7.03 (1 H, d, *J* = 2.8 Hz), 6.96 (1 H, dd, *J* = 8.5, 2.8 Hz), 6.23 (1 H, t, *J* = 4.5 Hz), 5.08 (2 H, s), 3.76 (1 H, d, *J* = 14.7 Hz), 3.47 (1 H, d, *J* = 14.7 Hz), 2.98 (2 H, d, *J* = 4.6 Hz), 2.50 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.8, 157.7, 141.0, 140.9, 136.0, 133.3, 133.2, 130.3, 130.1, 128.9, 128.7, 128.5, 128.1, 127.6, 127.5, 127.4, 127.3, 116.1, 114.3, 70.0, 69.5, 57.7, 57.4, 46.0; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{28}NO_3$ 450.2064; Found 450.2070; $[\alpha]_D$ +29.8° (*c* 1.00, CH_2Cl_2).

11.6.19 (*S*)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl benzoate (181)

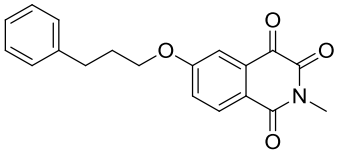


181

Isoquinoline **129** (0.020 g, 0.58 mmol) and triphenylphosphine (0.186 g, 0.710 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL) and cooled to -10°C.

Diisopropyl azodicarboxylate (138 μL, 0.700 mmol) was added and the reaction mixture stirred at -10°C for a further 10 minutes. Benzoic acid (0.072 g, 0.58 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL) and added to the reaction mixture which was then allowed to warm to room temperature and stirred for a further 3.5 hrs. The reaction mixture was concentrated under reduced pressure to afford an orange gummy solid which was purified by column chromatography (50:50, ethylacetate:petroleum spirits 40-60) to give the desired product as a pale orange solid (0.110 g, 42%). m.p. 136.5 - 138.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 - 8.04 (2 H, m), 7.57 - 7.49 (5 H, m), 7.48 - 7.31 (7 H, m), 7.06 (1 H, d, *J* = 8.6 Hz), 7.02 (1 H, d, *J* = 2.6 Hz), 6.95 (1 H, dd, *J* = 8.6, 2.6 Hz), 6.22 (1 H, t, *J* = 4.6 Hz), 5.07 (2 H, s), 3.72 (1 H, d, *J* = 14.4 Hz), 3.45 (1 H, d, *J* = 14.4 Hz), 3.01 - 2.88 (2 H, m), 2.53 - 2.39 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 166.8, 157.7, 141.0, 140.9, 136.0, 133.3, 133.2, 130.4, 130.1, 128.9, 128.8, 128.45, 128.1, 127.6, 127.5, 127.4, 127.3, 116.0, 114.3, 70.0, 69.6, 57.8, 57.4, 46.0; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{28}NO_3$ 450.2064; Found 450.2072; $[\alpha]_D$ -37.4° (*c* 1.01, CH_2Cl_2).

11.6.20 2-Methyl-6-(3-phenylpropoxy)isoquinoline-1,3,4(2*H*)-trione (182)

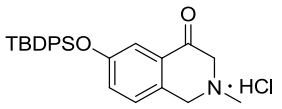


182

Isoquinoline **105** (0.101 g, 0.340 mmol) was dissolved in anhydrous dichloromethane (6 mL). Activated manganese dioxide (0.307 g, 3.50 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs. The reaction mixture was filtered through a 1 cm bed of celite, the filter cake was washed with dichloromethane (100 mL). The resulting filtrate was concentrated under reduced pressure to afford an orange gummy solid. This was purified by column chromatography (20% ethyl acetate in petroleum spirits 40-60) to give the title compound as a yellow solid (0.013 g, 12%). ^{1}H NMR($CDCl_3$) δ 8.26 (1 H, d, *J* = 8.7 Hz), 7.58 (1 H, d, *J* = 2.6 Hz), 7.36 (1 H, dd, *J* = 8.7, 2.6 Hz), 7.34 - 7.28 (2 H, m), 7.25 - 7.19 (3 H, m), 4.13 (2 H, t, *J* = 6.2 Hz), 3.47 (3 H, s), 2.84 (2 H, t, *J* = 7.5 Hz),

2.24 - 2.13 (2 H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 163.9, 162.3, 157.7, 140.9, 132.6, 132.0, 128.7, 128.6, 126.3, 123.8, 122.8, 110.9, 68.2, 32.1, 30.5, 27.5; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{18}NO_4$ 324.1230; Found 324.1230.

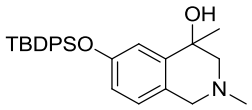
11.6.21 6-((*tert*-Butyldiphenylsilyl)oxy)-2-methyl-2,3-dihydroisoquinolin-4(1*H*)-one hydrochloride (187)



187

TBDPS protected phenol **152** (0.800 g, 1.92 mmol) was dissolved in acetone (60 mL) and cooled to -20°C. Jones reagent (1.3 M, 3.70 mL, 4.80 mmol) was added, and the reaction mixture was allowed to warm to 0°C. The reaction mixture was diluted with methanol (80 mL) and stirred at room temperature for 20 minutes. The resulting green suspension was separated by filtration and the filtrate was concentrated under reduced pressure to afford a green oil. This was diluted with HCl (1 M, 20 mL) and extracted with ethyl acetate (3×70 mL). The ethyl acetate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford a yellow gummy solid. This was dissolved in dichloromethane (100 mL) and concentrated under reduced pressure to afford a pale yellow solid (0.897 g), which contained a mixture of the desired product as the hydrochloride salt and starting material (60:40) which were not seperated due to poor stability of the free base. ^{1}H NMR ($CDCl_3$) δ 7.74 - 7.67 (4 H + starting material, m), 7.51 (1 H, d, *J* = 2.6 Hz), 7.46 - 7.33 (6 H + starting material, m), 6.92 (1 H, d, *J* = 8.4 Hz), 6.82 (1 H, dd, *J* = 8.4, 2.6 Hz), 3.62 (2 H, s), 3.25 (1 H, s), 2.46 (3 H, s), 1.13 - 1.08 (9 H + starting material, m) (note ^{1}H NMR spectrum reported as the free base).

11.6.22 6-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-4-ol (188)

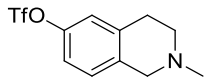


188

Methylmagnesium iodide (1 M, 1.5 mL, 1.5 mmol) was added to a solution of ketone **187** (0.100 g, 0.220 mmol) in anhydrous tetrahydrofuran (20 mL), and heated at 45°C for 18 hrs. The reaction mixture was concentrated under reduced pressure, diluted with sat. chloride solution (20 mL) and water (10 mL), and extracted with ethyl acetate (3×20 mL). The ethyl acetate fractions were combined, dried over magnesium sulfate and concentrated under reduced pressure to afford an orange gummy solid. This was purified by column chromatography (5% methanol, 1% sat. ammonia in dichloromethane) to afford the desired compound as a pale orange gummy solid (0.039 g, 41%). ^{1}H NMR ($CDCl_3$) δ 7.75 - 7.65 (4 H, m), 7.45 - 7.30 (6 H, m), 6.94 (1 H, d, *J* = 2.6 Hz), 6.69 (1 H, d, *J* = 8.2 Hz), 6.59 (1 H, dd, *J* = 8.2, 2.6 Hz), 3.54 (1 H, d, *J* = 14.4 Hz), 3.21 (1 H, d, *J* = 14.4 Hz), 2.75 (1 H, dd, *J* = 11.5, 1.4 Hz), 2.44 - 2.33 (4 H, m), 1.29 (3 H, s), 1.13 - 1.07 (9 H, m); ^{13}C NMR ($CDCl_3$) δ 154.8, 140.6, 135.7, 135.7, 130.0, 130.0, 127.9, 127.9, 127.8, 127.0, 119.4, 117.1, 68.6, 66.5, 57.8, 45.7, 26.7, 25.5, 19.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{34}NO_2Si$ 432.2353; Found 432.2355.

11.7 Modification of position 6

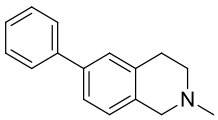
11.7.1 2-Methyl-1,2,3,4-tetrahydroisoquinolin-6-yl trifluoromethanesulfonate (189)



189

Phenol **175** (0.160 g, 0.980 mol) was dissolved in anhydrous dichloromethane (20 mL). Triethylamine (265 µL, 1.96 mmol) was added and the reaction mixture cooled to -78°C. Triflic anhydride (330 µL, 1.96 mmol) was added and the reaction mixture stirred for 2 hrs keeping the temperature below -10°C. Water (20 mL) was added, the organic phase separated, dried over magnesium sulfate, and concentrated under reduced pressure to afford an orange solid. This was purified by column chromatography (3% methanol in dichloromethane) to afford the desired product as a pale yellow gummy solid (0.103 g, 36%). ^{1}H NMR ($CDCl_3$) δ 7.10 7.05 - (1 H, m), 7.04 - 6.99 (2 H, m), 3.56 (2 H, s), 2.94 (2 H, t, *J* = 6.0 Hz), 2.68 (2 H, t, *J* = 5.9 Hz), 2.48 - 2.42 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 149.3, 132.9, 129.1, 127.3, 121.8, 120.8, 119.6 (q, J_{FC} = 160 Hz), 54.5, 51.3, 43.1, 25.2.

11.7.2 2-Methyl-6-phenyl-1,2,3,4-tetrahydroisoquinoline (190)

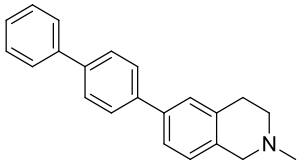


190

Triflate **189** (0.102 g, 0.340 mmol) was combined with phenylboronic acid (0.050 g, 0.41 mmol), triphenylphosphine (0.007 g, 0.03 mmol), potassium carbonate (0.195 g, 1.41 mmol), dioxane (4.0 mL), and water (4.0 mL). This mixture was degassed by bubbling with nitrogen for 15 minutes. Palladium acetate (0.0052 g, 0.020 mmol) was added and the reaction mixture heated to reflux for 6 hrs and subjected to workup method 3. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a

pale brown solid (0.025 g, 33%). m.p. 63 - 66.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 - 7.54 (2 H, m), 7.45 - 7.30 (5 H, m), 7.10 (1 H, d, *J* = 7.9 Hz), 3.70 (2 H, s), 3.02 (2 H, t, *J* = 6.1 Hz), 2.80 (2 H, t, *J* = 5.9 Hz), 2.53 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 141.2, 139.6, 134.0, 133.3, 128.9, 127.5, 127.3, 127.2, 127.0, 124.8, 57.6, 52.9, 45.9, 29.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}N$ 224.1439; Found 224.1434.

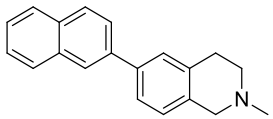
11.7.3 6-([1,1'-Biphenyl]-4-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (191)



191

Triflate **189** (0.100 g, 0.340 mmol) was treated with 4-biphenylboronic acid (0.084 g, 0.42 mmol), triphenylphosphine (0.0069 g, 0.030 mmol), potassium carbonate (0.193 g, 1.40 mmol), and palladium acetate (0.0056 g, 0.020 mmol), as described for **190** and subjected to workup method 3. The resulting brown solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a cream coloured solid (0.053 g, 52%). m.p. 161 - 163.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 - 7.60 (6 H, m), 7.49 - 7.33 (5 H, m), 7.14 - 7.09 (1 H, m), 3.65 (2 H, s), 3.01 (2 H, t, *J* = 5.9 Hz), 2.75 (2 H, t, *J* = 5.9 Hz), 2.50 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 140.9, 140.2, 140.1, 138.8, 134.4, 134.1, 128.9, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 124.6, 57.9, 53.1, 46.2, 29.5; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}N$ 300.1752; Found 300.1750.

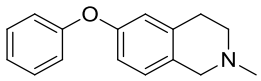
11.7.4 2-Methyl-6-(naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinoline (192)



192

Triflate **189** (0.100 g, 0.340 mmol) was treated with 2-napthylboronic acid (0.072 g, 0.41 mmol), triphenylphosphine (0.0072 g, 0.030 mmol), potassium carbonate (0.191 g, 1.38 mmol), and palladium acetate (0.0052 g, 0.020 mmol), as decribed for **190** and subjected to workup method 3. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as an orange solid (0.040 g, 43%). m.p. 92 - 95.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 - 7.99 (1 H, m), 7.92 - 7.82 (3 H, m), 7.73 (1 H, dd, *J* = 8.6, 1.8 Hz), 7.53 - 7.43 (4 H, m), 7.14 (1 H, d, *J* = 8.1 Hz), 3.68 (2 H, s), 3.04 (2 H, t, *J* = 5.9 Hz), 2.78 (2 H, t, *J* = 5.9 Hz), 2.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 139.3, 138.6, 134.3, 133.9, 132.7, 128.5, 128.3, 127.8, 127.7, 127.1, 126.4, 125.9, 125.69, 125.66, 125.0, 57.8, 53.0, 46.1, 29.4 (note some signals conincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{20}N$ 274.1596; Found 274.1591.

11.7.5 2-Methyl-6-phenoxy-1,2,3,4-tetrahydroisoquinoline (195)

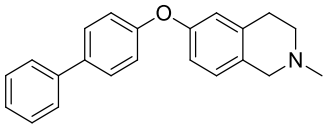


195

Isoquinoline **175** (0.101 g, 0.610 mmol), bromobenzene (54 μL, 0.51 mmol), 2-(di-*tert*-butyphosphino)biphenyl (0.0051 g, 0.017 mmol), tripotassium phosphate (0.219 g, 1.03 mmol) and anhydrous toluene were combined and degassed by bubbling with nitrogen for 15 minutes. Palladium acetate (0.0024 g, 0.010 mmol) was added and the reaction mixture heated at reflux for 24 hrs, and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a pale orange gummy solid (0.032 g, 22%). ^{1}H NMR ($CDCl_3$) δ 7.35 - 7.28 (2 H, m), 7.11 - 7.06 (1 H, m),

7.02 - 6.96 (3 H, m), 6.84 - 6.80 (1 H, m), 6.79 6.76 - (1 H, m), 3.71 (2 H, s), 3.00 - 2.90 (2 H, m), 2.87 - 2.79 (2 H, m), 2.56 (3 H, s) ;^{13}C NMR ($CDCl_3$) δ 157.5, 155.9, 134.9, 129.9, 127.9, 123.2, 118.9, 118.8, 117.3, 56.9, 52.4, 45.4, 28.5 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1385.

11.7.6 6-([1,1'-Biphenyl]-4-yloxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (197)

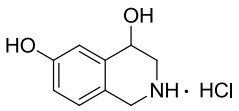


197

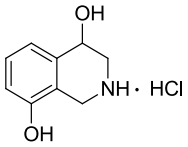
Isoquinoline **175** (0.102 g, 0.620 mmol) was treated with 4-bromobiphenyl (0.120 g, 0.510 mmol), 2(di-*tert*-butyphosphino)biphenyl (0.0049 g, 0.016 mmol), tripotassium phosphate (0.220 g, 1.04 mmol), and palladium acetate (0.0025 g, 0.010 mmol) as described for **195**, and subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a brown gummy solid which slowly crystallised (0.072 g, 37%). m.p. 91 - 94.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 - 7.53 (4 H, m), 7.47 - 7.41 (2 H, m), 7.36 - 7.31 (1 H, m), 7.08 - 7.04 (2 H, m), 7.03 (1 H, d, *J* = 7.8 Hz), 6.89 - 6.85 (1 H, m), 6.84 6.83 - (1 H, m), 3.64 (2 H, s), 2.95 (2 H, t, *J* = 6.1 Hz), 2.76 (2 H, t, *J* = 6.1 Hz), 2.52 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.3, 155.5, 140.7, 136.2, 135.4, 128.9, 128.5, 127.9, 127.1, 127.0, 119.1, 118.8, 117.2, 57.4, 52.6, 45.8, 29.0 (some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}NO$ 316.1701; Found 316.1699.

11.8 Modification of the Nitrogen

11.8.1 1,2,3,4-Tetrahydroisoquinoline-4,6-diol (200) and 1,2,3,4-tetrahydroisoquinoline-4,8-diol (201)



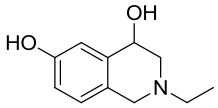
200



201

Formaldehyde (37%, 3.0 mL, 36 mmol) was added to a mixture of norphenylephrine hydrochloride (3.00 g, 15.8 mmol) in ethanol (30 mL). The resulting colourless solution was stirred at room temperature for 5 days. Filtration of the reaction mixture afforded a white powder which was recrystallised from ethanol to give the *ortho* substituted product **201** as colourless needles (0.39 g, 12%). Decomp. 210 °C; ^{1}H NMR (D_2O) δ 7.38 - 7.33 (1 H, m), 7.08 (1 H, dd, *J* = 7.6, 0.4 Hz), 6.98 (1 H, dd, *J* = 8.4, 0.8 Hz), 5.07 (1 H, t, *J* = 3.1 Hz), 4.47 (1 H, d, *J* = 16.5 Hz), 4.23 (1 H, d, *J* = 16.5 Hz), 3.63 (1 H, ddd, *J* = 13.5, 3.1, 1.0 Hz), 3.51 (1 H, dd, *J* = 13.5, 3.1 Hz); ^{13}C NMR (D_2O) δ 152.5, 134.1, 129.3, 120.8, 115.2, 115.1, 62.2, 47.2, 40.4. The ethanol mother liquor was concentrated under reduced pressure to afford a pale yellow gummy solid which was recrystallised from an ethanol ether mixture to afford the *para* substituted product (**200**) as a white solid (1.05 g, 33%). m.p. 210 - 211.2 °C; ^{1}H NMR (D_2O) δ 7.20 (1 H, d, *J* = 8.4 Hz), 7.01 (1 H, d, *J* = 2.5 Hz), 6.97 (1 H, dd, *J* = 8.4, 2.5 Hz), 5.04 (1 H, t, *J* = 3.6 Hz), 4.42 (1 H, d, *J* = 16.5 Hz), 4.32 (1 H, d, *J* = 16.5 Hz), 3.61 (1 H, ddd, *J* = 13.5, 3.6, 0.8 Hz), 3.54 (1 H, dd, *J* = 13.5, 3.6 Hz); ^{13}C NMR (D_2O) δ 155.5, 134.3, 128.2, 119.3, 116.8, 115.3, 62.4, 47.6, 43.9.

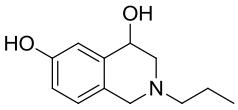
11.8.2 2-Ethyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (202)



202

Isoquinoline hydrochloride **200** (0.088 g, 0.44 mmol) was added to a solution of *N*,*N*-diisopropylethylamine (380 µL, 2.20 mmol) in anhydrous dimethylformamide. 1-Bromoethane (36 µL, 0.48 mmol) was added and the reaction mixture stirred for a further 1.5 days, and subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (10% methanol in dichloromethane) to afford the desired product as a white solid (0.047 g, 55%). m.p. 125.5 - 128.5 °C; ^{1}H NMR ($CDCl_3$) δ 6.85 (1 H, d, *J* = 8.4 Hz), 6.79 (1 H, d, *J* = 2.6 Hz), 6.67 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.53 (1 H, t, *J* = 3.3 Hz), 3.72 (1 H, d, *J* = 14.5 Hz), 3.31 (1 H, d, *J* = 14.5 Hz), 2.97 (1 H, dd, *J* = 11.8, 3.3 Hz), 2.67 - 2.54 (3 H, m), 1.22 - 1.08 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 155.3, 137.2, 127.6, 125.8, 116.1, 115.6, 66.9, 57.9, 55.0, 52.1, 11.9; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{16}NO_2$ 194.1176; Found 194.1172.

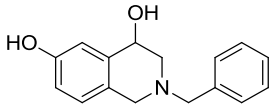
11.8.3 2-Propyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (203)



203

Isoquinoline hydrochloride **200** (0.082 g, 0.41 mmol) was treated with *N*,*N*-diisopropylethylamine (354 µL, 2.03 mmol) and 1-bromopropane (41 µL, 0.45 mmol) as described for **202** and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a white solid (0.040 g, 47%). m.p. 140 - 143.2 °C; ^{1}H NMR ($CDCl_3$) δ 6.93 - 6.82 (2 H, m), 6.70 (1 H, d, *J* = 8.4 Hz), 4.53 (1 H, br. s.), 3.84 - 3.69 (1 H, m), 3.37- 3.24 (1 H, m), 3.02 (1 H, d, *J* = 11.7 Hz), 2.64 - 2.40 (3 H, m), 1.73 - 1.53 (2 H, m), 1.10 - 0.83 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 155.2, 137.4, 127.7, 126.3, 116.0, 115.6, 67.2, 60.1, 58.3, 55.6, 20.1, 12.0; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{18}NO_2$ 208.1332; Found 208.1331.

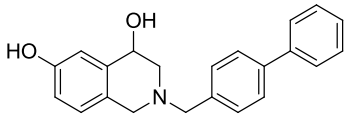
11.8.4 2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (204)



204

Isoquinoline hydrochloride **200** (0.187 g, 0.930 mmol) was treated with *N*,*N*-diisopropylethylamine (860 µL, 4.95 mmol) and benzyl bromide (125 µL, 1.05 mmol) as described for **202** and then subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid which slowly crystallised (0.210 g, 88%). m.p. 50 - 52.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 - 7.27 (5 H, m), 6.90 (1 H, d, *J* = 2.6 Hz), 6.85 (1 H, d, *J* = 8.4 Hz), 6.70 (1 H, dd, *J* = 8.4, 2.6 Hz), 4.53 (1 H, t, *J* = 2.9 Hz), 3.78 - 3.68 (3 H, m), 3.32 (1 H, d, *J* = 14.5 Hz), 3.04 (1 H, dt, *J* = 11.7, 1.6 Hz), 2.63 (1 H, dd, *J* = 11.7, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 155.4, 137.0, 136.6, 129.6, 128.7, 127.8, 127.7, 125.5, 116.1, 115.6, 67.0, 62.5, 57.8, 55.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$ 256.1332; Found 256.1330.

11.8.5 2-([1,1'-Biphenyl]-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (205)

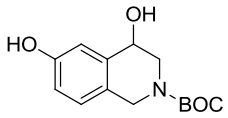


205

Isoquinoline hydrochloride **200** (0.100 g, 0.500 mmol) was treated with *N*,*N*-diisopropylethylamine (435 µL, 2.50 mmol) and 4-(chloromethyl)-1,1'-biphenyl **128** (0.111 g, 0.550 mmol) as described for **202** and then subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as a colourless gummy solid which slowly crystallised (0.111 g, 67%). m.p. 59 - 63.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 - 7.53 (4 H, m), 7.48 - 7.40 (4 H, m), 7.38 - 7.32 (1 H, m), 6.90 (1 H, d, *J* = 2.5 Hz), 6.85 (1 H, d, *J* = 8.3 Hz), 6.71 (1 H, dd, *J* = 8.3, 2.5 Hz), 4.55 (1 H, t, *J* = 3.1 Hz), 3.81 - 3.68 (3 H, m), 3.41 - 3.31 (1 H, m), 3.05 (1 H, dd, *J* = 11.7, 3.1 Hz),

2.66 (1 H, dd, J = 11.7, 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 155.3, 140.9, 140.5, 137.3, 136.5, 129.8, 128.9, 127.7, 127.4, 127.3, 127.2, 126.1, 116.0, 115.6, 67.3, 62.3, 58.1, 55.4; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_2$ 332.1651; Found 332.1644.

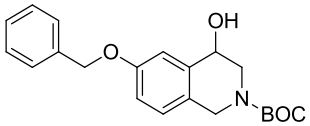
11.8.6 *tert*-Butyl 4,6-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (206)



206

Isoquinoline hydrochloride **200** (0.500 g, 2.48 mmol) was dissolved in methanol (10 mL). Triethylamine (1.2 mL, 8.6 mmol) was added and the reaction mixture stirred at room temperature for 10 minutes. Di-*tert*-butyl dicarbonate (0.820 g, 3.76 mmol) was added and the reaction mixture stirred at room temperature for a further 2 hrs. The reaction mixture was concentrated under reduced pressure, diluted with 10% isopropyl alcohol in ethyl acetate (20 mL) and washed with 1M hydrochloric acid (20 mL), followed by 5% sodium bicarbonate solution (20 mL). The ethyl acetate fraction was dried over magnesium sulfate, and concentrated under reduced pressure to afford a white solid (0.64 g, >95%). This was used without further purification. ^{1}H NMR ($CDCl_3$) δ 6.98 (1 H, d, J = 8.4 Hz), 6.94 (1 H, d, J = 2.7 Hz), 6.78 (1 H, dd, J = 8.4, 2.7 Hz), 4.70 - 4.59 (2 H, m), 4.40 (1 H, s), 3.87 - 3.75 (1 H, m), 3.66 - 3.58 (1 H, m), 1.50 (9 H, s).

11.8.7 *tert*-Butyl 6-(benzyloxy)-4-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (207)

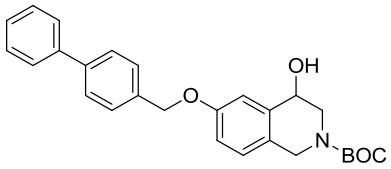


207

N-Protected phenol **206** (0.200 g, 0.750 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.037 g, 0.91 mmol) in anhydrous

dimethylformamide and the mixture stirred at room temperature for 30 minutes. Benzyl bromide (100 μL, 0.84 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs. The reaction was quenched with methanol (2 mL) and subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford the desired product as an orange gummy solid (0.222 g, 83%). ^{1}H NMR ($CDCl_3$) δ 7.47 - 7.31 (5 H, m), 7.11 (1 H, d, *J* = 2.6 Hz), 7.06 (1 H, d, *J* = 8.4 Hz), 6.93 (1 H, dd, *J* = 8.4, 2.6 Hz), 5.11 - 5.07 (2 H, m), 4.75 - 4.63 (2 H, m), 4.42 (1 H, d, *J* = 16.7 Hz), 3.83 (1 H, dd, *J* = 13.3, 5.4 Hz), 3.66 (1 H, dd, *J* = 13.3, 3.7 Hz), 1.54 - 1.46 (9 H, m).

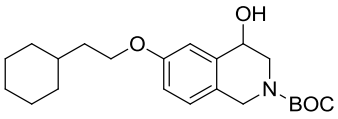
11.8.8 *tert*-Butyl 6-([1,1'-biphenyl]-4-ylmethoxy)-4-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (208)



208

N-Protected phenol **206** (0.200 g, 0.750 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.036 g, 0.90 mmol) and 4-(chloromethyl)-1,1'-biphenyl **128** (0.168 g, 0.830 mmol) as described for **207**, and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.269 g, 83%). ^{1}H NMR ($CDCl_3$) δ 7.66 - 7.56 (4 H, m), 7.54 - 7.41 (4 H, m), 7.40 - 7.33 (1 H, m), 7.14 (1 H, d, *J* = 2.6 Hz), 7.06 (1 H, d, *J* = 8.5 Hz), 6.94 (1 H, dd, *J* = 8.5, 2.6 Hz), 5.12 - 5.10 (2 H, m), 4.76 - 4.70 (1 H, m), 4.66 (1 H, d, *J* = 16.6 Hz), 4.43 (1 H, d, *J* = 16.6 Hz), 3.79 (1 H, dd, *J* = 13.4, 5.4 Hz), 3.68 (1 H, dd, *J* = 13.4, 3.8 Hz), 1.60 - 1.41 (9 H, m).

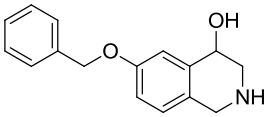
11.8.9 *tert*-Butyl 6-(2-cyclohexylethoxy)-4-hydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (209)



209

N-Protected phenol **206** (0.190 g, 0.720 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.036 g, 0.90 mmol) and 2-cyclohexylethyl tosylate **107** (0.230 g, 0.830 mmol) as described for **207**, and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.106 g, 39%). ^{1}H NMR ($CDCl_3$) δ 7.03 (1 H, d, *J* = 8.5 Hz), 6.99 (1 H, d, *J* = 2.6 Hz), 6.84 (1 H, dd, *J* = 8.5, 2.6 Hz), 4.73 - 4.66 (1 H, m), 4.40 (1 H, d, *J* = 16.5 Hz), 4.05 - 3.94 (3 H, m), 3.80 (1 H, d, *J* = 5.4 Hz), 3.65 (1 H, d, *J* = 3.6 Hz), 1.82 - 1.61 (7 H, m), 1.53 - 1.47 (9 H, m), 1.32 - 1.12 (4 H, m), 0.97 (2 H, dd, *J* = 11.5, 3.1 Hz). See pg. 238 for details on the synthesis of 2-cyclohexylethyl tosylate **107**.

11.8.10 6-(Benzyloxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (210)

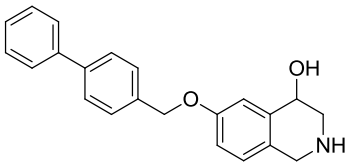


210

N-Protected isoquinoline **207** (0.194 g, 0.550 mmol) was dissolved in a mixture of anhydrous dichloromethane and trifluoroacetic acid (2:1) and stirred at room temperature for 20 minutes, and then subjected to workup method 2. The resulting brown gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a colourless gummy solid which slowly crystallised (0.058 g, 41%). m.p. 112.0 - 114.9 °C; ^{1}H NMR ($CDCl_3$) δ 7.47-7.29 (5 H, m), 7.01 (1 H, d, *J* = 2.6 Hz), 6.94 - 6.90 (1 H, m), 6.88 (1 H, dd, *J* = 8.4, 2.6 Hz), 5.10 - 5.02 (2 H, m), 4.54 - 4.48 (1 H, m), 3.84 (2 H, s), 3.21 (1 H, dd, *J* = 12.8, 3.2 Hz), 3.06 - 2.89 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 157.6, 138.0, 137.1, 128.7, 128.3, 128.1, 127.6, 127.4, 115.6, 114.9, 70.2,

66.1, 51.1, 47.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_2$ 256.1332; Found 256.1335.

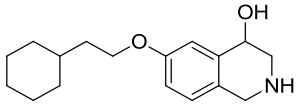
11.8.11 6-([1,1'-Biphenyl]-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (211)



211

N-Protected isoquinoline **208** (0.269 g, 0.620 mmol) was deprotected as described for **210**, and subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in dichloromethane) to afford the desired product as a white solid (0.112 g, 55%). m.p. 145.5 - 149°C; ^{1}H NMR (DMSO-d_6) δ 7.72 - 7.64 (4 H, m), 7.56 - 7.51 (2 H, m), 7.50 - 7.44 (2 H, m), 7.40- 7.35 (1 H, m), 7.10 (1 H, d, J = 2.8 Hz), 7.05 (1 H, d, J = 8.6 Hz), 6.93 (1 H, dd, J = 8.4, 2.8 Hz), 5.15 (2 H, s), 4.61 - 4.53 (1 H, m), 4.05 - 3.87 (2 H, m), 3.24 - 3.15 (1 H, m), 2.96 (1 H, dd, J = 12.5, 5.8 Hz); ^{13}C NMR (DMSO-d_6) δ 157.1, 139.8, 139.6, 138.6, 136.3, 128.9, 128.1, 127.5, 126.9, 126.7, 126.6, 125.1, 114.5, 114.0, 68.8, 63.4, 49.2, 45.4; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_2$ 332.1645; Found 332.1648.

11.8.12 6-(2-Cyclohexylethoxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (212)

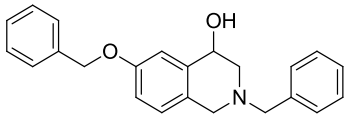


212

N-Protected isoquinoline **209** (0.106 g, 0.280 mmol) was deprotected as described for **210**, and subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (5% methanol, 0.5% sat. ammonia solution, in

dichloromethane) to afford the desired product as a colourless gummy solid (0.085 g, >95%). ^{1}H NMR ($CDCl_3$) δ 6.93 - 6.87 (2 H, m), 6.81 - 6.76 (1 H, m), 4.54 - 4.48 (1 H, m), 4.01 - 3.93 (2 H, m), 3.80 (2 H, s), 3.58 - 3.42 (1 H, m), 3.25 - 3.16 (1 H, m), 2.99 (1 H, dd, *J* = 12.9, 3.1 Hz), 1.83 - 1.61 (7 H, m), 1.56 1.43 - (1 H, m), 1.33 - 1.10 (3 H, m), 1.04 - 0.91 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 158.1, 137.5, 127.2, 126.9, 115.4, 114.5, 66.2, 65.6, 50.9, 47.1, 36.8, 34.7, 33.4, 26.6, 26.3; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{26}NO_2$ 276.1958; Found 276.1961.

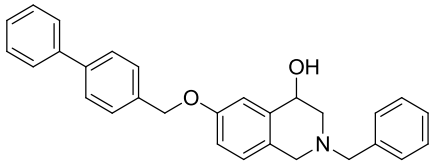
11.8.13 2-Benzyl-6-(benzyloxy)-1,2,3,4-tetrahydroisoquinolin-4-ol (213)



213

Phenol **204** (0.050 g, 0.22 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.009 g, 0.2 mmol), and benzyl bromide (26 μL, 0.22 mmol) as described for **207**, and subjected to workup method 1. The resulting yellow gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.051 g, 74%). ^{1}H NMR ($CDCl_3$) δ 7.47 - 7.28 (10 H, m), 7.06 (1 H, d, *J* = 2.6 Hz), 6.94 (1 H, d, *J* = 8.6 Hz), 6.88 (1 H, dd, *J* = 8.6, 2.6 Hz), 5.10 - 5.02 (2 H, m), 4.64 - 4.57 (1 H, m), 3.85 - 3.76 (3 H, m), 3.45 - 3.36 (1 H, m), 3.15 - 3.07 (1 H, m), 2.75 - 2.68 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 157.8, 138.0, 138.0, 137.2, 129.2, 128.7, 128.6, 128.1, 127.6, 127.54, 127.51, 127.4, 115.7, 114.5, 70.2, 67.6, 62.8, 58.3, 55.45; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{24}NO_2$ 346.1807; Found 346.1803.

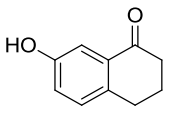
11.8.14 6-([1,1'-Biphenyl]-4-ylmethoxy)-2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-ol (214)



214

Phenol **204** (0.050 g, 0.22 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.009 g, 0.2 mmol), and 4-(chloromethyl)-1,1'-biphenyl **128** (0.045 g, 0.22 mmol) as described for **207**, and subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (1% methanol in dichloromethane) to afford the desired product as a colourless gummy solid (0.059 g, 70%). m.p. 105 - 108.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 - 7.58 (4 H, m), 7.53 - 7.42 (4 H, m), 7.41 - 7.33 (5 H, m), 7.33 - 7.28 (1 H, m), 7.07 (1 H, dd, *J* = 2.5, 0.4 Hz), 6.96 (1 H, d, *J* = 8.3 Hz), 6.90 (1 H, dd, *J* = 8.3, 2.5 Hz), 5.11 (2 H, dd, *J* = 1.9, 0.5 Hz), 4.59 (1 H, t, *J* = 3.1 Hz), 3.79 (1 H, d, *J* = 14.5 Hz), 3.75 (2 H, s), 3.37 (1 H, d, *J* = 14.5 Hz), 3.07 (1 H, ddd, *J* = 11.6, 3.4, 1.4 Hz), 2.68 (1 H, dd, *J* = 11.6, 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 157.8, 141.1, 141.0, 138.0, 137.9, 136.2, 129.2, 128.9, 128.6, 128.1, 127.60, 127.57, 127.52, 127.49, 127.4, 127.3, 115.7, 114.5, 70.0, 67.6, 62.8, 58.2, 55.5; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{28}NO_2$ 422.2120; Found 422.2113.

11.8.15 7-Hydroxy-3,4-dihydronaphthalen-1(2*H*)-one (216)

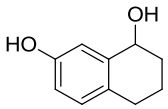


216

7-Methoxy-1-tetralone **215** (1.000 g, 5.71 mmol) was added to a suspension of aluminium trichloride (1.540 g, 11.55 mol) in anhydrous toluene (40 mL) and the reaction mixture heated at reflux for 3.5 hrs. The reaction was quenched with water (40 mL) and extracted with ethyl acetate (3×40 mL). The ethyl acetate fractions were combined, dried over magnesium sulfate and concentrated under reduced pressure to afford an orange solid. This was purified by column chromatography (20% ethyl

acetate in petroleum spirits 40-60) to afford the desired product as a white solid (0.480 g, 52%). ^{1}H NMR ($CDCl_3$) δ 7.53 (1 H, d, *J* = 2.8 Hz), 7.15 (1 H, d, *J* = 8.2 Hz), 7.03 (1 H, dd, *J* = 8.2, 2.8 Hz), 5.72 (1 H, s), 2.89 (2 H, t, *J* = 6.2 Hz), 2.65 – 2.62 (2 H, m), 2.16 - 2.06 (2 H, m).

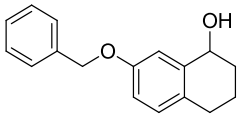
11.8.16 1,2,3,4-Tetrahydronaphthalene-1,7-diol (217)



217

Ketone **216** (0.480 g, 2.96 mmol) was dissolved in methanol (20 mL) and cooled to 0°C. Sodium borohydride (0.227 g, 6.00 mmol) was added and the reaction mixture allowed to warm to room temperature and then stirred for a further 45 minutes. The reaction mixture was concentrated under reduced pressure, diluted with water (30 mL), and extracted with ethyl acetate (3×30 mL). The ethyl acetate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford a white solid (0.462 g, 95%). m.p 144 - 145.5 °C; ^{1}H NMR (DMSO-d_6) δ 8.98 (1 H, s), 6.83 - 6.81 (2 H, m), 6.54 (1 H, dd, *J* = 8.4, 2.8 Hz), 4.97 (1 H, d, *J* = 6 Hz), 4.67 - 4.24 (1 H, m), 2.62 - 2.54 (2 H, m), 1.89 - 1.78 (2 H, m), 1.66 - 1.55 (2 H, m); ^{13}C NMR (DMSO-d_6) δ 155.1, 141.3, 129.0, 126.5, 114.4, 114.1, 66.6, 32.5, 28.0, 19.6.

11.8.17 7-(Benzyloxy)-1,2,3,4-tetrahydronaphthalen-1-ol (218)

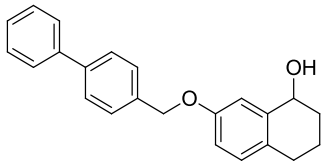


218

Phenol **217** (0.100 g, 0.610 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.031 g, 0.78 mmol), and benzyl bromide (80 μL, 0.67 mmol) as described for **207**, and subjected to workup method 1. The resulting brown oil was purified by column chromatography (20% ethyl acetate in petroleum spirits 40-60) to

afford the desired product as a colourless oil (0.130 g, 84%).^{1}H NMR ($CDCl_3$) δ 7.47 - 7.42 (2 H, m), 7.42 - 7.36 (2 H, m), 7.35 - 7.30 (1 H, m), 7.09 (1 H, d, *J* = 2.7 Hz), 7.03 (1 H, d, *J* = 8.4 Hz), 6.86 (1 H, dd, *J* = 8.4, 2.7 Hz), 5.11- 5.02 (2 H, m), 4.75 (1 H, t, *J* = 5.2 Hz), 2.83 - 2.73 (1 H, m), 2.71 - 2.59 (1 H, m), 2.08 - 1.71 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 157.4, 140.0, 137.3, 130.1, 129.6, 128.7, 128.0, 127.6, 115.3, 114.0, 70.2, 68.6, 32.5, 28.6, 19.3; HRMS *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_2$ 277.1204; Found 277.1212.

11.8.18 7-([1,1'-Biphenyl]-4-ylmethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (219)

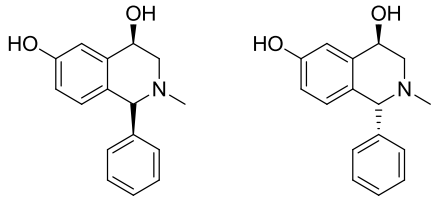


219

Phenol **217** (0.100 g, 0.610 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.030 g, 0.75 mmol), and 4-(chloromethyl)-1,1'-biphenyl **128** (0.137 g, 0.680 mmol) as described for **207**, and subjected to workup method 1. The resulting brown solid was purified by column chromatography (20% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a white solid (0.175 g, 87%). m.p. 124 - 126.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 - 7.58 (4 H, m), 7.55 - 7.49 (2 H, m), 7.49 - 7.43 (2 H, m), 7.40 - 7.34 (1 H, m), 7.14 - 7.11 (1 H, m), 7.05 (1 H, d, *J* = 8.4 Hz), 6.89 (1 H, dd, *J* = 8.4, 2.7 Hz), 5.16 - 5.07 (2 H, m), 4.76 (1 H, t, *J* = 5.2 Hz), 2.83 - 2.74 (1 H, m), 2.73 - 2.61 (1 H, m), 2.11 - 1.72 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 157.4, 141.0, 141.04, 140.97, 136.3, 130.2, 129.6, 128.9, 128.1, 127.5, 127.3, 115.3, 114.0, 70.0, 68.6, 32.6, 28.6, 19.3 (note some signals coincident); HRMS *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{22}NaO_2$ 353.1512; Found 353.1512.

11.9 Substitution of the methylene carbon

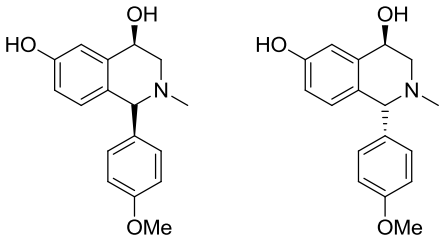
11.9.1 (4*R*)-2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (220 isomers A and B)



220A **220B**

Phenylephrine hydrochloride (0.201 g, 0.980 mmol) and benzaldehyde (100 µL, 0.98 mmol) were combined and heated at 130°C for 3 hrs, then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford isomer A as a cream coloured solid (0.035 g, 15%) m.p. 64.5 - 65.9 °C; ^{1}H NMR (DMSO-d_6) δ 9.19 (1 H, s), 7.36 - 7.19 (5 H, m), 6.77 (1 H, d, *J* = 2.5 Hz), 6.48 (1 H, dd, *J* = 8.4, 2.5 Hz), 6.34 (1 H, d, *J* = 8.4 Hz), 5.00 (1 H, d, *J* = 7.6 Hz), 4.52 - 4.43 (1 H, m), 4.15 (1 H, s), 2.91 (1 H, dd, *J* = 12.0, 4.1 Hz), 2.60 (1 H, dd, *J* = 12.0, 3.8 Hz), 2.07 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 155.9, 143.5, 138.6, 130.0, 129.4, 129.1, 128.3, 127.5, 115.1, 115.0, 69.6, 65.7, 58.6, 44.1 HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_2$ 256.1332; Found 256.1333; Further elution afforded isomer B as a pale yellow coloured solid (0.051 g, 21%). m.p. 130 - 133.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.16 (1 H, s), 7.38 - 7.17 (5 H, m), 6.94 (1 H, d, *J* = 2.3 Hz), 6.43 (1 H, dd, *J* = 8.4, 2.3 Hz), 6.28 (1 H, d, *J* = 8.4 Hz), 5.35 (1 H, d, *J* = 7.1 Hz), 4.87 - 4.75 (1 H, m), 4.09 (1 H, s), 3.12 (1 H, dd, *J* = 10.4, 5.6 Hz), 2.35 (1 H, t, *J* = 10.4 Hz), 2.07 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 155.8, 145.0, 141.0, 129.5, 129.3, 128.9, 128.6, 127.6, 114.4, 112.2, 71.3, 66.0, 60.8, 44.1; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{18}NO_2$ 256.1332; Found 256.1338.

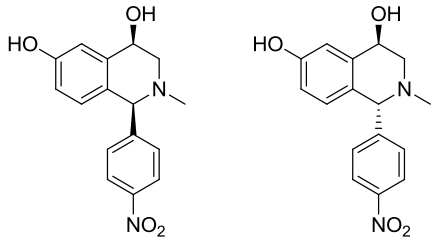
11.9.2 (4*R*)-1-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (221 isomer A and B)



221A **221B**

Phenylephrine hydrochloride (0.300 g, 1.47 mmol) and 4-methoxybenzaldehyde (180 µL, 1.47 mmol) were combined and heated at 130°C for 4 hrs then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford isomer A as a pale yellow coloured solid (0.071 g, 17%) m.p. 69.5 - 71.5 °C ;^{1}H NMR (DMSO-d_6) δ 9.18 (1 H, s), 7.23 - 7.11 (2 H, m), 6.92 - 6.82 (2 H, m), 6.77 (1 H, d, *J* = 2.6 Hz), 6.48 (1 H, dd, *J* = 8.4, 2.6 Hz), 6.35 (1 H, d, *J* = 8.4 Hz), 4.99 (1 H, d, *J* = 7.6 Hz), 4.53 - 4.39 (1 H, m), 4.09 (1 H, s), 3.74 (3 H, s), 2.90 (1 H, dd, *J* = 12.0, 4.0 Hz), 2.58 (1 H, dd, *J* = 12.0, 3.7 Hz), 2.06 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 158.3, 155.4, 138.2, 134.9, 130.6, 129.4, 128.7, 114.7, 114.5, 113.3, 68.5, 65.3, 58.1, 55.0, 43.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_3$ 286.1438; Found 286.1437; Further elution afforded isomer B as a pale yellow coloured solid (0.122 g, 29%) m.p. 149.5 - 152.9°C; ^{1}H NMR (DMSO-d_6) δ 9.14 (1 H, s), 7.13 (2 H, d, *J* = 8.6 Hz), 6.93 (1 H, d, *J* = 2.4 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 6.43 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.29 (1 H, d, *J* = 8.4 Hz), 5.32 (1 H, d, *J* = 7.1 Hz), 4.83 - 4.72 (1 H, m), 4.03 (1 H, s), 3.73 (3 H, s), 3.11 (1 H, dd, *J* = 10.4, 5.5 Hz), 2.33 (1 H, t, *J* = 10.4 Hz), 2.06 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 158.3, 155.3, 140.5, 136.4, 130.1, 129.2, 128.5, 113.9, 113.5, 111.7, 70.2, 65.6, 60.5, 55.0, 43.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_3$ 286.1438; Found 286.1437.

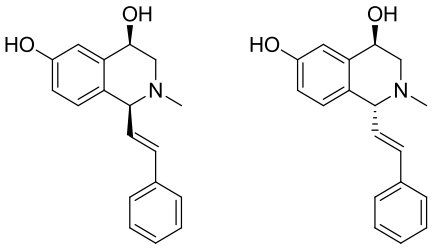
11.9.3 (4*R*)-2-Methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (222 isomer A and B)



222A **222B**

Phenylephrine hydrochloride (0.302 g, 1.47 mmol) and 4-nitrobenzaldehyde (0.223 g, 1.47 mmol) were combined and heated at 130°C for 4 hrs then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (3% methanol in dichloromethane) to afford isomer A as a yellow coloured solid (0.160 g, 36%) m.p. 95 - 97.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.30 (1 H, s), 8.22 - 8.15 (2 H, m), 7.61 (2 H, d, *J* = 8.7 Hz), 6.80 (1 H, d, *J* = 2.5 Hz), 6.51 (1 H, dd, *J* = 8.5, 2.5 Hz), 6.34 (1 H, d, *J* = 8.5 Hz), 5.13 (1 H, d, *J* = 7.8 Hz), 4.58 - 4.43 (1 H, m), 4.35 (1 H, s), 2.92 (1 H, dd, *J* = 12.1, 3.9 Hz), 2.65 (1 H, dd, *J* = 12.1, 3.5 Hz), 2.10 (3 H, s); ^{13}C NMR (DMSO-d6) δ 155.7, 151.6, 146.7, 138.1, 130.7, 128.6, 127.6, 123.2, 115.0, 114.9, 68.2, 65.1, 58.0, 43.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_4$ 301.1183; Found 301.1186; Further elution afforded isomer B as a pale yellow coloured solid (0.141 g, 32%). m.p. 93 - 95 °C; ^{1}H NMR (DMSO-d_6) δ 9.26 (1 H, s), 8.17 (2 H, d, *J* = 8.6 Hz), 7.54 (2 H, d, *J* = 8.6 Hz), 6.98 (1 H, d, *J* = 2.4 Hz), 6.45 (1 H, dd, *J* = 8.4, 2.4 Hz), 6.28 (1 H, d, *J* = 8.4 Hz), 5.43 (1 H, d, *J* = 6.9 Hz), 4.89 - 4.77 (1 H, m), 4.32 (1 H, s), 3.13 (1 H, dd, *J* = 10.4, 5.5 Hz), 2.38 (1 H, t, *J* = 10.4 Hz), 2.09 (3 H, s); ^{13}C NMR (DMSO-d6) δ 155.7, 152.7, 146.7, 140.7, 130.2, 128.4, 127.4, 123.5, 114.2, 112.0, 69.7, 65.5, 59.9, 43.6; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_4$ 301.1183; Found 301.1186.

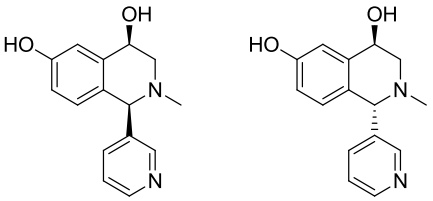
11.9.4 (4*R*)-2-Methyl-1-((*E*)-styryl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (223 isomer A and B)



223A **223B**

Phenylephrine hydrochloride (0.300 g, 1.47 mmol) and cinnamaldehyde (185 µL, 1.47 mmol) were combined and heated at 130°C for 7 hrs, then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford isomer A as a brown coloured solid (0.037 g, 9%) m.p. 84.5 - 88 °C; ^{1}H NMR (DMSO-d_6) δ 9.22 (1 H, s), 7.48 - 7.40 (2 H, m), 7.36 - 7.29 (2 H, m), 7.27 - 7.18 (1 H, m), 6.88 - 6.79 (2 H, m), 6.67 - 6.55 (2 H, m), 6.25 (1 H, dd, *J* = 15.9, 8.8 Hz), 5.03 (1 H, d, *J* = 7.4 Hz), 4.54 - 4.41 (1 H, m), 3.88 (1 H, d, *J* = 8.9 Hz), 2.87 (1 H, dd, *J* = 11.8, 5.9 Hz), 2.65 (1 H, dd, *J* = 11.8, 4.7 Hz), 2.33 (3 H, s); ^{13}C NMR (DMSO) δ 155.8, 138.9, 136.6, 132.0, 130.5, 128.7, 128.2, 127.5, 127.1, 126.3, 114.5, 114.3, 66.5, 65.2, 56.8, 43.4; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}NO_2$ 282.1489; Found 282.1492, and isomer B a brown coloured solid (0.064 g, 15%) m.p. 180.2 - 84.5°C; ^{1}H NMR (DMSO-d_6) δ 9.21 (1 H, s), 7.51 - 7.44 (2 H, m), 7.35 - 7.29 (2 H, m), 7.27 - 7.21 (1 H, m), 6.96 - 6.92 (1 H, m), 6.86 - 6.78 (1 H, m), 6.67 (1 H, d, *J* = 16.0 Hz), 6.60 - 6.53 (1 H, m), 6.01 (1 H, dd, *J* = 16.0, 8.8 Hz), 5.28 (1 H, d, *J* = 7.1 Hz), 4.69 - 4.56 (1 H, m), 3.73 (1 H, d, *J* = 8.9 Hz), 3.08 (1 H, dd, *J* = 10.7, 5.6 Hz), 2.32 (3 H, s), 2.30 - 2.23 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 155.8, 140.6, 136.5, 132.4, 131.8, 128.6, 127.9, 127.5, 126.4, 126.3, 114.0, 112.5, 68.8, 65.4, 59.6, 43.8; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}NO_2$ 282.1489; Found 282.1491.

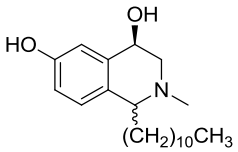
11.9.5 (4*R*)-2-Methyl-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline-4,6-diol (224 isomer A and B)



224A **224B**

Phenylephrine hydrochloride (0.302 g, 1.47 mmol) and 3-pyridinecarboxaldehyde (138 µL, 1.47 mmol) were combined and heated at 130°C for 3 hrs then subjected to workup method 1. The resulting yellow solid was purified by column chromatography (4% methanol in dichloromethane) to afford isomer A as a pale yellow coloured solid (0.041 g, 11%) decomp. 180 °C; ^{1}H NMR (DMSO-d_6) δ 9.21 (1 H, s), 8.51 - 8.43 (1 H, m), 7.66 (1 H, td, *J* = 7.6, 1.8 Hz), 7.20 (1 H, ddd, *J* = 7.6, 4.9, 1.2 Hz), 7.12 - 6.94 (3 H, m), 6.56 (1 H, dd, *J* = 7.6, 1.3 Hz), 5.33 (1 H, d, *J* = 7.4 Hz), 4.85 (1 H, s), 4.72 - 4.62 (1 H, m), 2.83 (1 H, dd, *J* = 11.4, 8.2 Hz), 2.68 (1 H, dd, *J* = 11.4, 5.6 Hz), 2.27 - 2.19 (3 H, m); ^{13}C NMR (DMSO-d_6) δ 160.2, 153.3, 147.9, 140.5, 135.5, 127.1, 123.6, 123.5, 121.7, 117.6, 113.1, 65.0, 63.6, 53.5, 42.7; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1286; Isomer B could not be separated from isomer A.

11.9.6 (4*R*)-2-Methyl-1-undecyl-1,2,3,4-tetrahydroisoquinoline-4,6-diol (225)

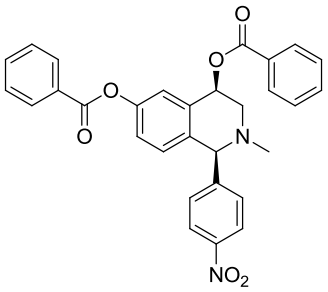


225

Phenylephrine hydrochloride (300 mg, 1.47 mmol) and dodecanal (326 µL, 1.47 mmol) were combined and heated at 130°C for 7 hrs, and subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (5% methanol in dichloromethane) to afford a mixture of isomers A

and B (66:34) as an orange gummy solid (213 mg, 43%) ^{1}H NMR (DMSO-d_6, selected peaks of isomer A) δ 9.09 (1 H, d, J = 5.4 Hz), 6.81 (1 H, d, J = 2.4Hz), 4.86 (1 H, d, J = 0.8 Hz), 2.79 (1 H, dd, J = 12.6, 7.8 Hz), 2.70 (1 H, dd, J = 12.6, 5.4 Hz), 2.37 (3 H, s). ^{1}H NMR (DMSO-d_6, selected peaks of isomer B) δ 9.22 (1 H, d, J = 8.0 Hz), 6.92 (1 H, d, J = 8.8 Hz), 5.16 (1 H, d, J = 0.8 Hz), 2.96 (1 H, dd, J = 10.8, 5.2 Hz), 2.32 (3 H, s), 2.22 (1 H, dd, J = 10.8, 8.8 Hz); ^{13}C NMR (DMSO-d_6) δ 155.8, 155.5, 142, 139.7, 129.4, 128.2, 127.9, 126.8, 114.7, 114.4, 114.2, 112.4, 65.8, 64.0, 62.8, 62.4, 60.3, 54.6, 43.8, 43.2, 34.3, 32.8, 31.8, 31.7, 29.9, 29.7, 29.5, 29.5, 29.5, 29.4, 29.2, 29.2, 26.1, 23.4, 22.6, 14.4 (note some peak coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{36}NO_2$ 334.2741; Found 334.2744.

11.9.7 (1*S*,4*R*)-2-Methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diyl dibenzoate (226)

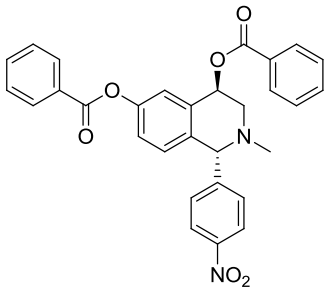


226

Phenol **222A** (0.020 g, 0.070 mmol) was dissolved in anhydrous dichloromethane (2mL). Triethylamine (39 μL, 0.28 mmol) was added followed by benzoyl chloride (24 μL, 0.21 mmol) and the reaction mixture stirred at room temperature for 24 hrs. A second portion of triethylamine (39 μL, 0.28 mmol) and benzoyl chloride (24 μL, 0.21 mmol) were added and the reaction mixture was stirred at room temperature for a further 24 hrs. The reaction mixture was diluted with water (5 mL) and dichloromethane (5 mL). The organic phase was separated, dried over magnesium sulfate, and concentrated under reduced pressure to afford an orange gummy solid which was purified by column chromatography (10% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a colourless gummy solid (0.016 g, 45%). ^{1}H NMR ($CDCl_3$) δ 8.28 - 8.22 (2 H, m), 8.18 - 8.10 (4 H, m), 7.66 - 7.56 (4 H, m), 7.52 - 7.43 (4 H, m), 7.37 (1 H, d, J = 2.3 Hz), 7.06 (1 H, dd, J = 8.6, 2.5 Hz),

6.73 (1 H, d, *J* = 8.6 Hz), 6.23 (1 H, t, *J* = 2.7 Hz), 4.42 (1 H, s), 3.43 (1 H, dd, *J* = 13.2, 2.6 Hz), 3.05 - 2.98 (1 H, m), 2.26 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.6, 165.2, 151.0, 149.8, 147.8, 136.3, 133.9, 133.3, 133.2, 130.5, 130.4, 130.3, 130.0, 129.5, 128.7, 128.6, 128.3, 124.0, 123.01, 122.7, 69.9, 68.6, 56.2, 44.2.

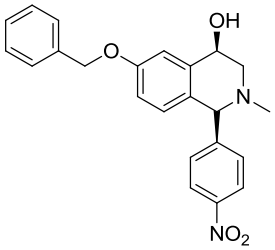
11.9.8 (1*R*,4*R*)-2-Methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-4,6-diyl dibenzoate (227)



227

Phenol **222B** (0.020 g, 0.070 mmol) was dissolved in anhydrous dichloromethane (2mL). Triethylamine (80 µL, 0.57 mmol) was added followed by benzoyl chloride (48 µL, 0.42 mmol) and the reaction mixture was stirred at room temperature for 24 hrs. The reaction mixture was diluted with water (5 mL) and dichloromethane (5 mL). The organic phase was separated, dried over magnesium sulfate, and concentrated under reduced pressure to afford an orange gummy solid which was purified by column chromatography (10% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a colourless gummy solid (0.027 g, 76%). ^{1}H NMR ($CDCl_3$) δ 8.27 - 8.21 (2 H, m), 8.18 - 8.10 (4 H, m), 7.65 - 7.57 (2 H, m), 7.56 - 7.52 (2 H, m), 7.52 - 7.45 (4 H, m), 7.28 (1 H, dd, *J* = 2.5, 1.0 Hz), 7.03 (1 H, ddd, *J* = 8.5, 2.5, 0.6 Hz), 6.72 (1 H, d, *J* = 8.5 Hz), 6.56 - 6.50 (1 H, m), 4.55 (1 H, s), 3.56 (1 H, dd, *J* = 11.1, 5.7 Hz), 2.79 (1 H, dd, *J* = 11.1, 9.0 Hz), 2.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.5, 165.2, 150.6, 150.0, 147.8, 135.7, 135.3, 133.9, 133.5, 130.4, 130.3, 130.0, 129.9, 129.5, 129.4, 128.72, 128.68, 124.0, 121.7, 119.6, 70.2, 68.9, 55.8, 44.0.

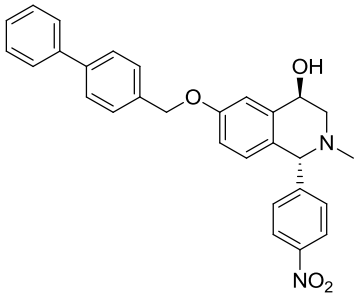
11.9.9 (4*R*)-6-(Benzyloxy)-2-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (228)



228

Isoquinoline **222A** (0.050 g, 0.17 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.008 g, 0.2 mmol) and benzyl bromide (24 μL, 0.20 mmol) as described for **230**, and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (3% methanol in dichloromethane) to afford the desired product as a pale yellow gummy solid (0.046 g, 69%). ^{1}H NMR ($CDCl_3$) δ 8.24 - 8.18 (2 H, m), 7.51 - 7.45 (2 H, m), 7.43 - 7.29 (5 H, m), 7.01 (1 H, d, *J* = 2.7 Hz), 6.74 (1 H, dd, *J* = 8.7, 2.7 Hz), 6.45 (1 H, d, *J* = 8.7 Hz), 5.04 (2 H, dd, *J* = 1.6, 0.5 Hz), 4.64 - 4.56 (1 H, m), 4.27 (1 H, s), 3.22 (1 H, dd, *J* = 12.1, 2.6 Hz), 2.85 (1 H, ddd, *J* = 12.1, 2.0, 0.6 Hz), 2.23 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 157.9, 151.1, 147.7, 137.6, 136.9, 130.3, 129.6, 129.4, 128.8, 128.2, 127.6, 124.0, 115.9, 114.6, 70.9, 70.2, 67.2, 60.0, 44.2; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{23}N_2O_4$ 391.1652; Found 391.1657.

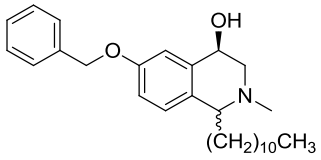
11.9.10 (4*R*)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (229)



229

Isoquinoline **222B** (0.050 g, 0.17 mmol) was was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.008 g, 0.2 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes. 4-(Chloromethyl)-1,1'-biphenyl **128** (0.040 g, 0.19 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs. The reaction was quenched with methanol (2 mL) and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (3% methanol in dichloromethane) to afford the desired product as a white solid (0.035 g, 44%). m.p. 143.5 - 145.5°C; ^{1}H NMR ($CDCl_3$) δ 8.21 - 8.15 (2 H, m), 7.64 - 7.55 (4 H, m), 7.52 - 7.32 (7 H, m), 7.29 - 7.22 (1 H, m), 6.76 (1 H, dd, *J* = 8.6, 2.8 Hz), 6.54 6.49 - (1 H, m), 5.13 - 5.07 (2 H, m), 5.03 (1 H, br. s.), 4.46 (1 H, s), 3.30 (1 H, dd, *J* = 11.2, 5.1 Hz), 2.57 (1 H, dd, *J* = 11.2, 8.3 Hz), 2.23 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 158.0, 150.5, 147.6, 141.2, 140.9, 139.4, 135.9, 130.4, 129.6, 129.3, 129.0, 128.2, 127.6, 127.5, 127.3, 123.7, 115.3, 111.7, 70.0, 69.8, 67.3, 59.2, 43.9; HRMS *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{27}N_2O_4$ 467.1965; Found 467.1972.

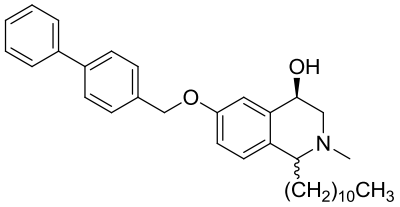
11.9.11 (4*R*)-6-(Benzyloxy)-2-methyl-1-undecyl-1,2,3,4-tetrahydroisoquinolin-4-ol (230)



230

Isoquinoline **225** (as a mixture of isomers A and B , 0.060 g, 0.18 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.009 g, 0.2 mmol) in anhydrous dimethylformamide and the mixture stirred at room temperature for 30 minutes. Benzyl bromide (24 μL, 0.20 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs. The reaction was quenched with methanol (2 mL) and then subjected to workup method 1. The resulting orange gummy solid was purified by column chromatography (3% methanol in dichloromethane) to afford the desired product as a pale yellow gummy solid (0.017 g, 22%). Only one isomer was isolated. ^{1}H NMR ($CDCl_3$) δ 7.46 - 7.36 (4 H, m), 7.35 - 7.30 (1 H, m), 7.11 (1 H, d, *J* = 8.5 Hz), 6.93 (1 H, d, *J* = 2.7 Hz), 6.90 (1 H, dd, *J* = 8.5, 2.7 Hz), 5.09 - 5.02 (2 H, m), 4.48 - 4.39 (1 H, m), 3.42 - 3.35 (1 H, m), 3.02 (1 H, dd, *J* = 11.5, 3.3 Hz), 2.70 (1 H, ddd, *J* = 11.5, 1.6, 0.6 Hz), 2.48 (3 H, s), 2.08 - 1.93 (1 H, m), 1.91 - 1.79 (1 H, m), 1.38 - 1.06 (18 H, m), 0.91 - 0.82 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 157.3, 139.0, 137.2, 130.5, 128.7, 128.1, 127.7, 127.2, 115.8, 114.1, 70.2, 67.3, 64.0, 59.5, 43.5, 32.2, 32.1, 30.2, 29.80, 29.75, 29.67, 29.5, 22.9, 22.8, 14.3; HRMS *m/z*: $[M]^+$ Calcd for $C_{28}H_{40}NO_2$ (iminium species) 422.3054; Found 422.3057.

11.9.12 (4*R*)-6-([1,1'-Biphenyl]-4-ylmethoxy)-2-methyl-1-undecyl-1,2,3,4-tetrahydroisoquinolin-4-ol (231)

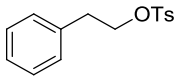


231

Isoquinoline **225** (0.061 g, 0.18 mmol) was treated with sodium hydride (60% dispersion in mineral oil, 0.010 g, 0.25 mmol), 4-(chloromethyl)-1,1'-biphenyl **128** (0.041 g, 0.20 mmol), and sodium iodide (0.055 g, 0.36 mmol) as described for **230**, and then subjected to workup method 1. The resulting brown gummy solid was purified by column chromatography (3% methanol in dichloromethane) to afford the desired product as a pale orange gummy solid (0.049 g, 54%). Only one isomer was isolated. ^{1}H NMR ($CDCl_3$) δ 7.65 - 7.57 (4 H, m), 7.54 - 7.49 (2 H, m), 7.49 - 7.42 (2 H, m), 7.39 - 7.34 (1 H, m), 7.14 (1 H, d, *J* = 8.6 Hz), 6.97 - 6.94 (1 H, m), 6.93 (1 H, d, *J* = 2.8 Hz), 5.16 - 5.04 (2 H, m), 4.48 - 4.39 (1 H, m), 3.44 - 3.35 (1 H, m), 3.06 - 2.93 (1 H, m), 2.71 (1 H, dt, *J* = 11.5, 1.1 Hz), 2.51 - 2.42 (3 H, m), 2.08 - 1.93 (1 H, m), 1.92 - 1.80 (1 H, m), 1.35 - 1.15 (18 H, m), 0.93 - 0.84 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 157.3, 141.1, 141.0, 139.0, 136.2, 130.5, 128.9, 128.2, 127.5, 127.3, 115.8, 114.1, 70.0, 67.4, 64.0, 59.6, 43.5, 32.2, 32.1, 30.2, 29.80, 29.76, 29.7, 29.5, 22.9, 22.8, 14.3 (note some signals coincident); HRMS *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{46}NO_2$ 500.3523; Found 500.3524.

11.10 Intermediates

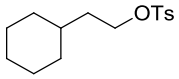
11.10.1 Phenylethyl tosylate (102)



102

2-Phenylethanol (2.0 mL, 17 mmol) was dissolved in anhydrous dichloromethane and triethylamine (4.7 mL, 34 mmol). 4-Toluenesulfonyl chloride (4.76 g, 25.0 mmol) was added slowy with cooling at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 24 hrs. The reaction mixture was diluted with water and stirred for 1 hour, followed by dilution with ether. This was then washed sequentially with water, 1M hydrochloric acid, 5% sodium bicarbonate, and finally water. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The resulting orange liquid was purified by column chromatography (10% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a colourless oil (1.64 g, 36%). ^{1}H NMR ($CDCl_3$) δ 7.73 - 7.70 (2 H, m), 7.32 - 7.24 (5 H, m), 7.15 - 7.13 (2 H, m), 4.24 (2 H, t, *J* = 7.0 Hz), 2.98 (2 H, t, *J* = 7.0 Hz), 2.46 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 144.8, 136.3, 133.1, 129.9, 129.0, 128.7, 127.9, 126.95, 70.7, 35.4, 21.7.

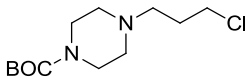
11.10.2 2-Cyclohexylethyl tosylate (107)



107

2-Cyclohexylethanol (1.02 g, 8.00 mmol) was treated with 4-toluenesulfonyl chloride (1.84 g, 9.65 mmol) and triethylamine (2.20 mL, 15.6 mmol) as described for **102**. The resulting colourless oil was used without further purification (2.20 g, 97%). ^{1}H NMR ($CDCl_3$) δ 7.79 - 7.77 (2 H, m), 7.35 - 7.33 (2 H, m), 4.05 (2 H, t, *J* = 6.6 Hz), 2.44 (3 H, s), 1.67 - 1.54 (6 H, m), 1.51 (2 H, apparent q, *J* = 6.6 Hz), 1.37 - 1.27 (1 H, m), 1.22 - 1.04 (2 H, m), 0.87 - 0.77 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 144.7, 133.3, 129.9, 128.0, 68.9, 36.2, 33.9, 32.9, 26.4, 26.1, 21.7

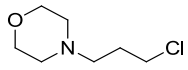
11.10.3 *tert*-Butyl 4-(3-chloropropyl)piperazine-1-carboxylate (115)



115

1-BOC-piperazine (1.01 g, 5.24 mmol), and triethylamine (0.900 mL, 6.50 mmol) were dissolved in dichloromethane (10 mL). 1-Bromo-3-chloropropane (0.640 mL, 6.50 mmol) was added and the reaction mixture stirred at room temperature for 2 days. The reaction mixture was washed with water (10 mL) followed by sat. brine (10 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to afford a white gummy solid. This gummy solid was purified by column chromatography (20-100% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a pale yellow oil (0.70 g, 50%). ^{1}H NMR ($CDCl_3$) δ 3.59 (2 H, t, *J* = 6.8 Hz), 3.41 (4 H, t, *J* = 4.9 Hz), 2.48 (2 H, t, *J* = 6.8 Hz), 2.37 (4 H, t, *J* = 4.9 Hz), 1.97 - 1.90 (2 H, m), 1.45 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 154.7, 79.6, 55.4, 53.0, 43.1, 29.8, 28.4.

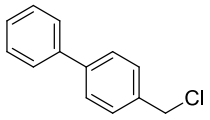
11.10.4 4-(3-Chloropropyl)morpholine (117)



117

Morpholine (2.00 mL, 23.2 mmol) and 1-bromo-3-chloropropane (2.30 mL, 23.2 mmol), and triethylamine (4.00 mL, 28.7 mmol) were dissolved in anhydrous dichloromethane (20 mL) and heated at reflux for 2 hrs. The reaction mixture was then diluted with water (40 mL), separated, and the aqueous layer extracted with dichloromethane (2 × 40 mL). The dichloromethane fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford a pale yellow oil containing a fine white solid. The oil was dissolved in tetrahydrofuran and filtered, to remove the white solid, to afford the desired product as a pale yellow oil (2.95 g, 78%). ^{1}H NMR ($CDCl_3$) δ 3.69 (4 H, t, *J* = 4.7 Hz), 3.59 (2 H, t, *J* = 6.8 Hz), 2.47 (2 H, t, *J* = 6.8 Hz), 2.44 - 2.42 (4 H, m), 1.94 (2 H, quin, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 67.0, 55.9, 53.8, 43.2, 29.6.

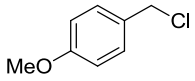
11.10.5 4-(Chloromethyl)-1,1'-biphenyl (128)



128

4-Biphenymethanol **244** (1.020 g, 5.540 mmol) was treated with thionyl chloride (0.800 mL, 10.9 mmol) as described for **240**. The resulting white solid was purified by column chromatography (10% ethyl acetate in petroleum spirits 40-60) to afford the desired product as a white solid (0.392 g, 35%). m.p. 71 - 73°C (68 - 69°C lit[216]); ^{1}H NMR ($CDCl_3$) δ 7.62 - 7.58 (4 H, m), 7.49 - 7.44 (4 H, m), 7.40 - 7.35 (1 H, m), 4.65 (2 H, s); ^{13}C NMR ($CDCl_3$) δ 141.6, 140.7, 136.6, 129.2, 129.0, 127.7, 127.6, 127.3, 46.2.

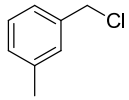
11.10.6 1-(Chloromethyl)-4-methoxybenzene (240)



240

4-Methoxybenzyl alcohol (1.80 mL, 14.5 mmol) was dissolved in anhydrous ether (2 mL/mmol of alcohol). Thionyl chloride (2.1 mL, 29 mmol) was added and the reaction mixture stirred at room temperature for 24 hrs. The reaction was quenched with water, and extracted twice with dichloromethane. The dichloromethane fractions were combined and washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting pale yellow liquid was used without further purification (2.20 g, 97%). ^{1}H NMR ($CDCl_3$) δ 7.34 - 7.30 (2 H, m), 6.91 - 6.87 (2 H, m), 4.43 (2 H, s), 3.65 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 159.7, 130.1, 129.7, 114.2, 55.3, 46.3.

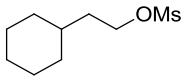
11.10.7 3-Methylbenzyl chloride (241)



241

3-Methylbenzyl alcohol (1.50 mL, 12.5 mmol) was treated with thionyl chloride (1.80 mL, 25.0 mmol) as described for **240**. The resulting colourless oil was used without further purification (1.54 g, 88%). ^{1}H NMR ($CDCl_3$) δ 7.28 - 7.13 (4 H, m), 4.60 (2 H, s), 2.40 (3 H, s); ^{13}C NMR ($CDCl_3$) δ138.6, 137.5, 129.4, 129.3, 128.8, 125.8, 46.5, 21.4.

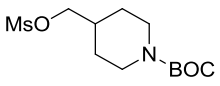
11.10.8 2-Cyclohexylethyl methanesulfonate (242)



242

2-Cyclohexylethanol (0.504 g, 3.90 mmol) was treated with methanesulfonyl chloride (365 µ, 4.70 mmol), and triethylamine (820 µL, 5.90 mmol) as described for **243**. The resulting pale yellow oil (0.794 g, >95%) was used without further purification. ^{1}H NMR ($CDCl_3$) δ 4.26 (2 H, t, *J* = 6.8 Hz), 2.99 (3 H, s), 1.77 - 1.54 (7 H, m), 1.51 - 1.36 (1 H, m), 1.31 - 1.09 (3 H, m), 1.01 - 0.85 (2 H, m).

11.10.9 *tert*-Butyl 4-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (243)

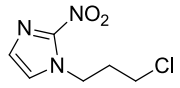


243

N-BOC-4-piperidinemethanol (0.507 g, 2.35 mmol) was dissolved in anhydrous dichloromethane and triethylamine (0.50 mL, 3.5 mmol). The reaction mixture was cooled to 0°C and methanesulfonyl chloride (0.22 mL, 2.84 mmol) was added. The reaction mixture was stirred at 0-10°C for a further 1 hour. The reaction mixture was

diluted with water and stirred for 30 minutes, then diluted with dichloromethane. The organic phase was separated, washed with 5% sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting pale yellow oil was purified by column chromatography (50:50: ethyl acetate : petroleum spirits 40-60) to afford the desired product as a colourless oil which slowly crystallised (0.467 g, 68%). m.p. 81 - 83°C (76 - 78°C lit[217]); ^{1}H NMR ($CDCl_3$) δ 4.15 (2 H, d, *J* = 13.0 Hz), 4.07 (2 H, d, *J* = 6.5 Hz), 3.01 (3 H, s), 2.75 - 2.67 (2 H, m), 1.97 - 1.86 (1 H, m), 1.74 (2 H, d, *J* = 13.0 Hz), 1.45 (9 H, s), 1.29 - 1.16 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 154.9, 79.8, 73.5, 43.4, 37.5, 36.2, 28.6, 28.4.

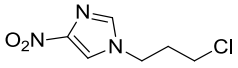
11.10.10 1-(3-Chloropropyl)-2-nitro-1*H*-imidazole (122)



122

2-Nitroimidazole (0.500 g, 4.42 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.212 g, 5.30 mmol) in anhydrous dimethylformamide (15 mL) and the mixture stirred at room temperature for 30 minutes. 1-Bromo-3-chloropropane (525 μL, 5.30 mmol) was added and the mixture stirred at room temperature for a further 19 hrs, then subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (50:50, ethyl acetate:petroleum spirit 40-60) to afford the desired product as a yellow oil which slowly crystallised (0.107 g, 13%). The product contained a small amount of the terminal alkene product, obtained from elimination of the chlorine atom, but was used without further purification. ^{1}H NMR (DMSO-d_6) δ 7.67 (1 H, d, *J* = 1.2 Hz), 7.19 (1 H, d, *J* = 1.2 Hz), 4.59 - 4.38 (2 H, m), 3.74 - 3.58 (2 H, m), 2.32 - 2.16 (2 H, m).

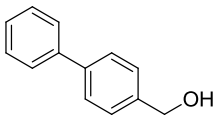
11.10.11 1-(3-Chloropropyl)-4-nitro-1*H*-imidazole (125)



125

4-Nitroimidazole (0.499 g, 4.42 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0. 212 g, 5.30 mmol) in anhydrous dimethylformamide (15 mL) and the mixture stirred at room temperature for 30 minutes. 1-Bromo-3-chloropropane (524 μL, 5.30 mmol) was added and the mixture stirred at room temperature for a further 24 hrs, then subjected to workup method 2. The resulting orange gummy solid was purified by column chromatography (50:50, ethyl acetate:petroleum spirit 40-60) to afford the desired product as a yellow oil which slowly crystallised (0.325 g, 39%). The product contained a small amount of the terminal alkene product, obtained from elimination of the chlorine atom, but was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.45 (1 H, d, J = 1.6 Hz), 7.89 (1 H, d, J = 1.6 Hz), 4.26 - 4.13 (2 H, m), 3.62 (2 H, t, J = 6.5 Hz), 2.27 (2 H, quin, J = 6.5 Hz).

11.10.12 [1,1'-Biphenyl]-4-ylmethanol (244)

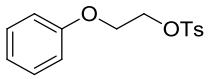


244

Biphenyl-4-carboxylic acid (0.500 g, 2.52 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL) and lithium aluminium hydride (0.293 g, 7.72 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 4 hrs. The reaction was quenched slowly with water (5 mL) and stirring was continued for 30 minutes. HCl (2 M, 30 mL) was added to dissolve the white precipitate. This was then extracted with ether (3 × 40 mL). The ether fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to afford a white solid (0.456 g, 98%) which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.63

- 7.59 (4 H, m), 7.49 - 7.43 (4 H, m), 7.39 - 7.34 (1 H, m), 4.76 (2 H, s), 1.75 (1 H, s).

11.10.13 2-Phenoxyethyl tosylate (245)



245

2-Phenoxyethanol (2.01 g, 14.6 mmol) was treated with 4-toluenesulfonyl chloride (3.31 g, 17.3 mmol) and triethylamine (4.0 mL, 29 mmol) as described for **102**. The resulting white solid was used without further purification (3.82 g, 90%). m.p. 76 - 79°C (80°C lit[218]); ^{1}H NMR ($CDCl_3$) δ 7.83 - 7.80 (2 H, m), 7.36 - 7.32 (2 H, m), 7.27 - 7.23 (2 H, m), 6.98 - 6.93 (1 H, m), 6.81 - 6.77 (2 H, m), 4.41 - 4.38 (2 H, m), 4.18 - 4.16 (2 H, m), 2.47 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 158.1, 145.1, 133.1, 130.0, 129.6, 128.1, 121.5, 114.7, 68.3, 65.5, 21.8.

12 References

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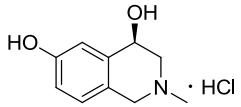
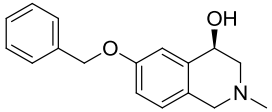
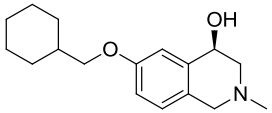
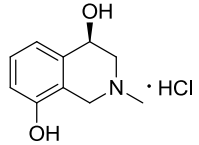
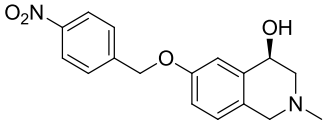
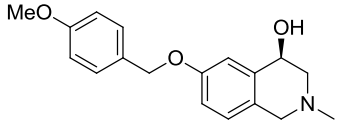
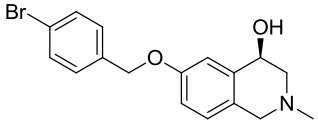
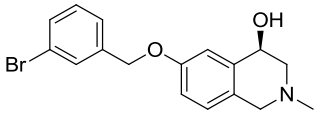
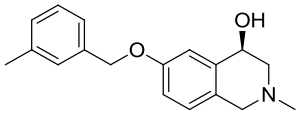
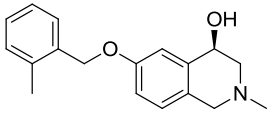
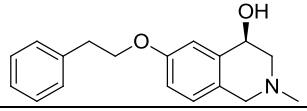
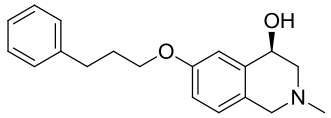
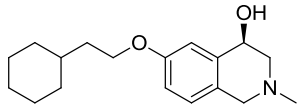
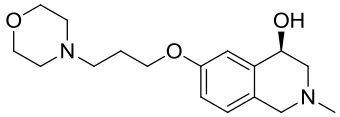
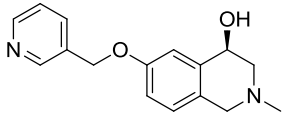
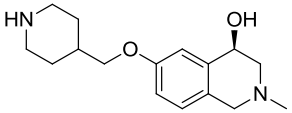
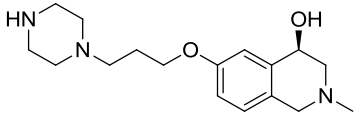
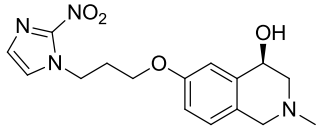
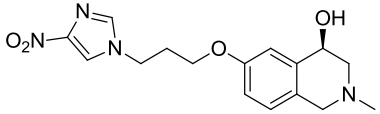
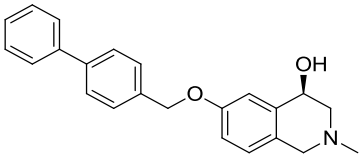
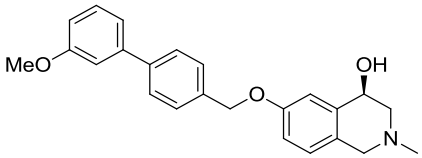
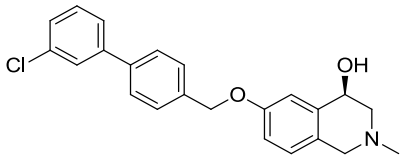
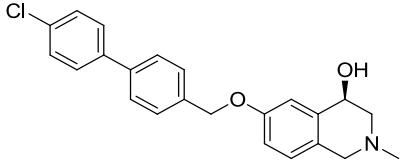
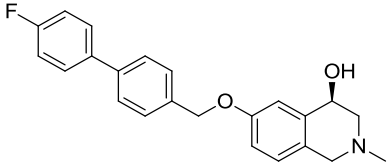
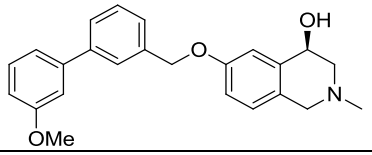
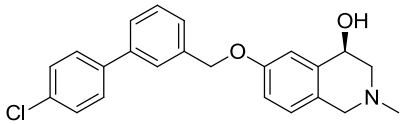
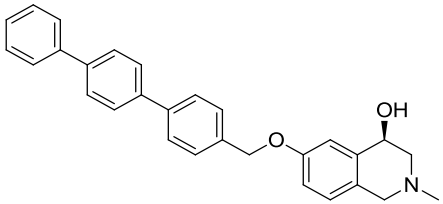
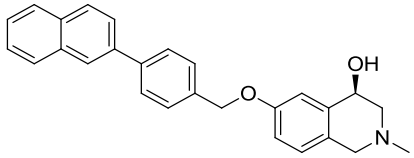
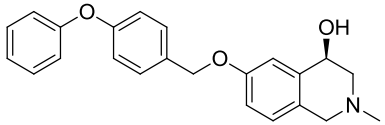
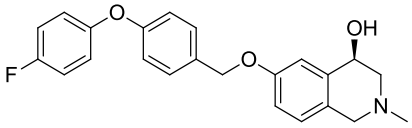
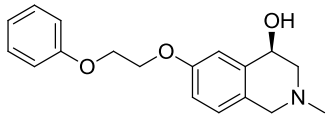
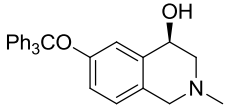
Appendix A – Summary of biological results

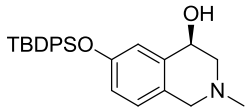
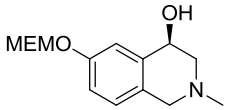
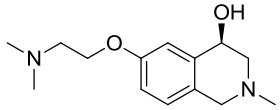
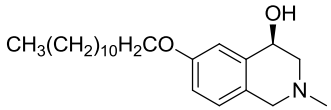
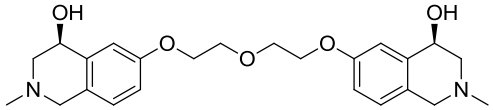
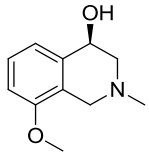
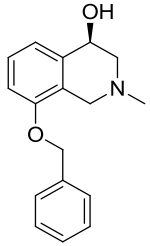
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
Control	Pyrimethamine	>25	0.10 ± 0.04	25.1 ± 6.9	>100	-
Control	Cycloguanil	>25	0.05 ± 0.02	4.9 ± 1.5	>50	-
Control	WR99210	0.20 ± 0.01	0.0034 ± 0.0002	0.005 ± 0.001	>100	-
Control	Ellipticine	-	-	-	2.2 ± 0.3	-
86		>100	>100	>100	>100	0.37
87		25.6 ± 0.9	5.2 ± 1.0	15.1 ± 3.9	>100	2.26
88		2.8 ± 0.1	19.8 ± 1.3	77.9 ± 14.1	65.6 ± 2.3	2.65

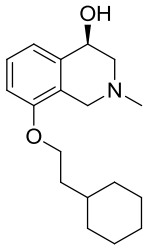
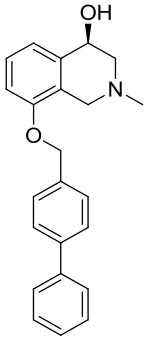
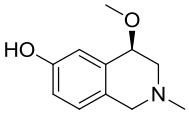
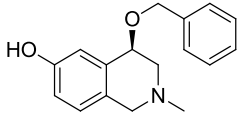
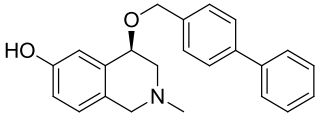
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
90		>100	>100	>100	>100	0.37
96		16.9 ± 1.2	1.6 ± 0.7	3.0 ± 0.3	>50	2.20
97		17.5 ± 0.7	7.3 ± 1.4	14.9 ± 2.6	>50	2.10
98		2.5 ± 0.1	14.4 ± 3.6	5.4 ± 1.2	37.0 ± 6.0	3.03
99		2.2 ± 0.1	12.2 ± 1.6	5.2 ± 0.8	60.3 ± 34.8	3.03
100		20.3 ± 0.9	13.7 ± 1.0	10.3 ± 2.2	>50	2.77
101		20.7 ± 0.6	27.8 ± 3.1	11.0 ± 2.6	>100	2.77
103		17.9 ± 1.7	23.8 ± 1.3	14.9 ±2.6	>50	2.55

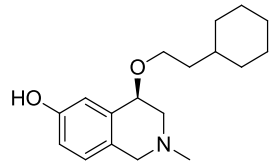
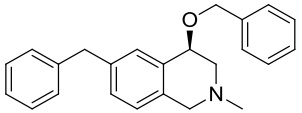
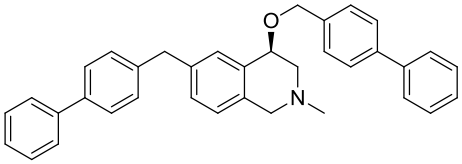
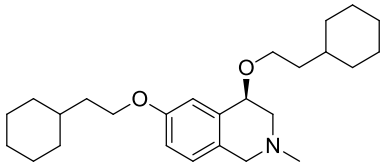
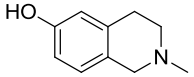
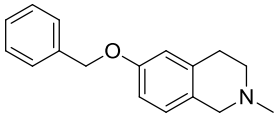
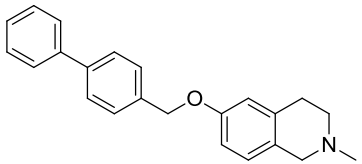
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
105		18.7 ± 0.9	4.3 ± 0.4	0.7 ± 0.1	>50	2.99
108		2.5 ± 0.1	16.9 ± 1.8	6.6 ± 1.5	>50	3.01
111		27.6 ± 0.2	>50	>50	>50	0.24
112		>50	25.0 ± 3.3	21.7 ± 6.4	>50	1.04
118		>100	>100	>100	>100	-2.13
119		>100	59.0 ± 9.4	>100	>100	-1.76
126		21.7 ± 1.0	5.0 ± 1.7	13.7 ± 6.5	>50	1.12
127		>50	>50	>50	>50	1.03

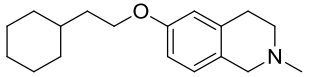
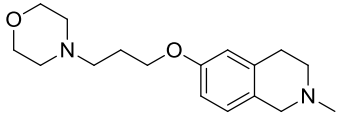
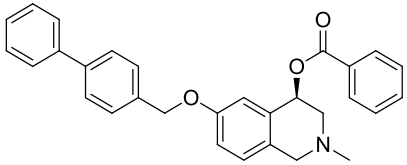
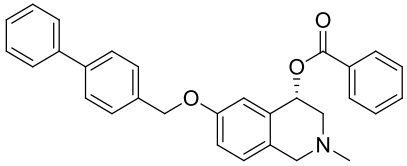
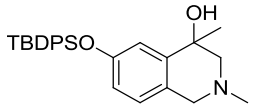
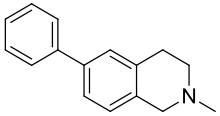
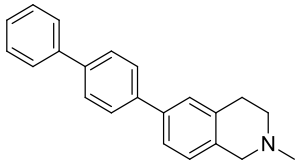
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
129		2.9 ± 0.1	24.5 ± 0.3	21.3 ± 2.9	23.0 ± 2.1	3.91
130		2.8 ± 0.1	17.6 ± 1.1	17.0 ± 2.6	10.8 ± 4.2	3.75
131		2.8 ± 0.1	17.5 ± 4.6	18.3 ± 1.4	25.5 ± 3.0	4.51
132		0.28 ± 0.1	7.4 ± 0.5	17.6 ± 0.8	24.1 ± 4.3	4.51
133		1.4 ± 0.1	20.9 ± 2.4	20.1 ± 0.9	33.8 ± 16.7	4.05
136		2.9 ± 0.1	7.0 ± 0.8	6.3 ± 1.8	24.3 ± 3.8	3.75

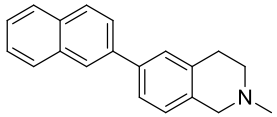
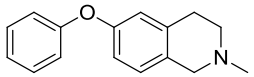
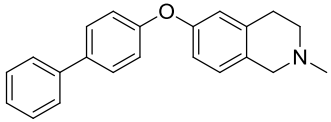
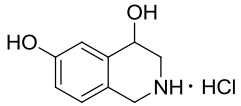
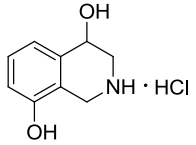
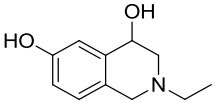
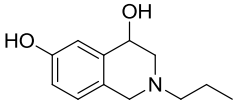
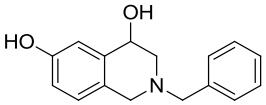
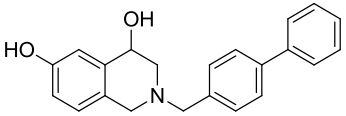
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
138		2.9 ± 0.1	12.8 ± 4.1	7.8 ± 3.3	27.3 ± 2.6	4.51
140		0.28 ± 0.01	3.7 ± 0.2	3.6 ± 0.9	0.28 ± 0.04	5.55
142		0.24 ± 0.01	7.4 ± 1.1	7.5 ± 1.0	0.31 ± 0.01	4.90
148		2.7 ± 0.2	3.6 ± 1.0	16.2 ± 5.6	3.4 ± 0.8	3.76
149		2.7 ± 0.2	2.7 ± 1.0	2.9 ± 1.5	5.6 ± 0.1	3.90
150		17.9 ± 0.2	52.2 ± 1.1	23.9 ± 2.1	>100	2.18
151		20.8 ± 0.4	41.5 ± 5.9	43.1 ± 5.0	87.9 ± 7.1	5.70

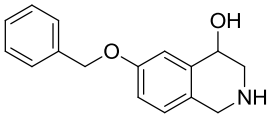
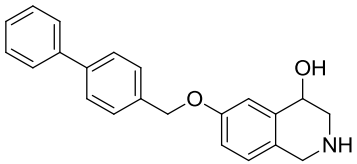
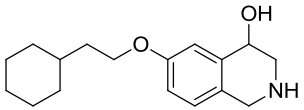
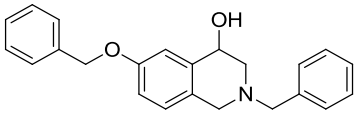
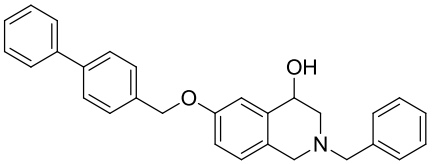
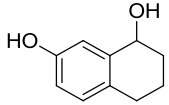
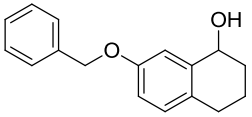
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
152		2.8 ± 0.1	2.7 ± 1.5	3.2 ± 0.5	19.1 ± 0.6	5.72
153		>50	>50	>50	>50	0.56
154		>50	>50	>50	>50	-0.82
155		2.4 ± 0.1	19.8 ± 1.6	19.4 ± 4.4	18.3 ± 3.7	5.41
157		>100	66.0 ± 0.9	77.9 ± 14.1	>100	0.85
158		>100	>100	>100	>100	0.63
159		67.8 ± 0.5	72.0 ± 13.6	19.9 ± 3.2	>100	2.39

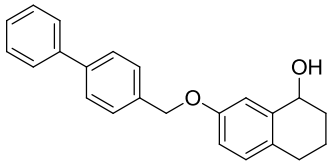
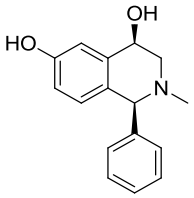
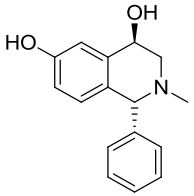
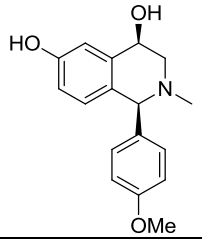
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
160		13.0 ± 0.2	20.2 ± 3.2	3.2 ± 0.9	62.7 ± 9.1	3.15
161		3.1 ± 0.1	21.2 ± 4.3	18.8 ± 6.0	>50	4.04
162		>100	>100	>100	>100	0.98
166		>50	>50	>50	>50	2.76
167		6.4 ± 1.1	2.2 ± 0.2	27.1 ± 8.1	>50	4.41

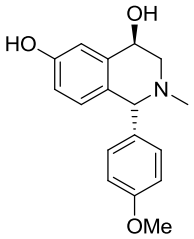
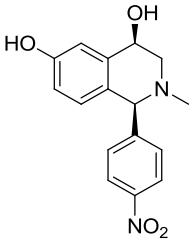
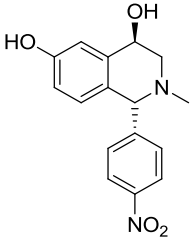
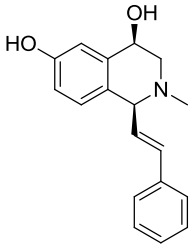
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
168		19.1 ± 0.2	19.6 ± 1.6	28.7 ± 13.1	>50	3.50
169		2.8 ± 0.2	19.4 ± 4.5	17.1 ± 4.3	23.5 ± 1.4	4.65
170		2.8 ± 0.2	>10	>10	>10	7.95
172		2.3 ± 0.2	6.7 ± 1.6	12.8 ± 0.9	23.6 ± 1.5	6.14
175		>100	>100	>100	>100	0.85
176		4.4 ± 0.3	57.9 ± 8.4	26.7 ± 3.6	>100	2.74
177		2.3 ± 0.1	>20	>20	16.5 ± 2.8	4.39

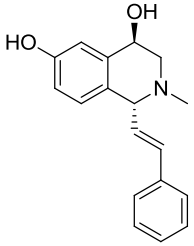
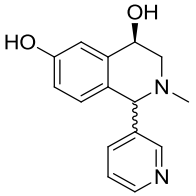
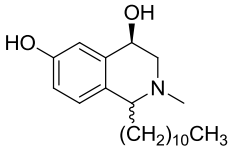
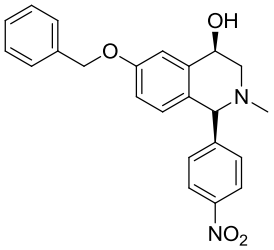
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
178		2.9 ± 0.1	13.5 ± 2.8	14.0 ± 3.8	25.0 ± 3.9	3.50
179		25.9 ± 2.2	>50	>50	>50	0.71
180		16.4 ± 0.7	3.0 ± 0.7	2.3 ± 0.6	10.5 ± 4.1	6.67
181		16.3 ± 0.7	2.8 ± 0.5	2.8 ± 0.4	12.9 ± 2.3	6.67
188		2.7 ± 0.1	4.3 ± 0.4	3.3 ± 0.6	22.2 ± 1.1	5.60
190		3.0 ± 0.1	26.5 ± 2.9	30.9 ± 13.0	>50	2.29
191		0.27 ± 0.01	5.7 ± 1.8	10.1 ± 2.0	15.6 ± 0.3	3.94

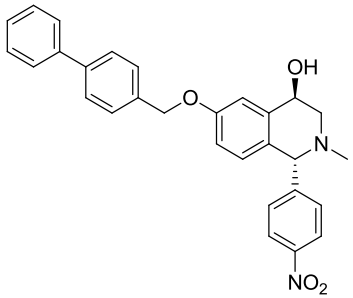
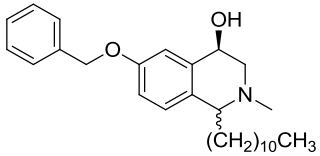
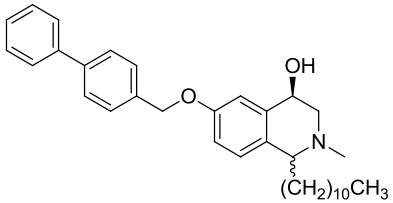
No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
192		2.7 ± 0.1	21.6 ± 1.2	21.4 ± 1.4	24.1 ± 2.2	3.28
195		19.8 ± 0.6	>100	>100	>100	2.72
197		2.7 ± 0.1	41.4 ± 11.6	41.2 ± 6.3	22.3 ± 0.4	4.37
200		>100	>100	>100	>100	-0.06
201		>100	>100	>100	>100	-0.06
202		>100	>100	>100	>100	1.08
203		>100	>100	>100	>100	1.32
204		70.5 ± 0.5	>50	40.2 ± 6.3	>100	2.73
205		5.4 ± 0.7	19.0 ± 2.4	13.7 ± 1.7	>50	4.32

No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
210		17.4 ± 2.3	27.9 ± 10.1	18.3 ± 3.5	>50	1.31
211		0.25 ± 0.02	7.7 ± 0.4	14.4 ± 2.3	20.8 ± 0.8	2.96
212		2.5 ±0.2	19.8 ± 0.9	4.8 ± 1.7	>50	2.07
213		8.4 ± 1.1	3.7 ± 0.3	3.5 ± 0.1	31.8 ± 6.7	4.62
214		2.7 ± 0.1	3.9 ± 0.4	3.4 ± 0.3	14.8 ± 5.5	6.26
217		>100	3.3 ± 0.22	>100	>100	1.89
218		65.9 ± 0.6	>100	>100	39.0 ± 10.4	3.76

No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
219		>100	>100	>100	>100	5.41
220A		>100	>100	60.6 ± 25.9	>100	2.00
220B		>100	>100	73.8 ± 7.2	>100	2.00
221A		>100	>100	>100	>100	2.07

No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
221B		>100	>100	>100	>100	2.07
222A		>50	>50	>50	>50	2.35
222B		>50	>50	>50	>50	2.35
223A		17.5 ± 1.3	24.2 ± 0.7	19.7 ± 2.0	>50	2.88

No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
223B		16.9 ± 0.9	12.0 ± 1.4	19.7 ± 1.8	>50	2.88
224A		>100	>100	>100	>100	1.17
225		0.39 ± 0.04	5.2 ± 2.4	3.1 ± 0.9	24.3 ± 2.9	4.83
228		19.2 ± 0.6	4.9 ± 1.2	22.3 ± 5.0	26.8 ± 4.1	4.23

No.	Structure	IC_{50} *T. b. rhodesiense* (µM)	IC_{50} *P. falciparum* Wildtype (µM)	IC_{50} *P. falciparum* Multi drug resistant (µM)	Cytotoxicity (µM)	LogD (pH 7.4)
229		19.4 ± 1.0	9.9 ± 1.3	22.1 ± 3.7	37.6 ± 4.1	5.87
230		0.32 ± 0.01	2.8 ± 0.2	2.1 ± 0.7	3.2 ± 0.2	6.72
231		2.5 ± 0.2	16.6 ± 4.9	2.9 ± 0.8	3.6 ±0.7	8.37

Appendix B –Biological results from different labs

At the beginning of this research biological testing was originally carried out by the School of Veterinary and Biomedical Science at Murdoch University. However, shortly thereafter samples were no longer able to be sent to this lab. Following this biological testing was carried out by the Eskitis Institute for Cell and Molecular Therapies at Griffith University. Assays run at this lab however were for the inhibition of *T. b. brucei* (type that infects only animals) rather than *T. b. rhodesiense*. Finally biological testing was carried out by the BIOTEC Medical Molecular Biology Research Unit in Thailand. All samples previously sent to Murdoch University and the Eskitis institute were also sent to BIOTEC. Therefore all biological activities reported in this thesis have been obtained from BIOTEC. The table below shows the results for compounds tested at more than one lab, where the IC_{50} values for most compounds are comparable between labs.

No.	IC_{50} *T. b. rhodesiense* (µM) Biotech[1]	IC_{50} *T. b. rhodesiense* (µM) Murdoch[2]	IC_{50} *T. b. brucei* (µM) Eskitis[3]
108	2.5 ± 0.1	6.5	7.9
129	2.9 ± 0.1	6.7	7.4
87	25.6 ± 0.9	16.5	
96	16.9 ± 1.2	20.1	
97	17.5 ± 0.7	21.8	
100	20.3 ± 0.9	17.4	
101	20.7 ± 0.6	18.2	
103	17.9 ± 1.7	26.8	
105	18.7 ± 0.9	18.2	
150	17.9 ± 0.2	46.7	
169	2.8 ± 0.2	18.2	
88	2.8 ± 0.1		13.2
98	2.5 ± 0.1		13.3
99	2.2 ± 0.1		20.0
111	27.6 ± 0.2		27.6
130	2.8 ± 0.1		7.3
136	2.9 ± 0.1		27.3
132	0.28 ± 0.01		4.0
131	2.8 ± 0.1		2.8
138	2.8 ± 0.1		9.7
133	1.4 ± 0.1		1.4

No.	IC_{50} *T. b. rhodesiense* (µM) Biotech[1]	IC_{50} *T. b. rhodesiense* (µM) Murdoch[2]	IC_{50} *T. b. brucei* (µM) Eskitis[3]
152	2.8 ± 0.1		8.9

[1] Testing was carried out by Sumalee Kamchonwongpaisan, Jutharat Pengon, and Roonglawan Rattanajak from BIOTEC Medical Molecular Biology Research Unit, National Science and Technology Development Agency, 113 Thailand Science Park, Phahonyothin Road, Khlong Nueng, Khlong Luang, Pathum Thani 12120, Thailand. See experimental section for details.

[2] Testing was carried out by the School of Veterinary and Biomedical Science, Murdoch University, Murdoch, Western Australia 6150.

[3] Testing was carried out at the Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane Innovation Park, Don Young Road, Nathan, Queensland 4111, Australia. In accordance with the procedure described by Sykes et al.[219]

Appendix C – Crystallography details

Description of the crystal structure

The crystal structure of compound **227** was determined *via* synchrotron X-ray diffraction data on single crystals obtained by slow evaporation of a DCM/ petroleum ether 40-60 solution. In the unit cell two independent molecules (tagged with letters A and B in the discussion) co-exist. **Figure A1** shows the molecular structure of molecule A with its partial labelling scheme. Selected bond distances are listed in **Table A2**. The molecules possesses two chiral centres (C7 and C10) of absolute configuration R, R. The configuration of C7 was known from the retention of the chiral centre during the synthetic procedure, and the configuration of C10 could be assigned by solving the solid-state structure.

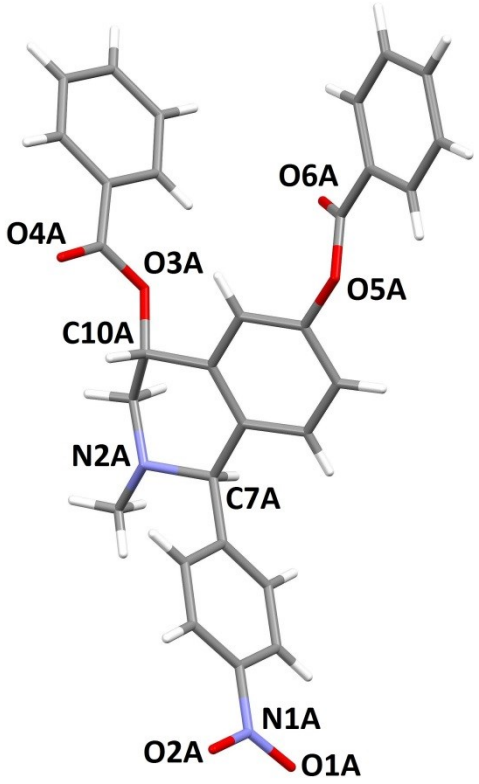


Figure A1 Molecular structure of the independent molecule A of compound **227**.

Table A1 Crystal data and structure refinement information for **227**.

Compound	X
empirical formula	$C_{30}H_{24}N_2O_6$
M	508.51
crys syst	Monoclinic
space group	*P21*
a/Å	7.9505(1)
b/Å	21.9068(2)
c/Å	14.7482(1)
V/Å^3	2526.40(4)
Z	4
T/K	100(2)
ρ /g cm^{-3}	1.337
μ /mm^{-1}	0.091
F(000)	1064
total reflections	41787
unique reflections (R_{int})	13671 (0.0439)
observed reflections $[F_o>4\sigma(F_o)]$	12913
GOF on F^{2a}	1.010
R indices $[F_o>4\sigma(F_o)]^b R_1$, wR_2	0.0421, 0.1221
largest diff. peak and hole (eÅ^{-3})	0.326, -0.316

[a]Goodness-of-fit S = $[\Sigma w(F_o^2-F_c^2)^2/ (n-p)]1/2$, where n is the number of reflections and p the number of parameters. [b]$R_1 = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$, $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

Table A2 Selected bond distances (Å) for **227**.

N1A-O1A	1.223(1)	N1B-O1B	1.234(1)
N1A-O2A	1.226(1)	N1B-O2B	1.221(1)
N2A-C7A	1.467(1)	N2B-C7B	1.471(1)
O3A-C10A	1.445(1)	O3B-C10B	1.452(1)
C13A-O3A	1.342(1)	C13B-O3B	1.315(1)
C13A-O4A	1.209(1)	C13B-O4B	1.212(1)
C24A-O5A	1.368(1)	C24B-O5B	1.360(1)
C24A-O6A	1.200(1)	C24B-O6B	1.208(1)

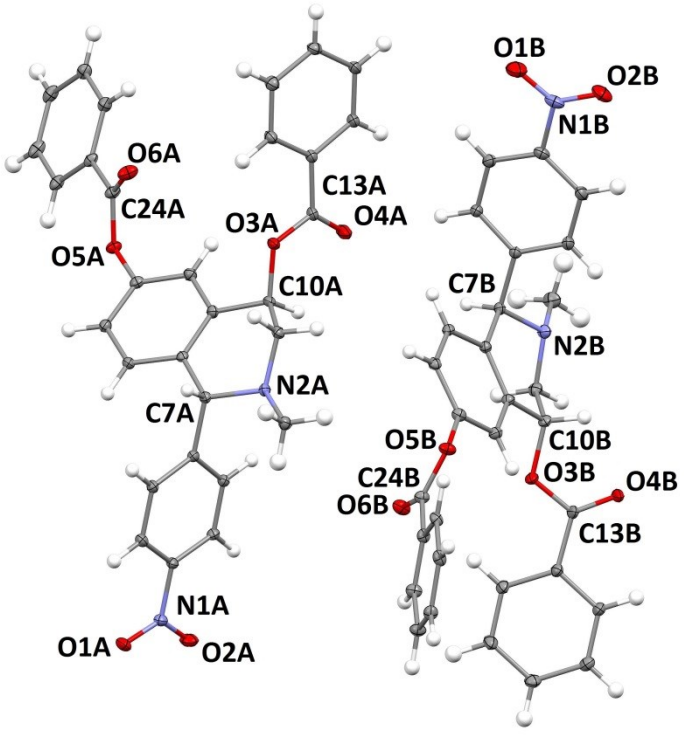


Figure A2 Ortep view (20% probability labels) of the two independent molecules of compound **227**.

Appendix D – NMR spectra

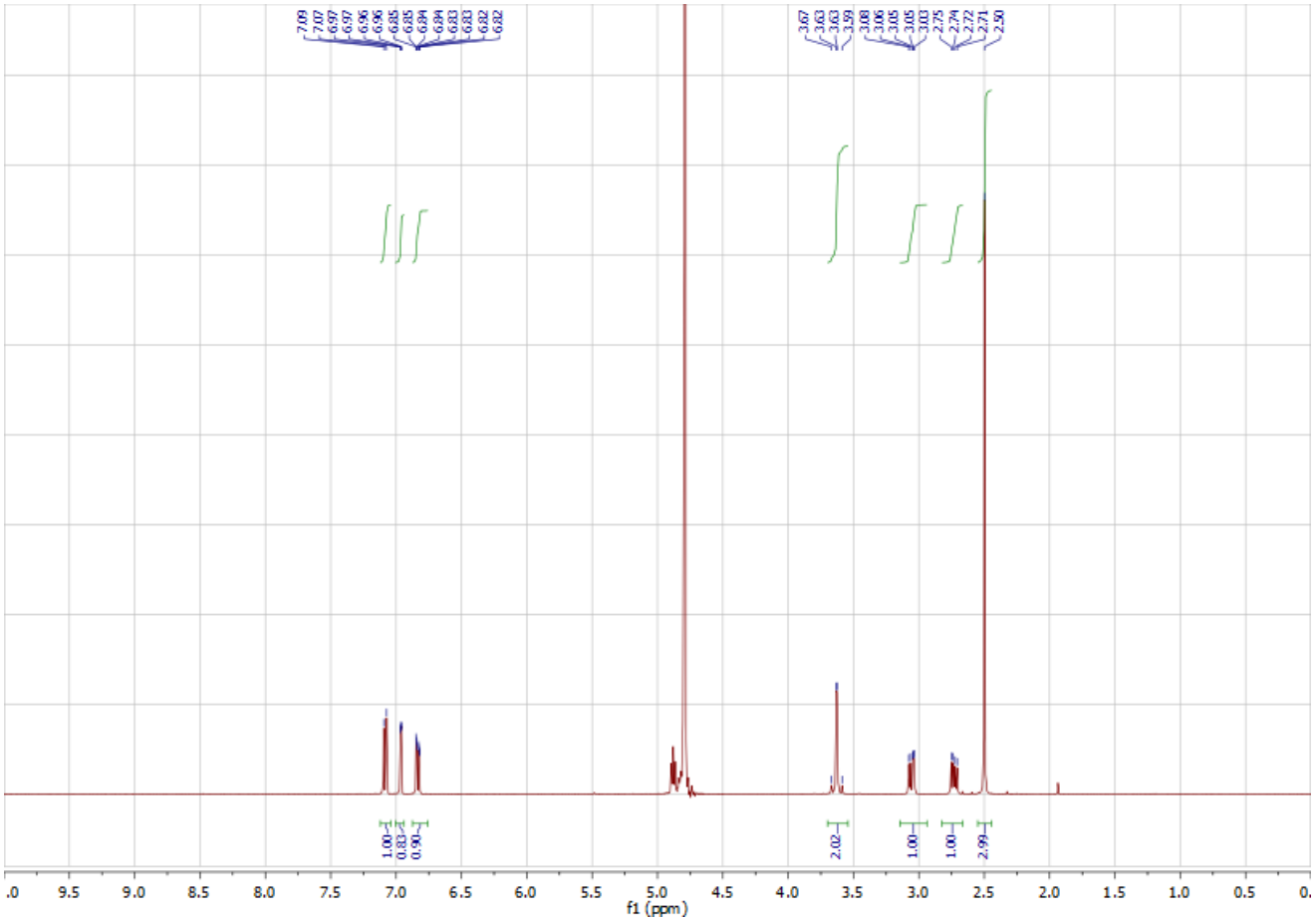


Figure A3 ^{1}H NMR spectra of **86** (D_2O).

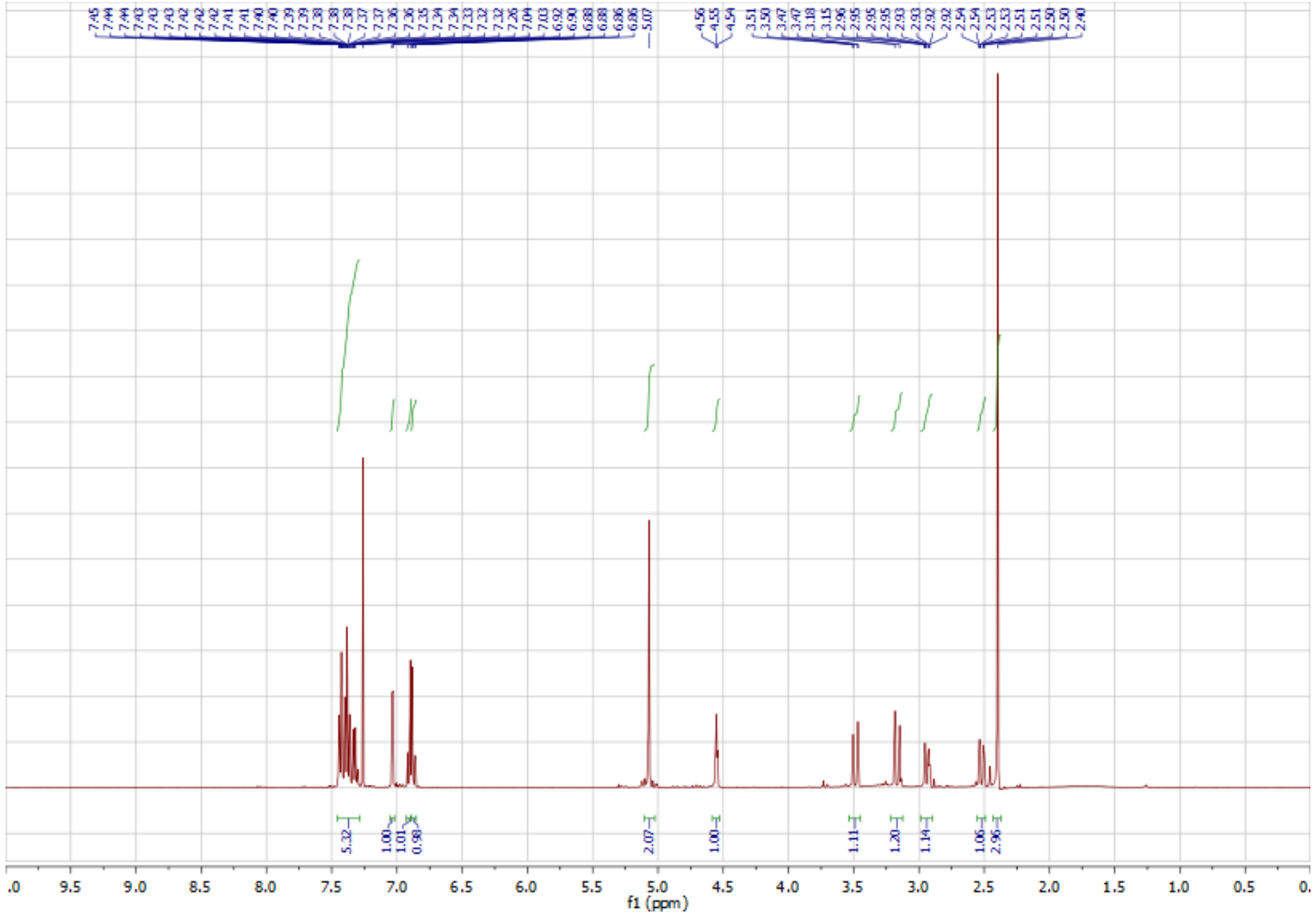


Figure A4 ^{1}H NMR spectra of 87 (D_2O).

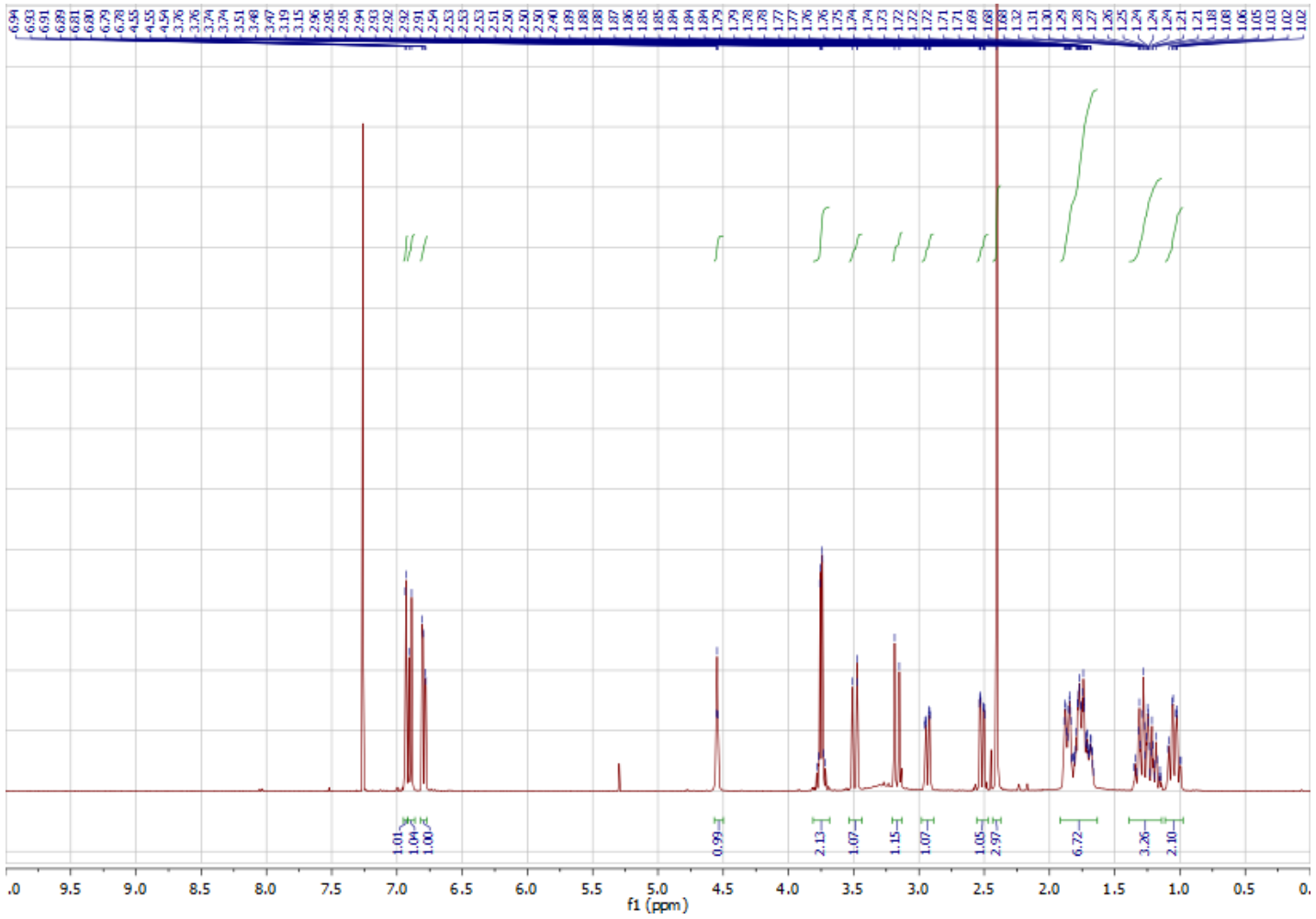


Figure A5 ^{1}H NMR spectra of **88** ($CDCl_3$).

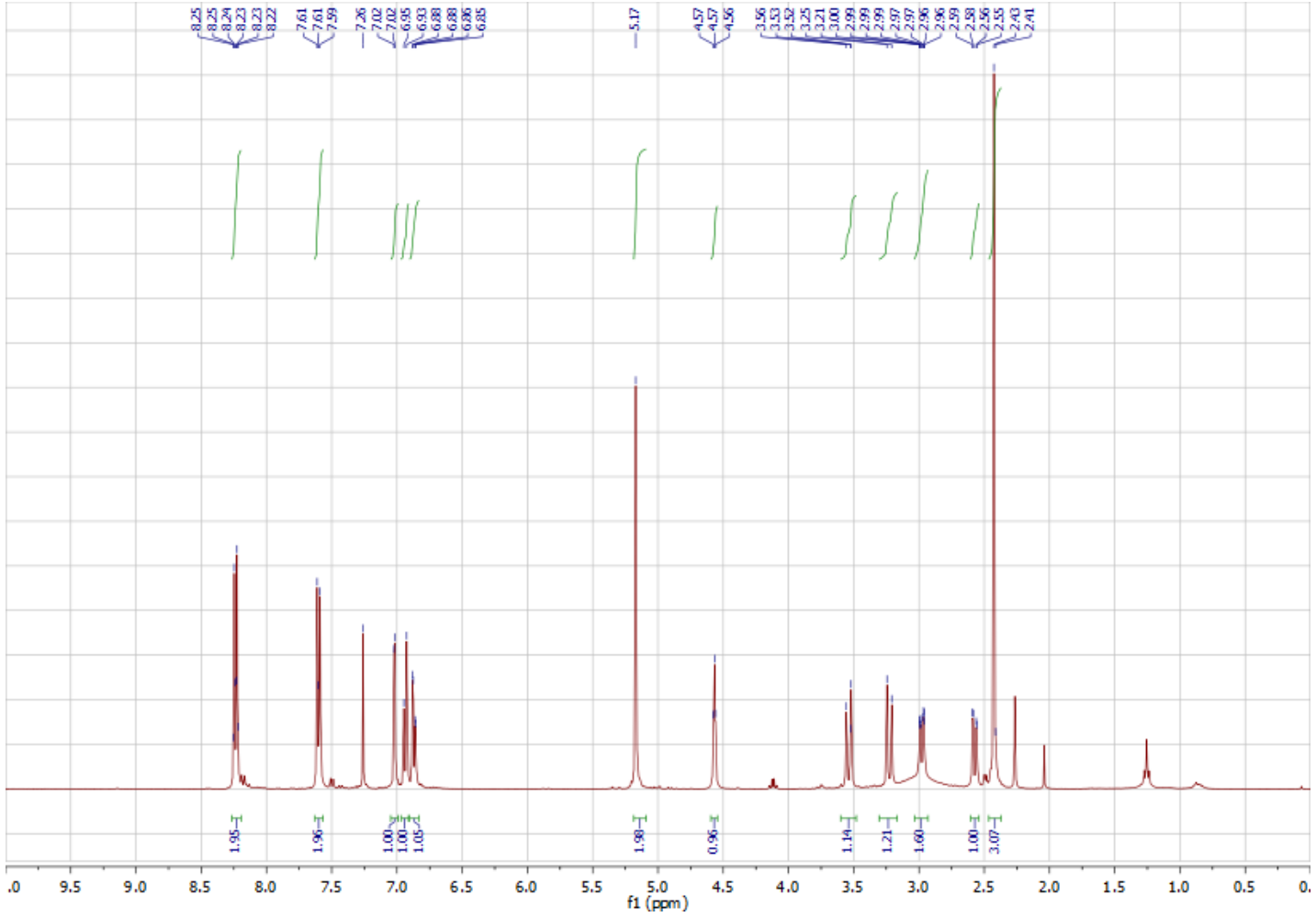


Figure A6 ^{1}H NMR spectra of **96** ($CDCl_3$).

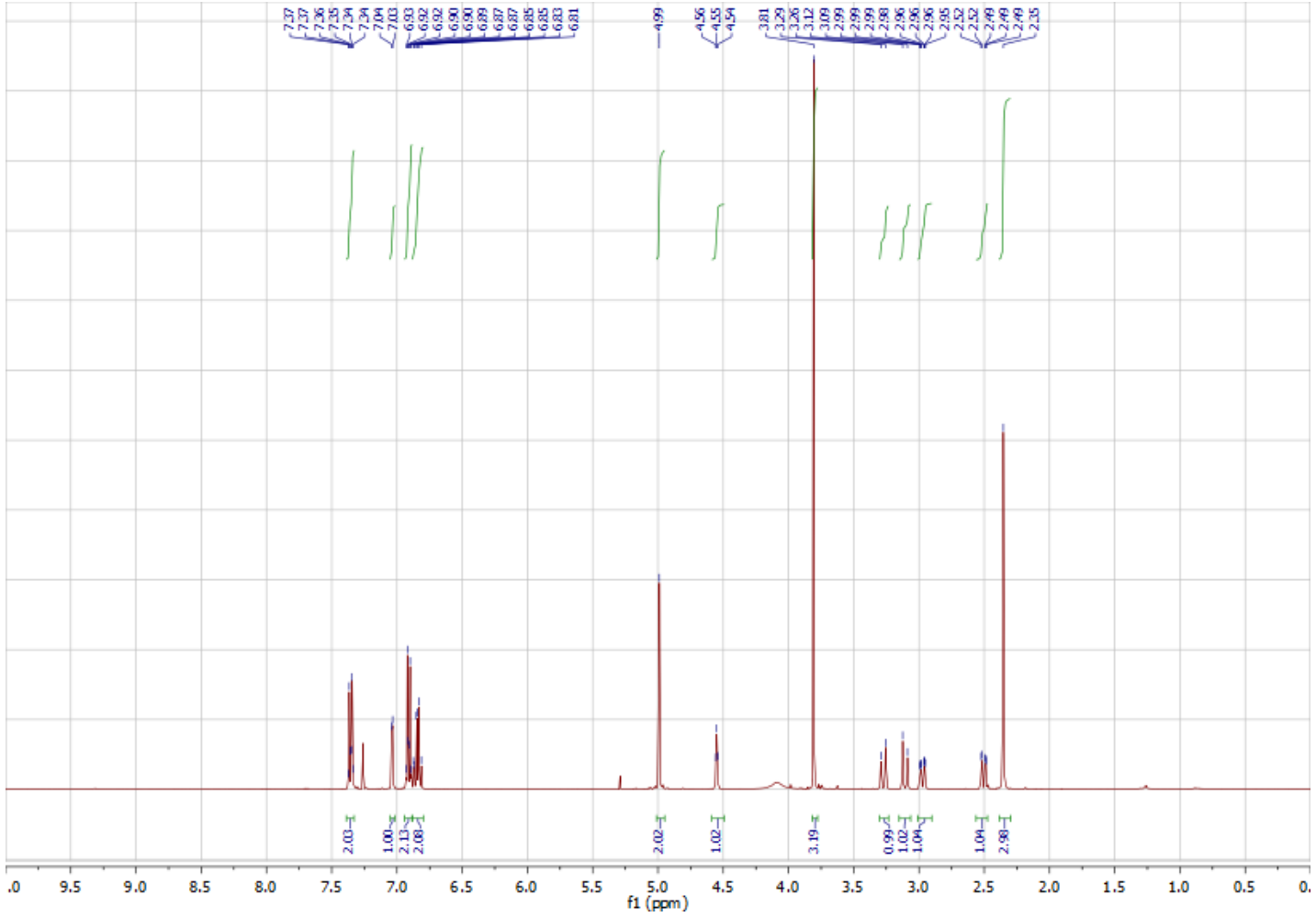


Figure A7 ^{1}H NMR spectra of **97** ($CDCl_3$).

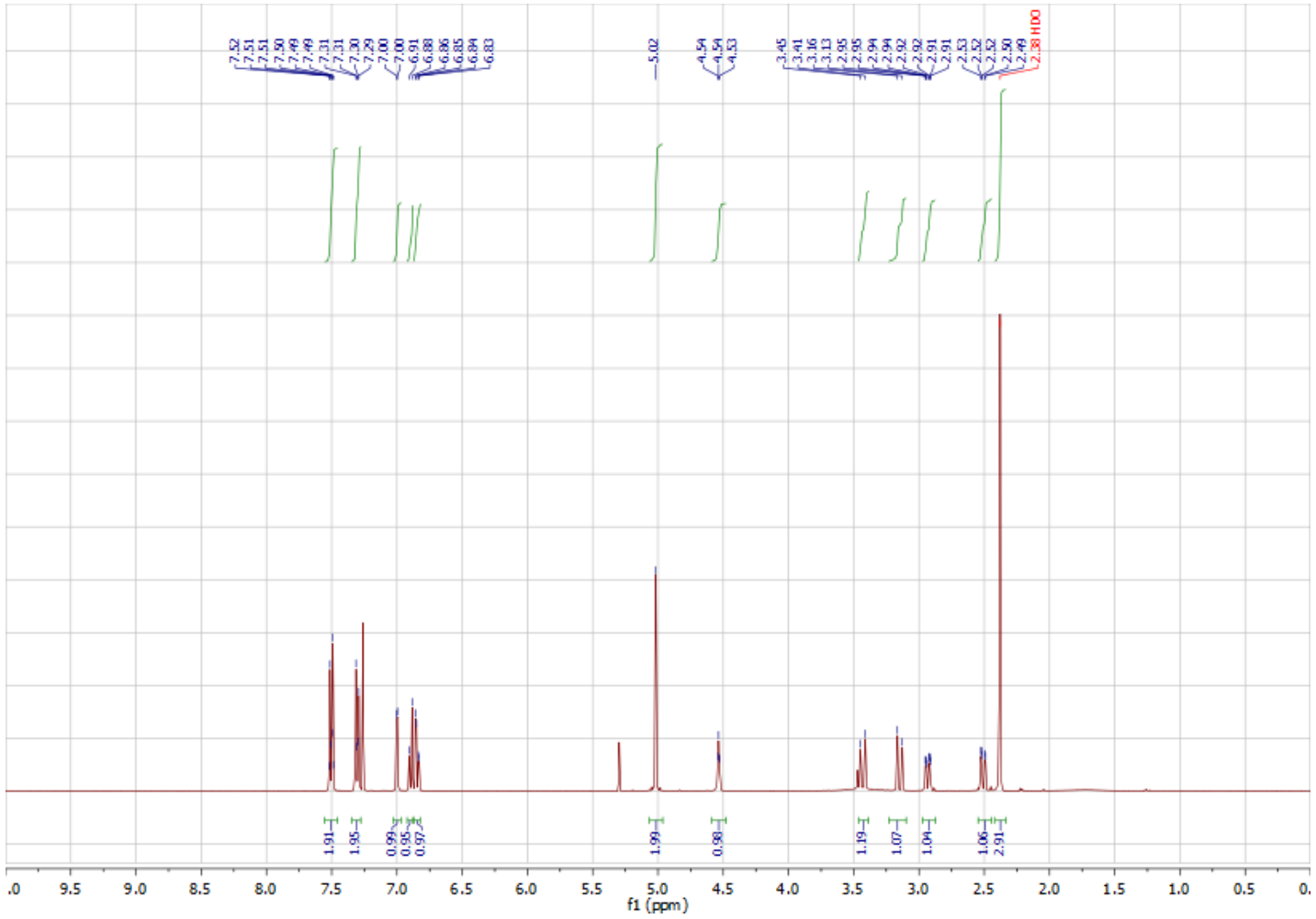


Figure A8 ^{1}H NMR spectra of **98** ($CDCl_3$).

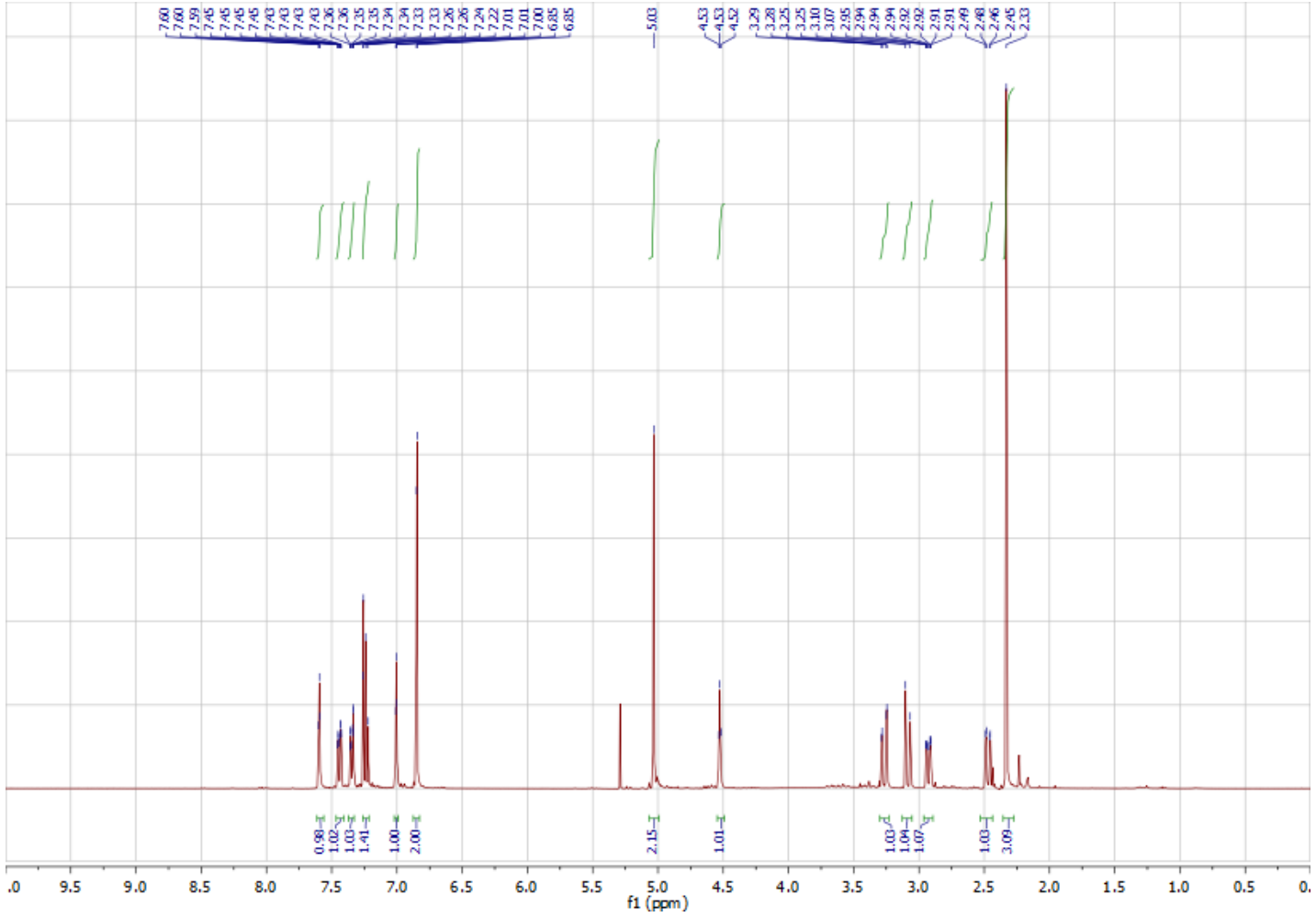


Figure A9 ^{1}H NMR spectra of **99** ($CDCl_3$).

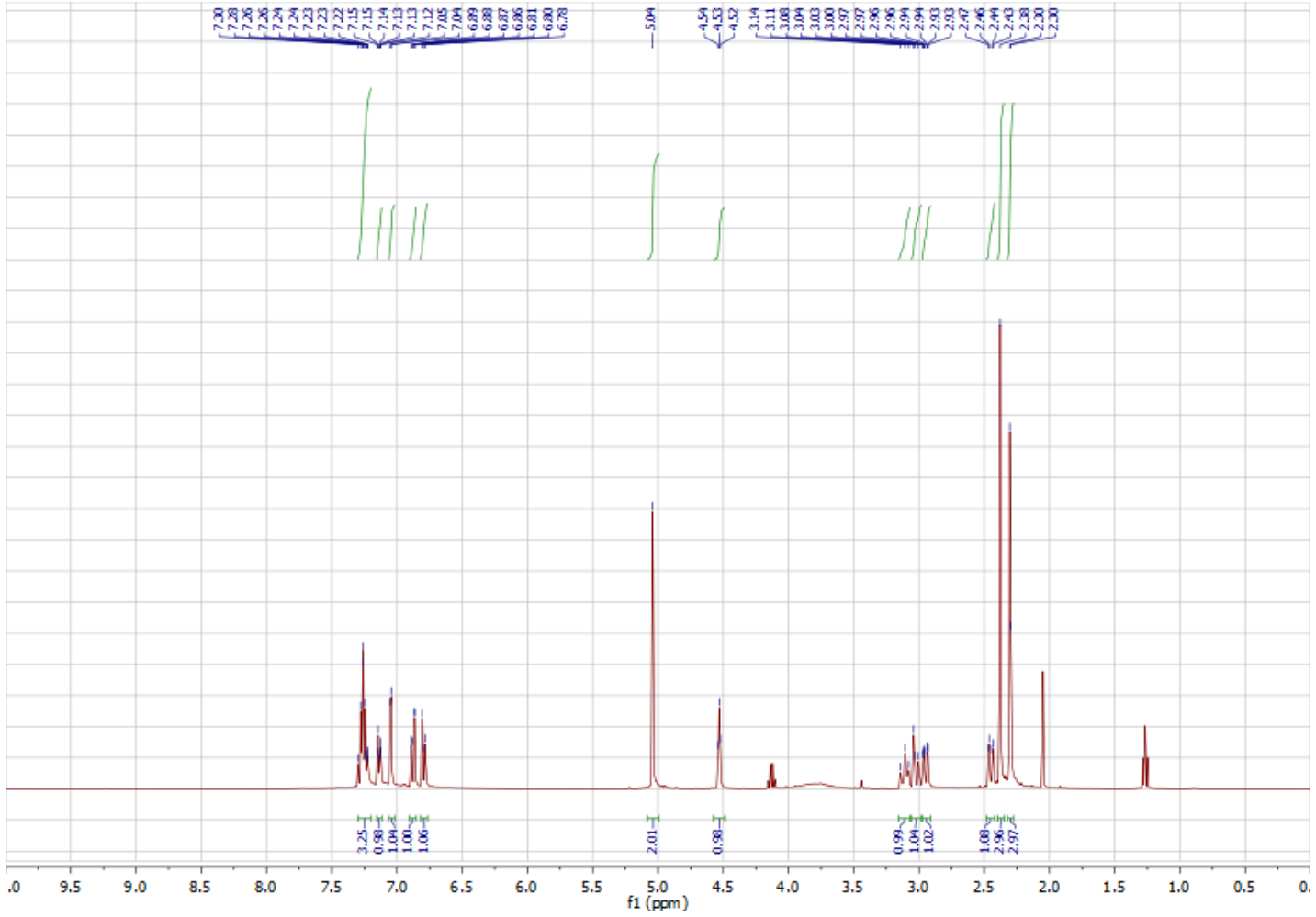


Figure A10 ^{1}H NMR spectra of **100** ($CDCl_3$).

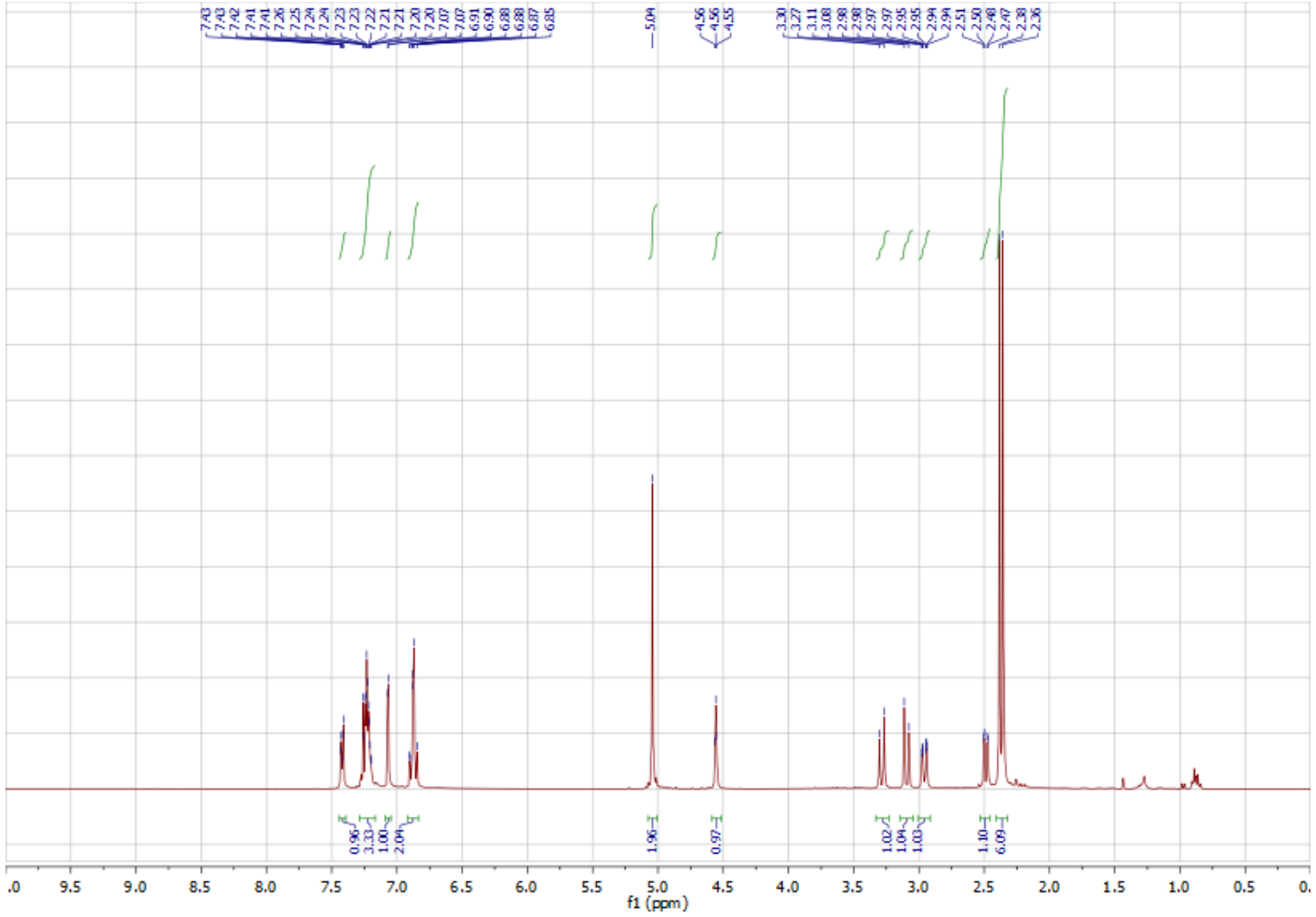


Figure A11 ^{1}H NMR spectra of **101**($CDCl_3$).

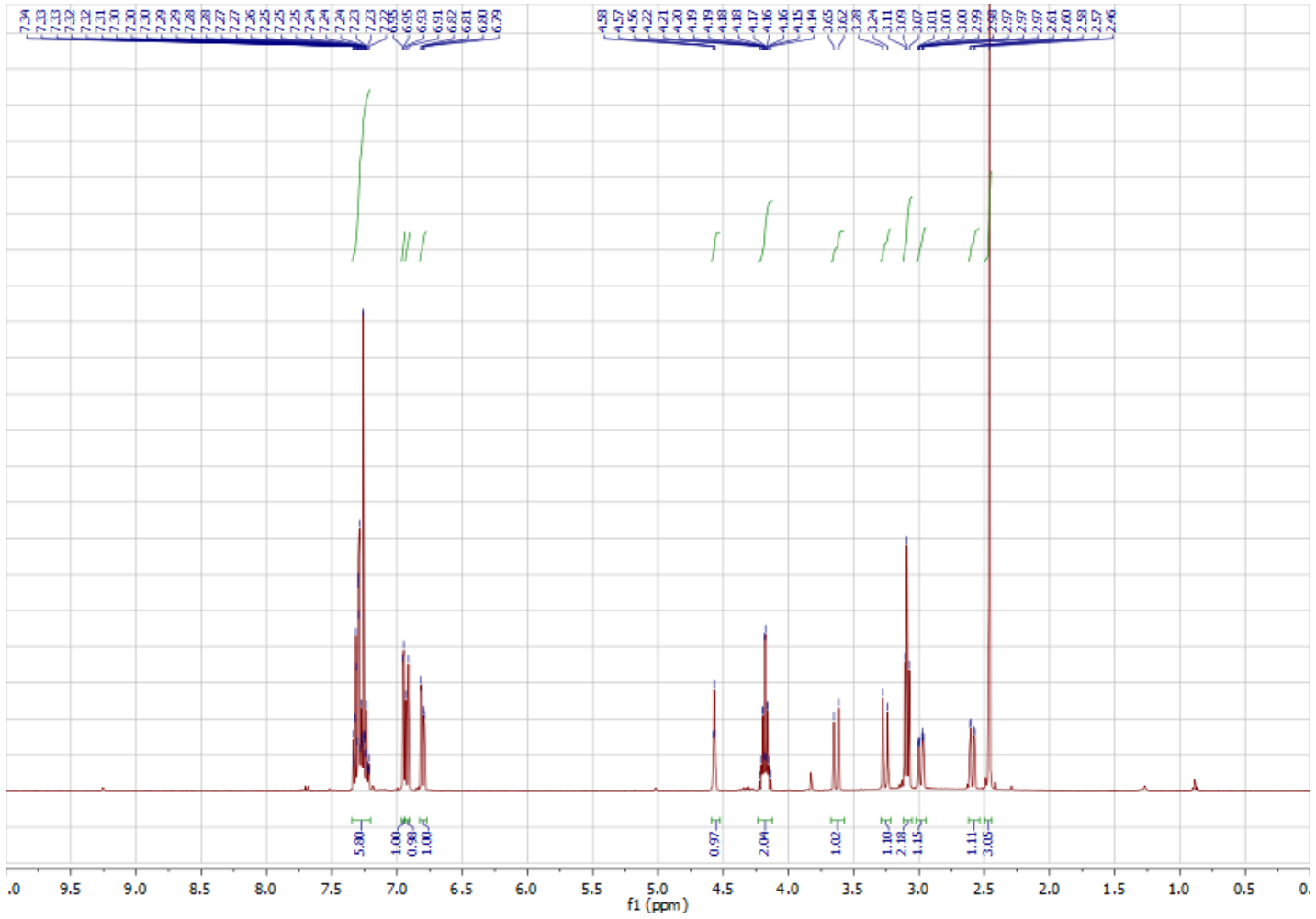


Figure A12 ^{1}H NMR spectra of **103** ($CDCl_3$).

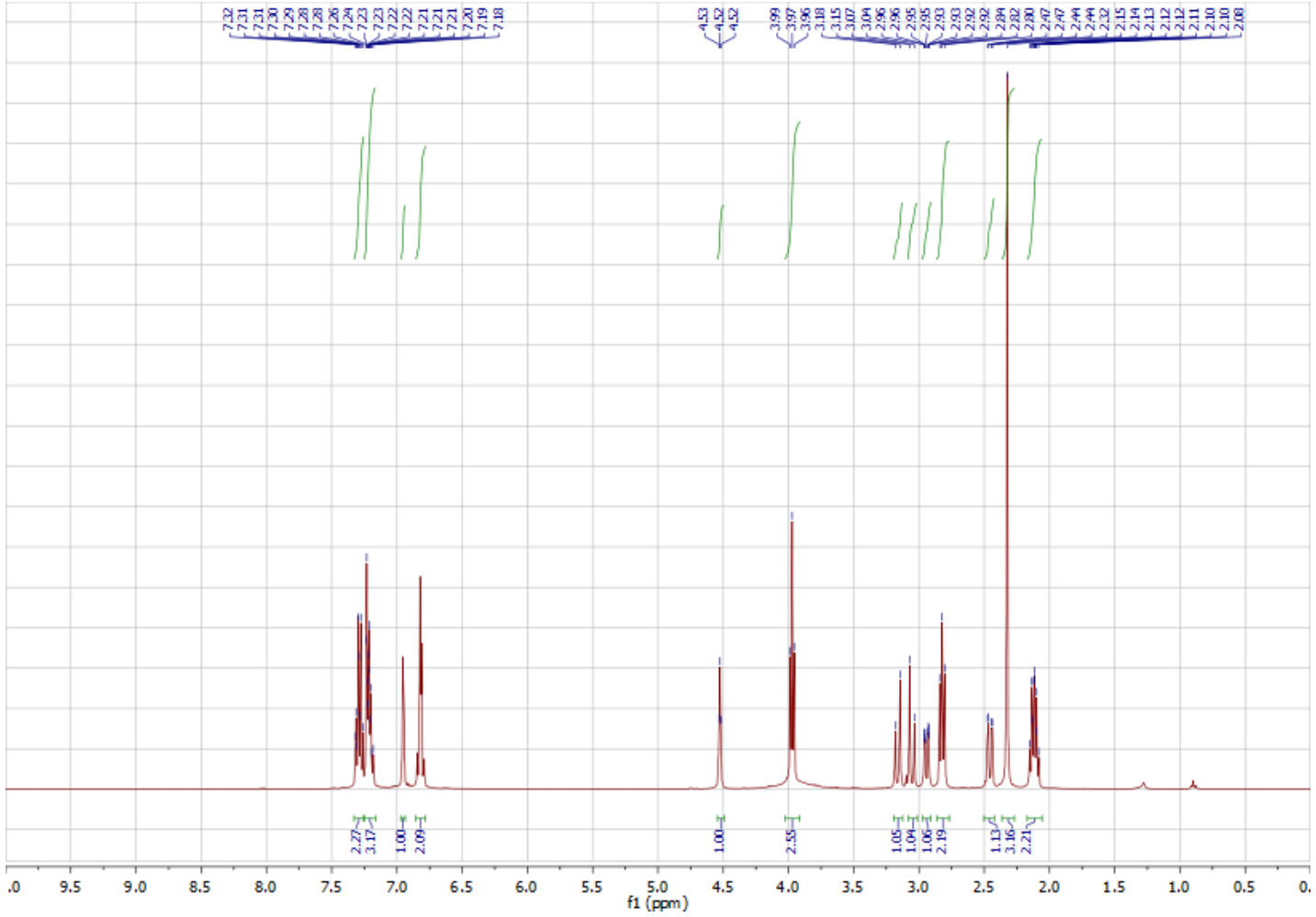


Figure A13 ^{1}H NMR spectra of **105** ($CDCl_3$).

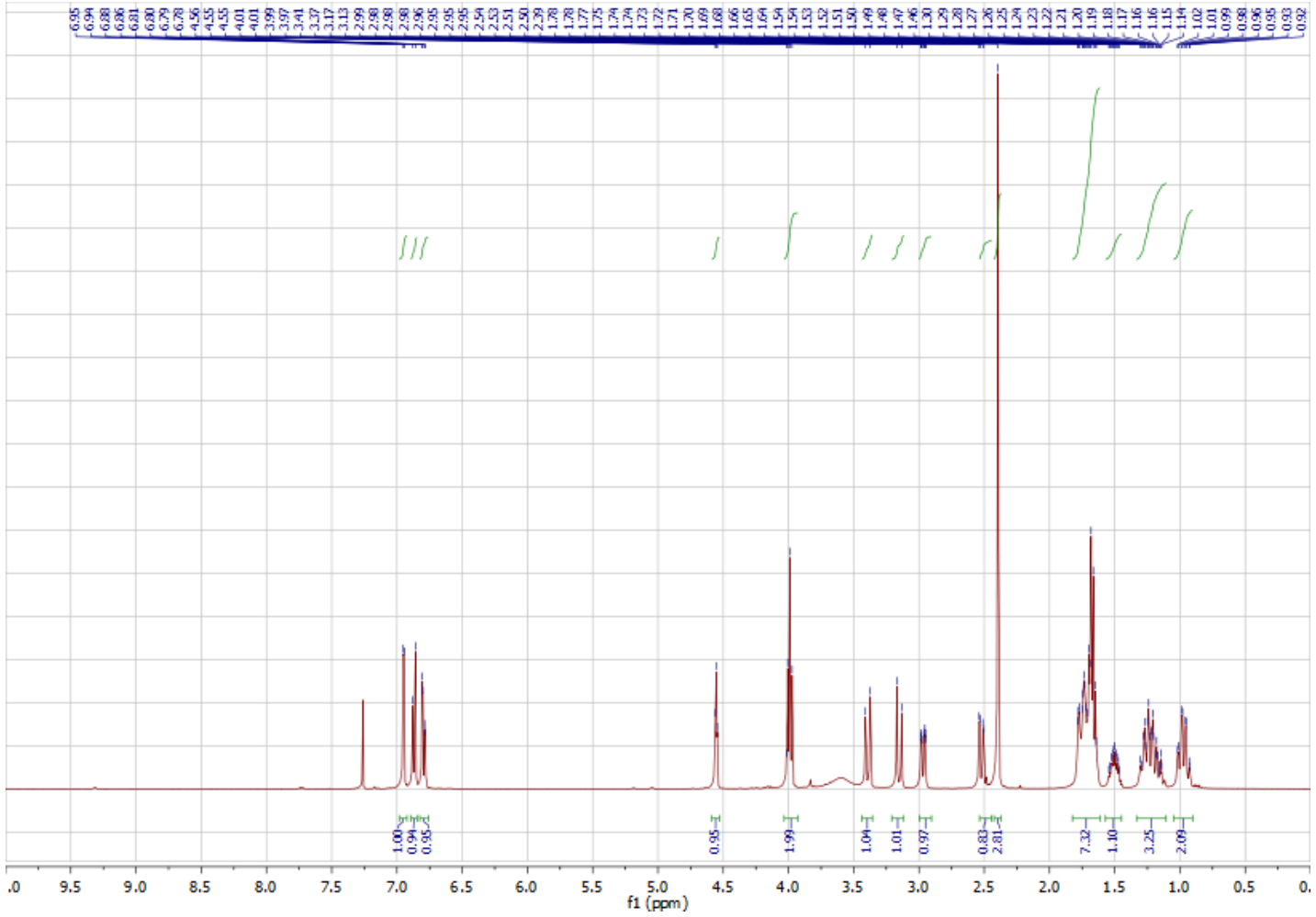


Figure A14 ^{1}H NMR spectra of **108** ($CDCl_3$).

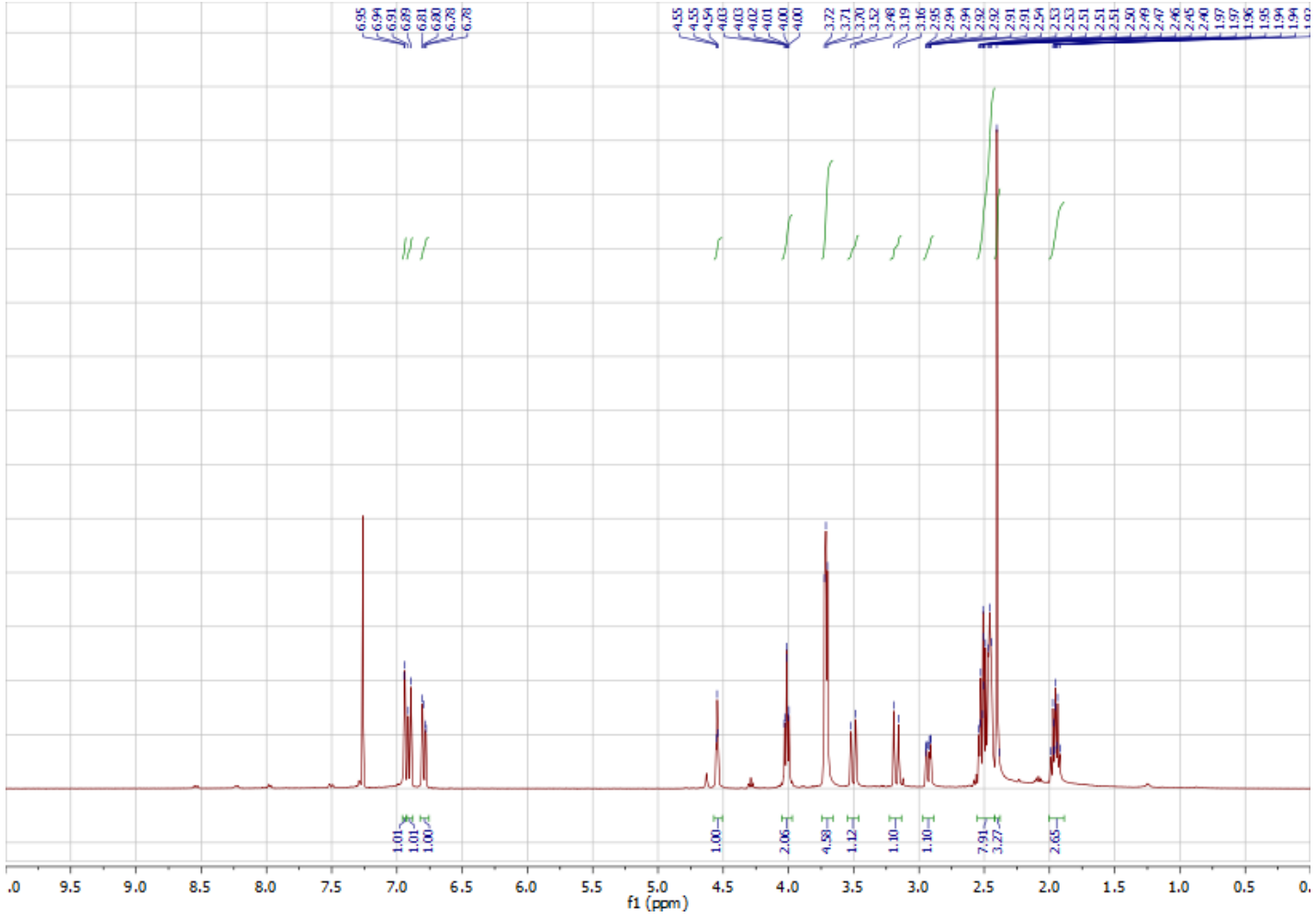


Figure A15 ^{1}H NMR spectra of **111** ($CDCl_3$).

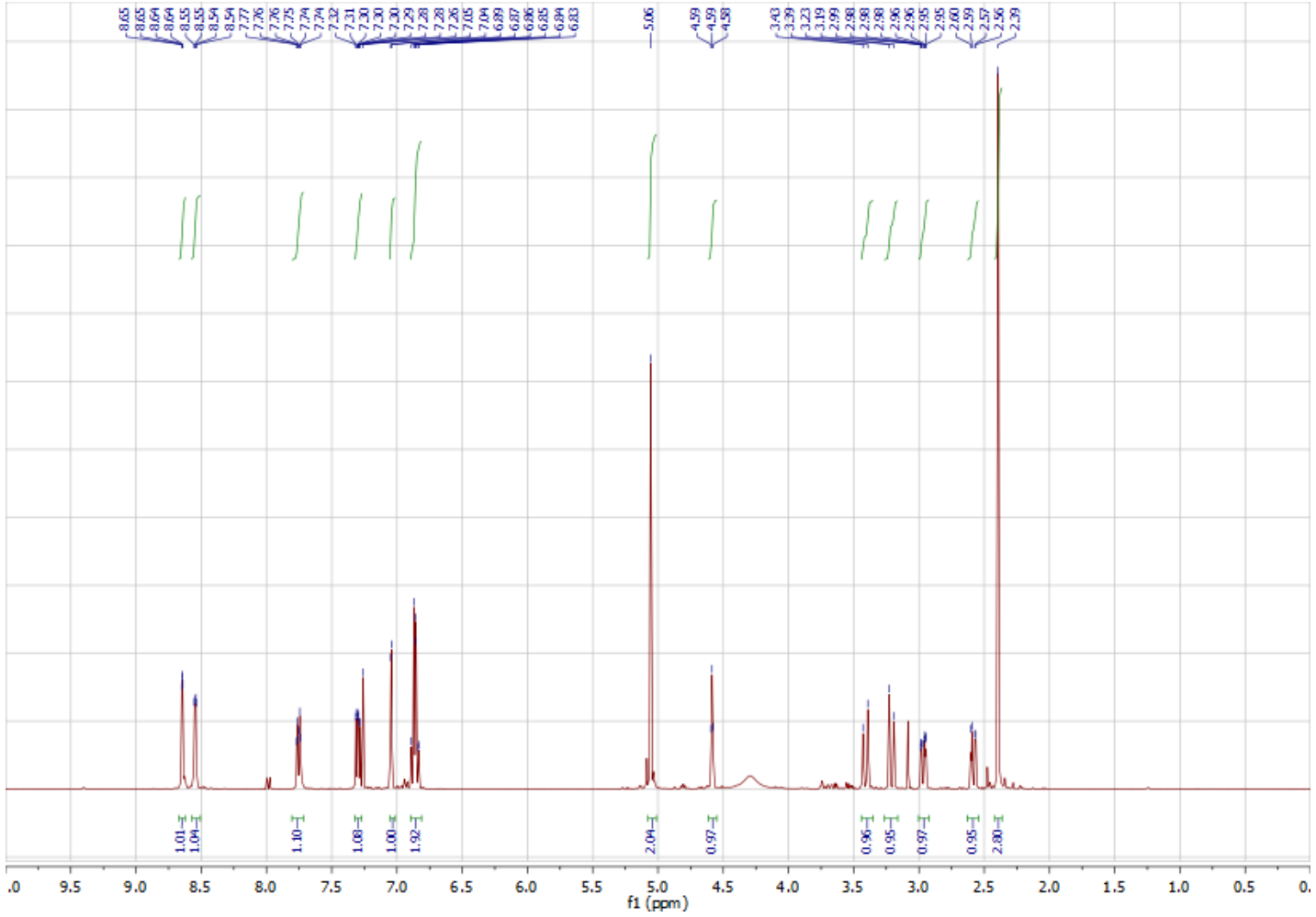


Figure A16 ^{1}H NMR spectra of **112** ($CDCl_3$).

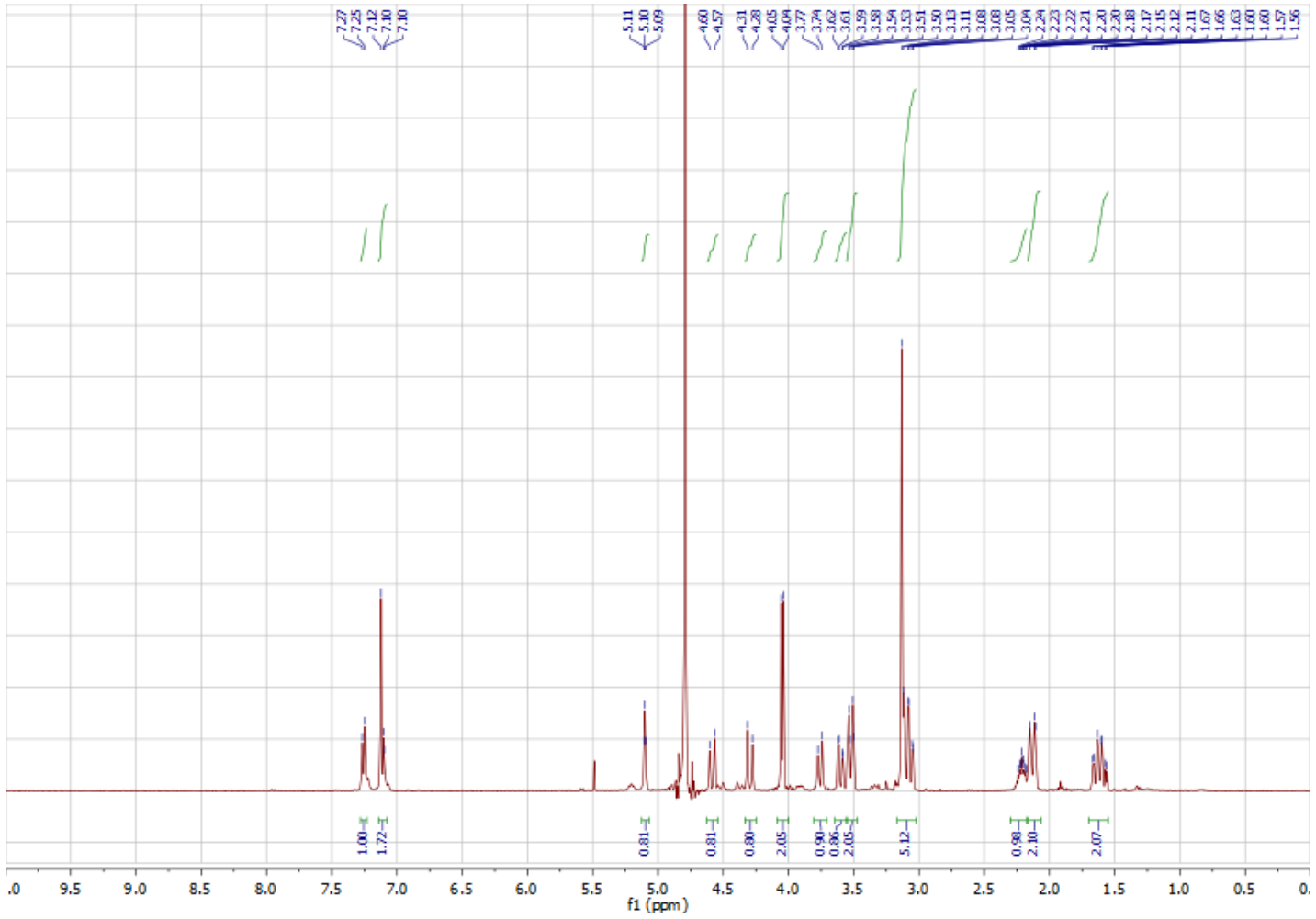


Figure A17 ^{1}H NMR spectra of **118** (D_2O).

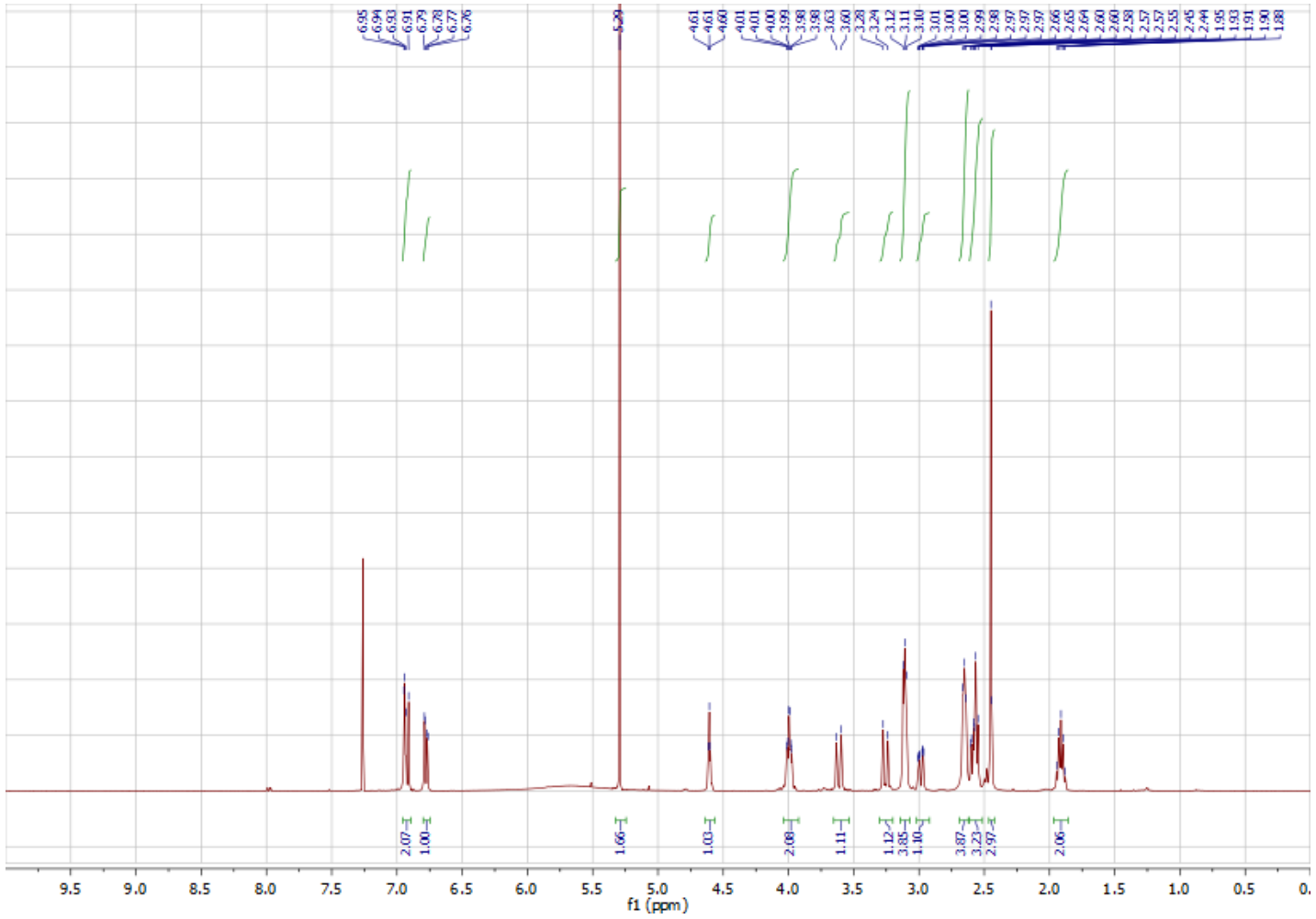


Figure A18 ^{1}H NMR spectra of **119** ($CDCl_3$).

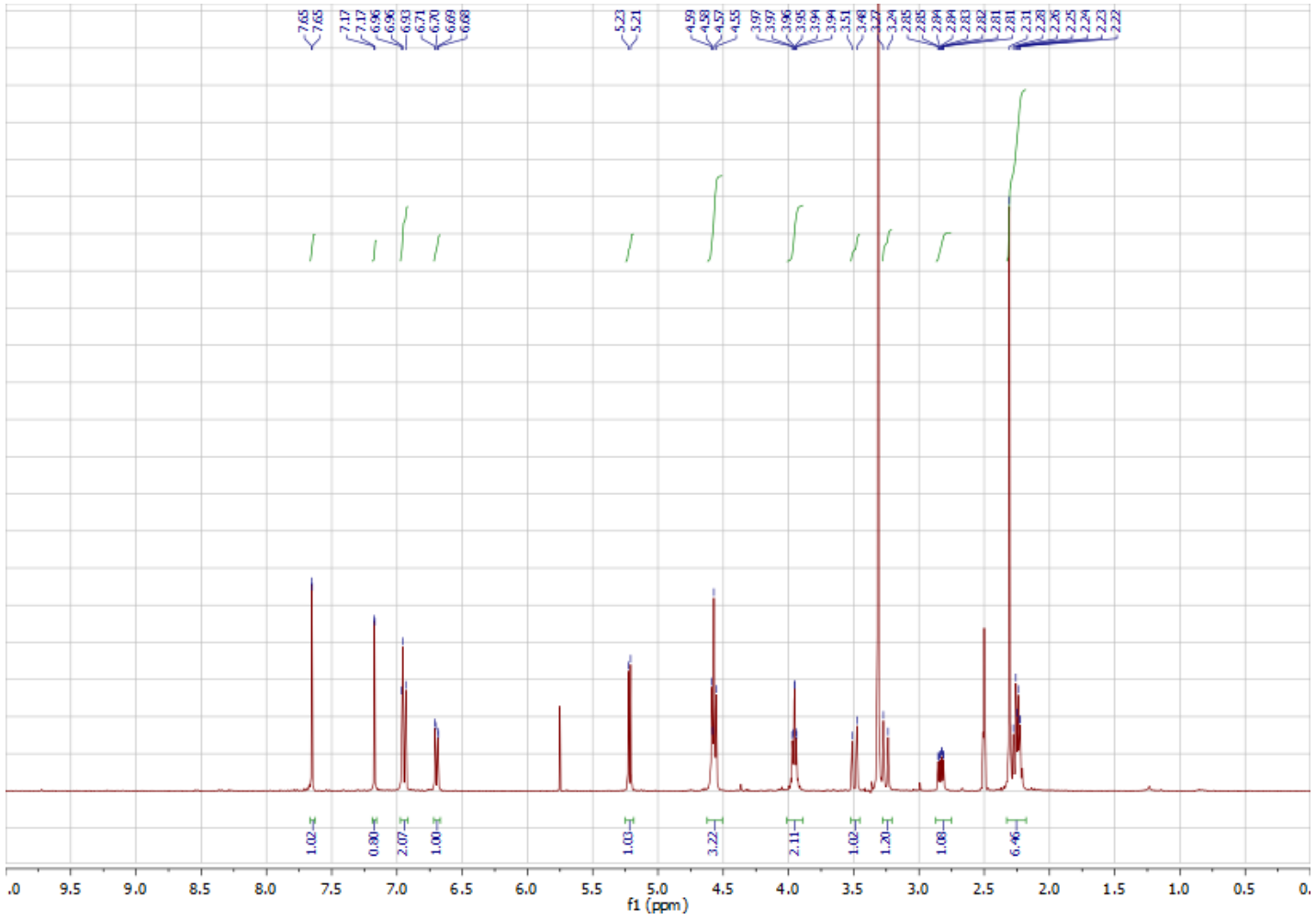


Figure A19 ^{1}H NMR spectra of **126** (DMSO-d_6).

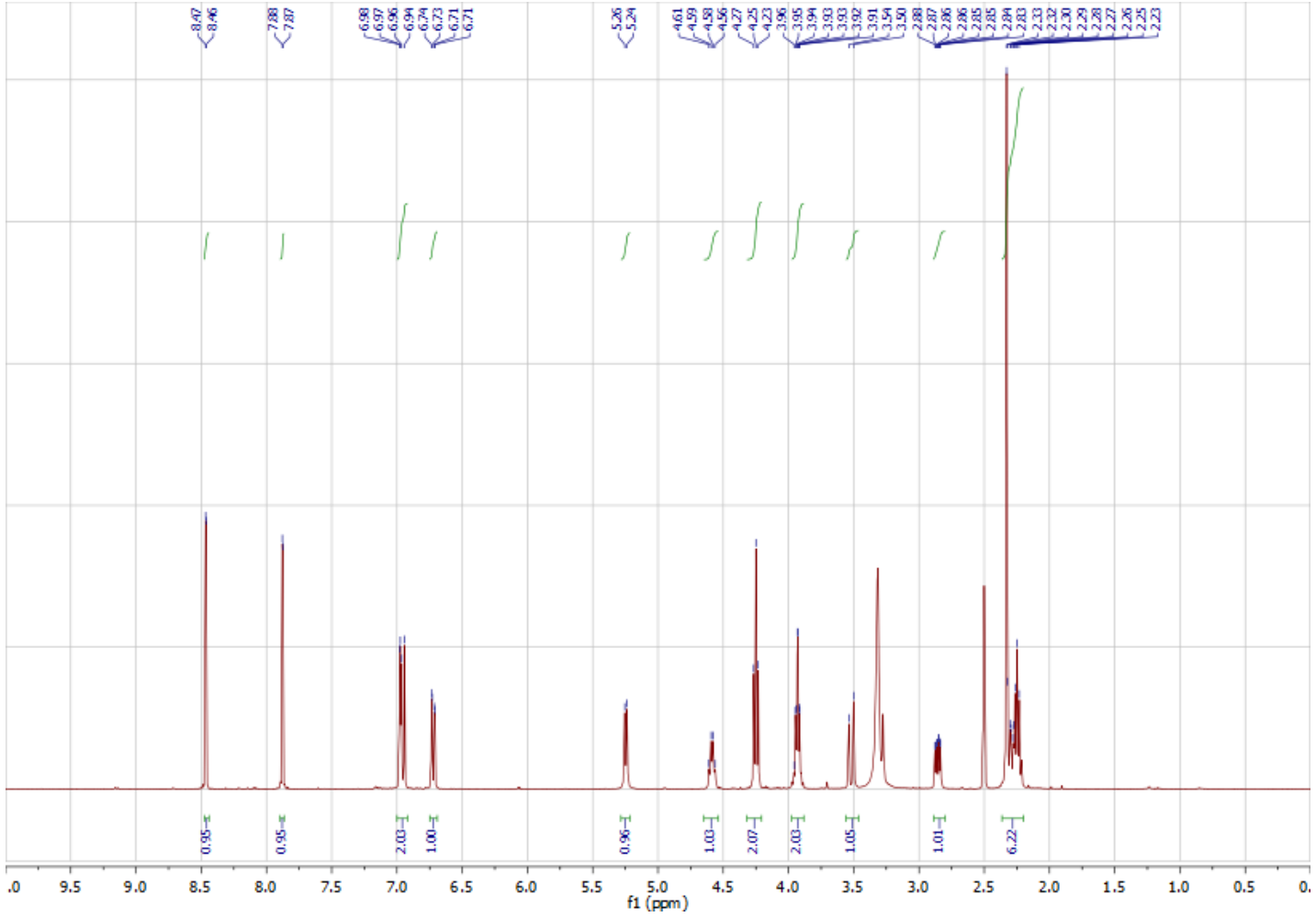


Figure A20 ^{1}H NMR spectra of **127** (DMSO-d_6).

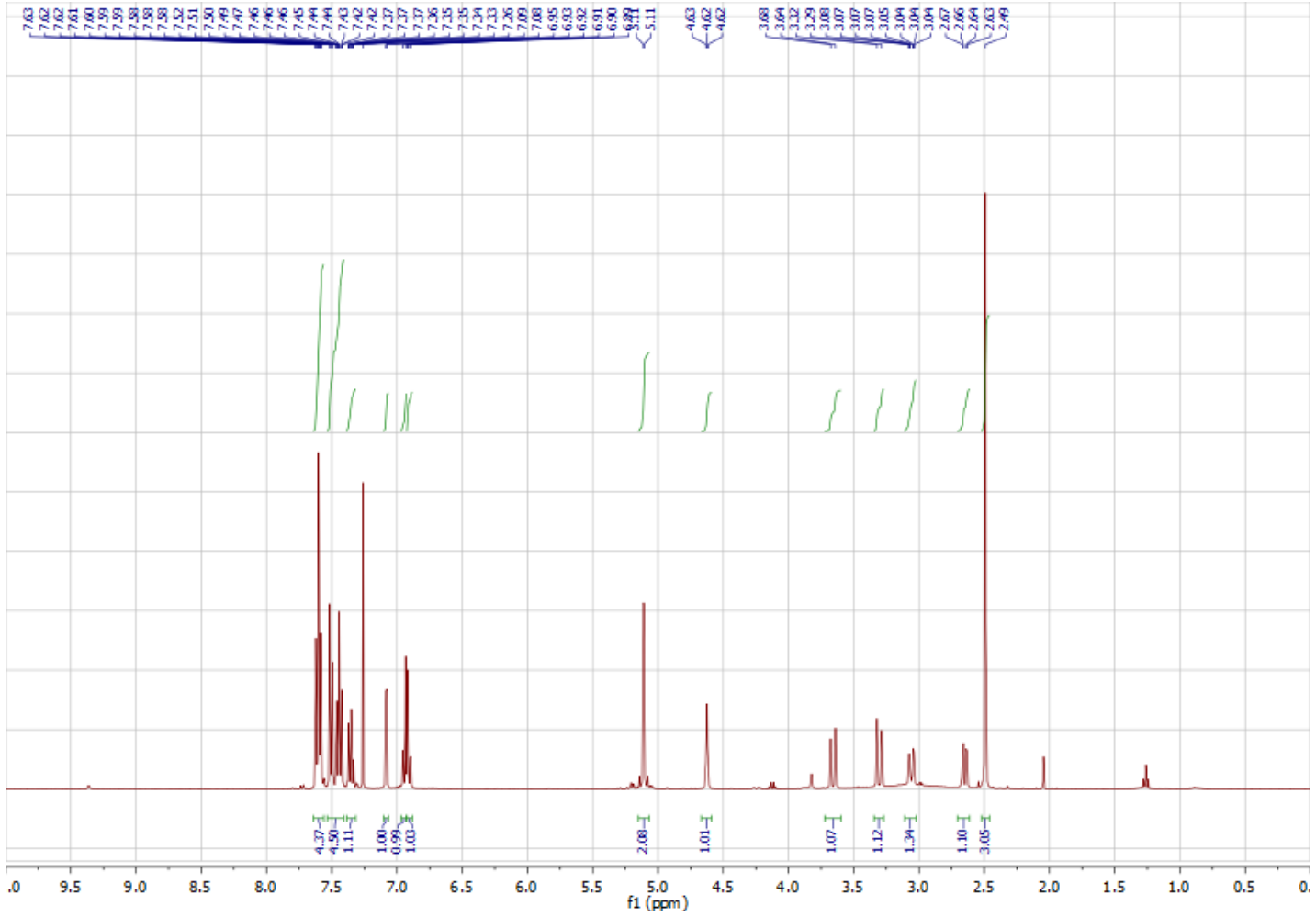


Figure A21 ^{1}H NMR spectra of **129** ($CDCl_3$).

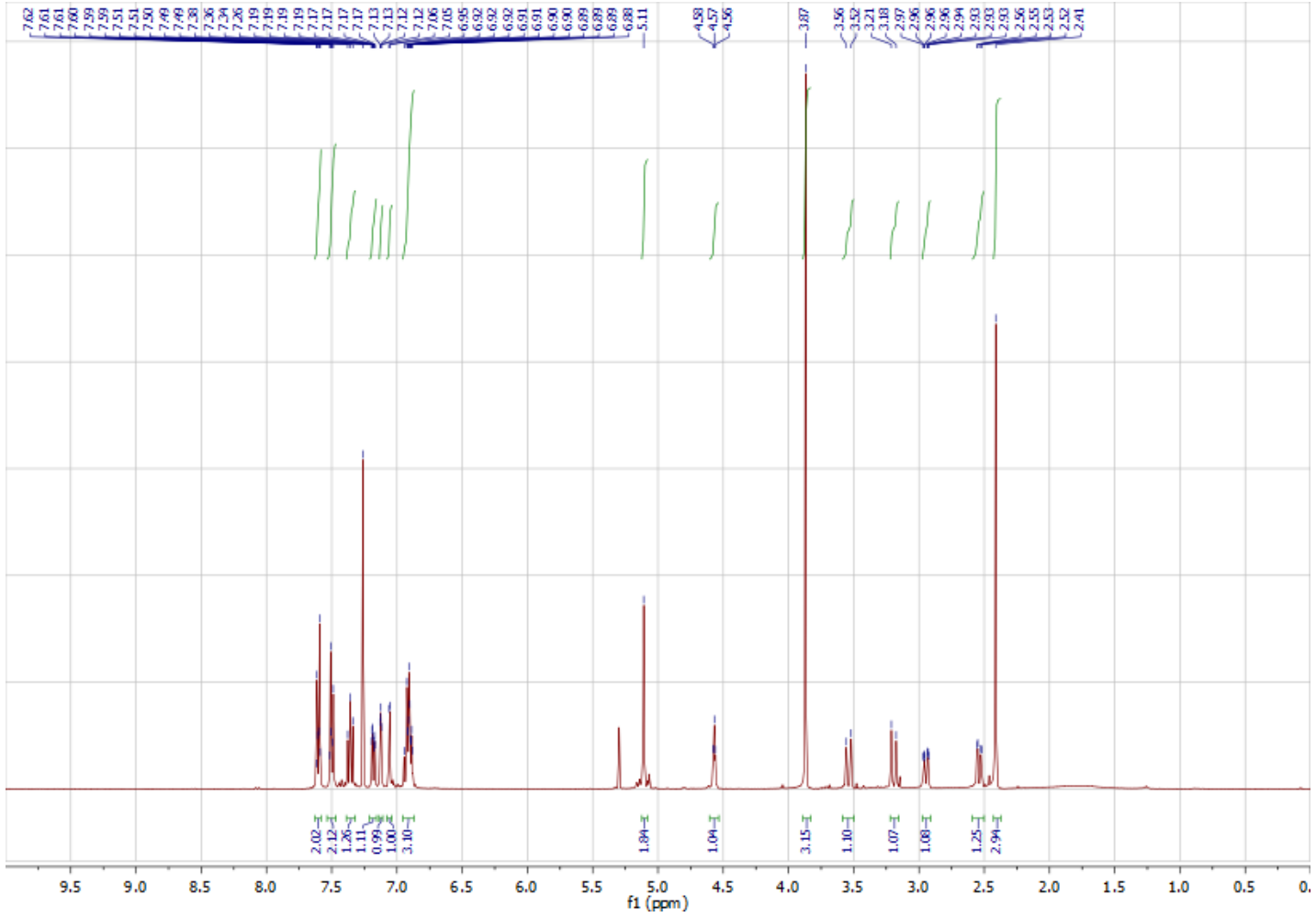


Figure A22 ^{1}H NMR spectra of **130** ($CDCl_3$).

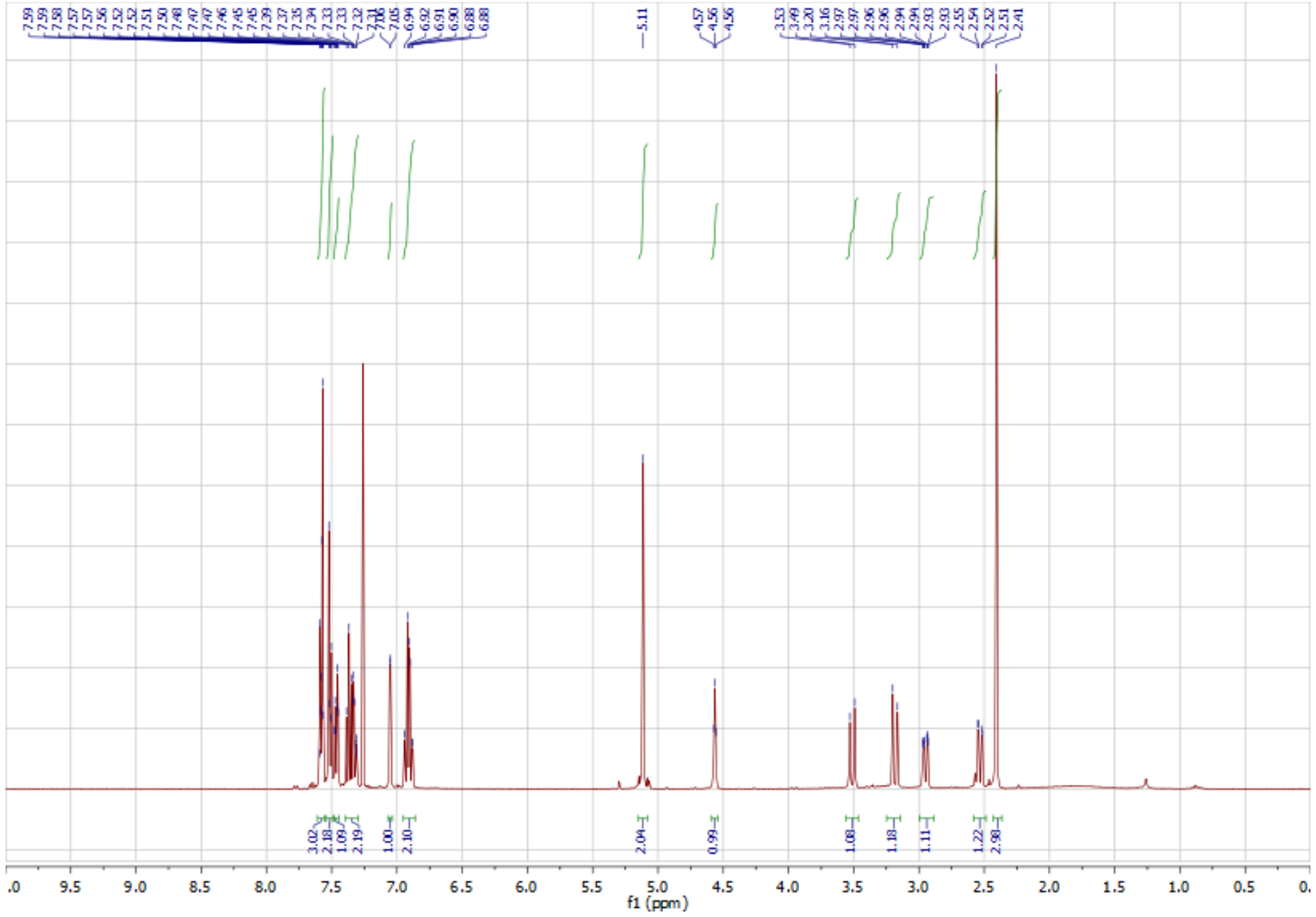


Figure A23 ^{1}H NMR spectra of **131** ($CDCl_3$).

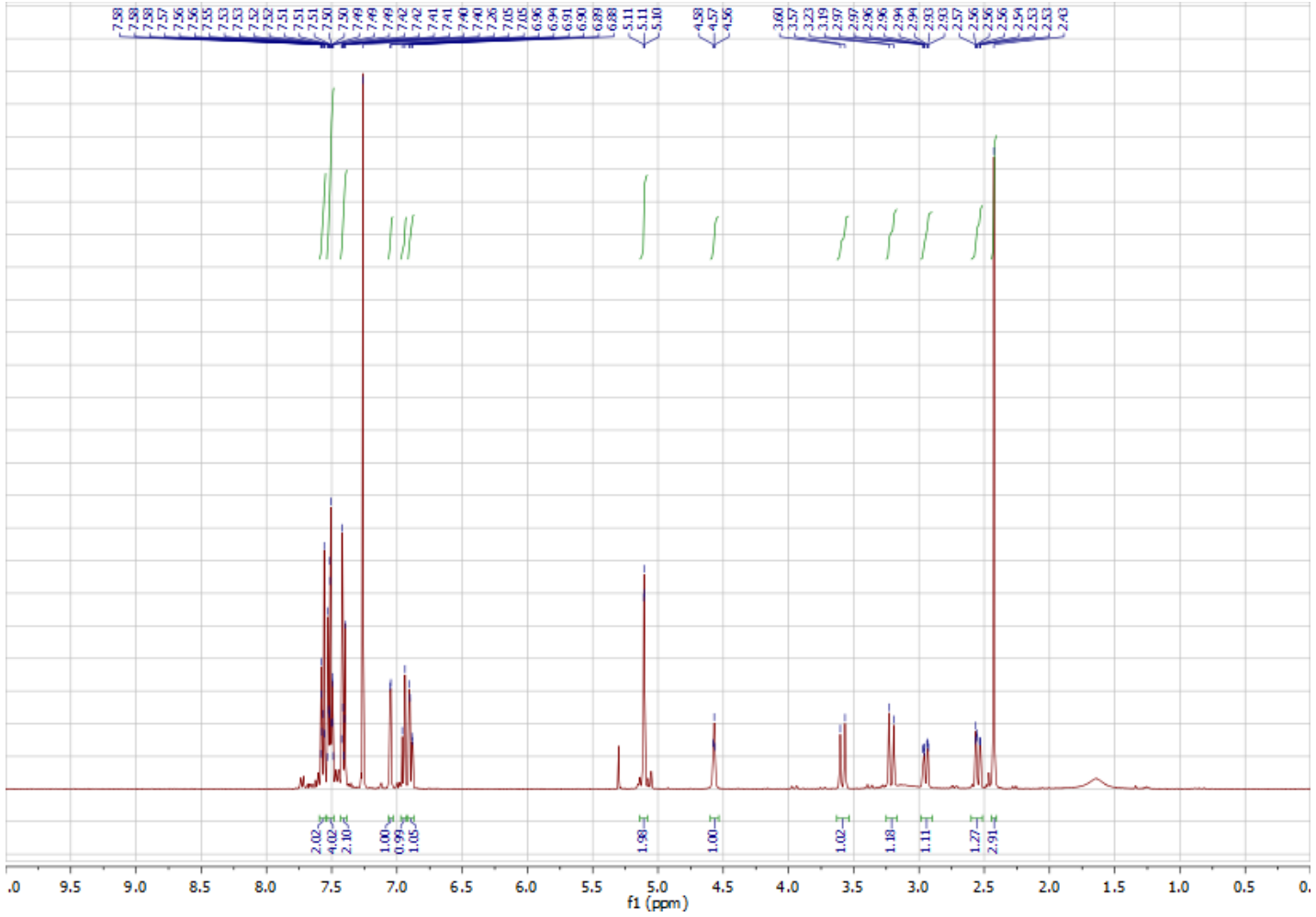


Figure A24 ^{1}H NMR spectra of **132** ($CDCl_3$).

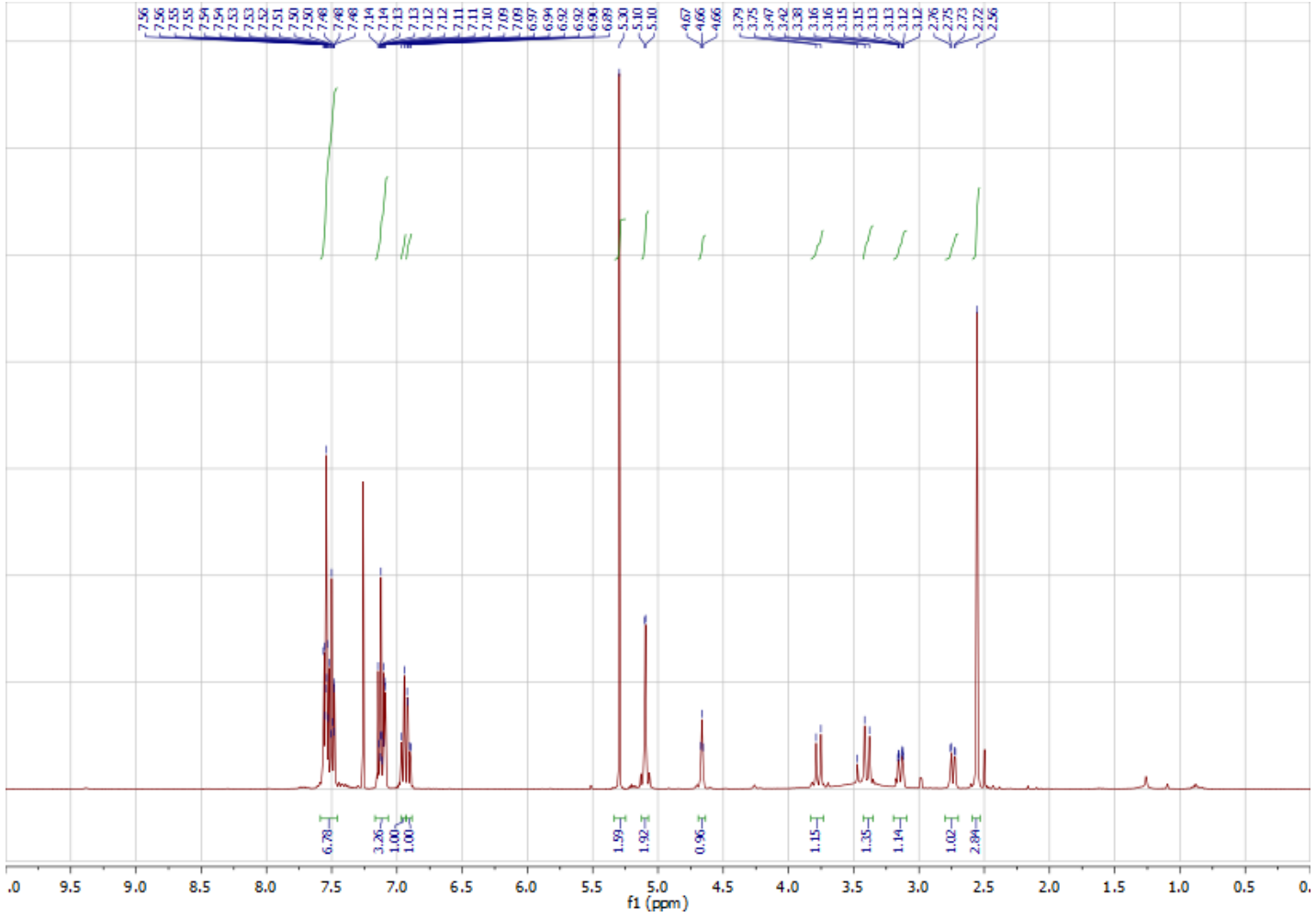


Figure A25 ^{1}H NMR spectra of **133** ($CDCl_3$).

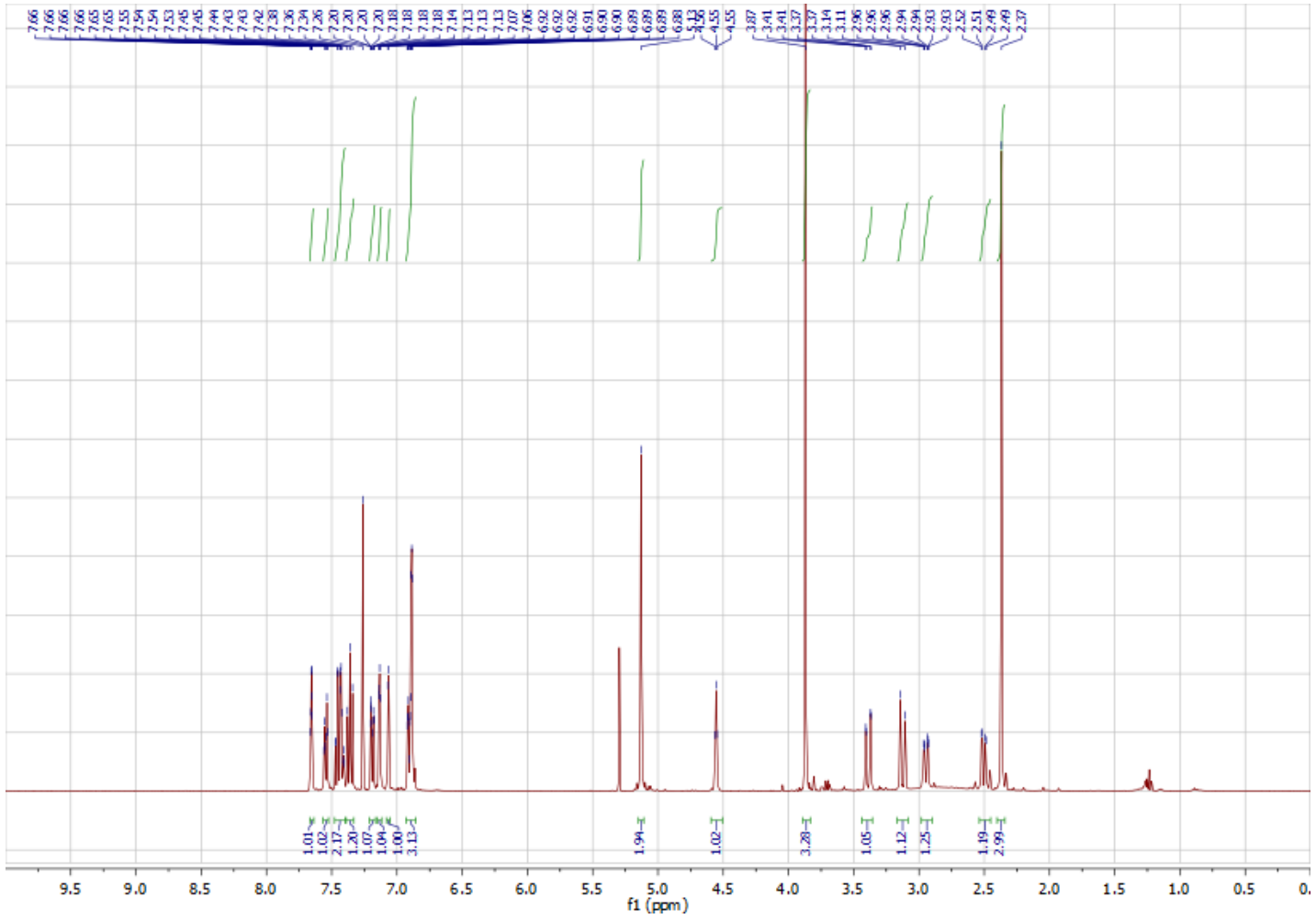


Figure A26 ^{1}H NMR spectra of **136** ($CDCl_3$).

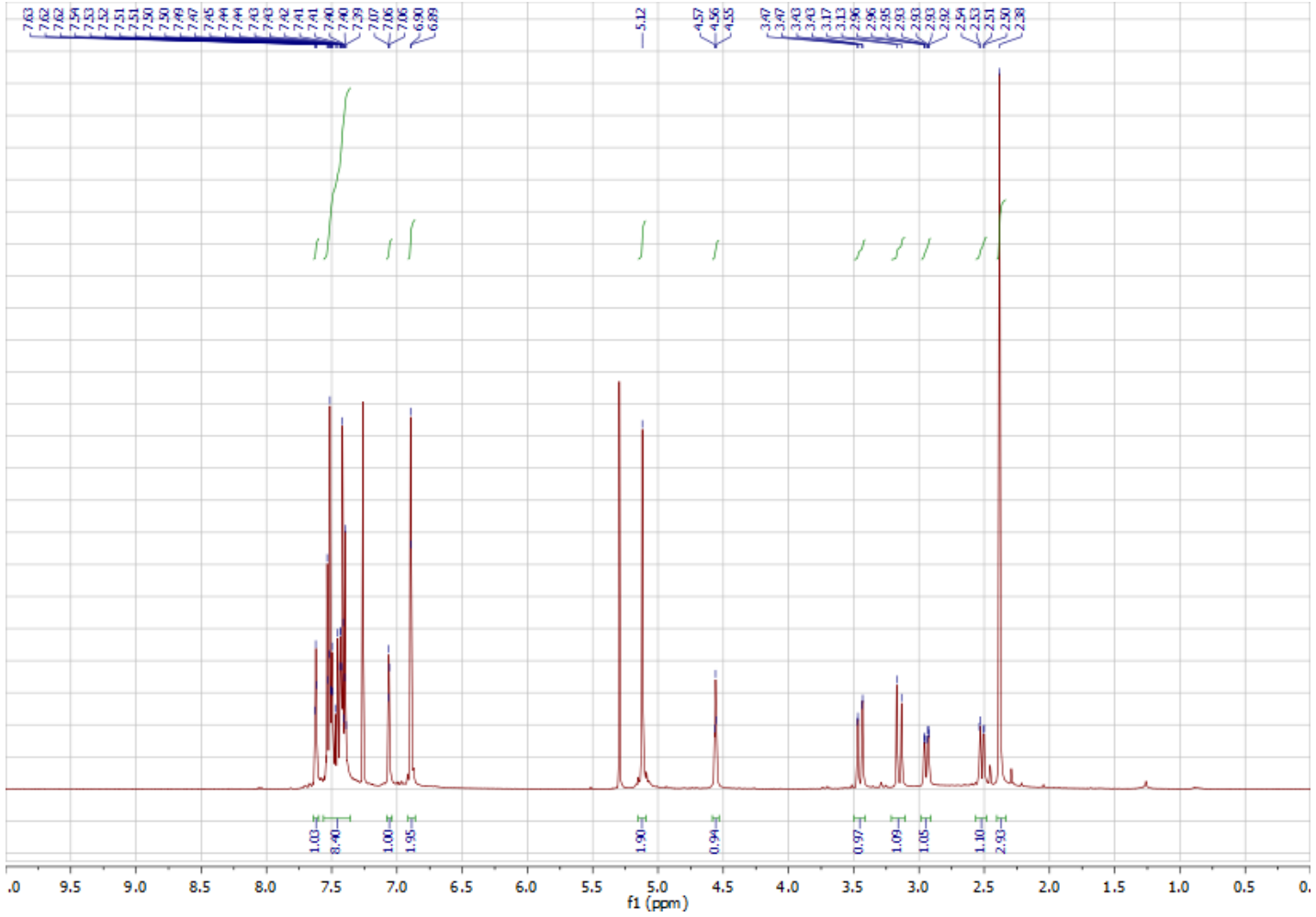


Figure A27 ^{1}H NMR spectra of **138** ($CDCl_3$).

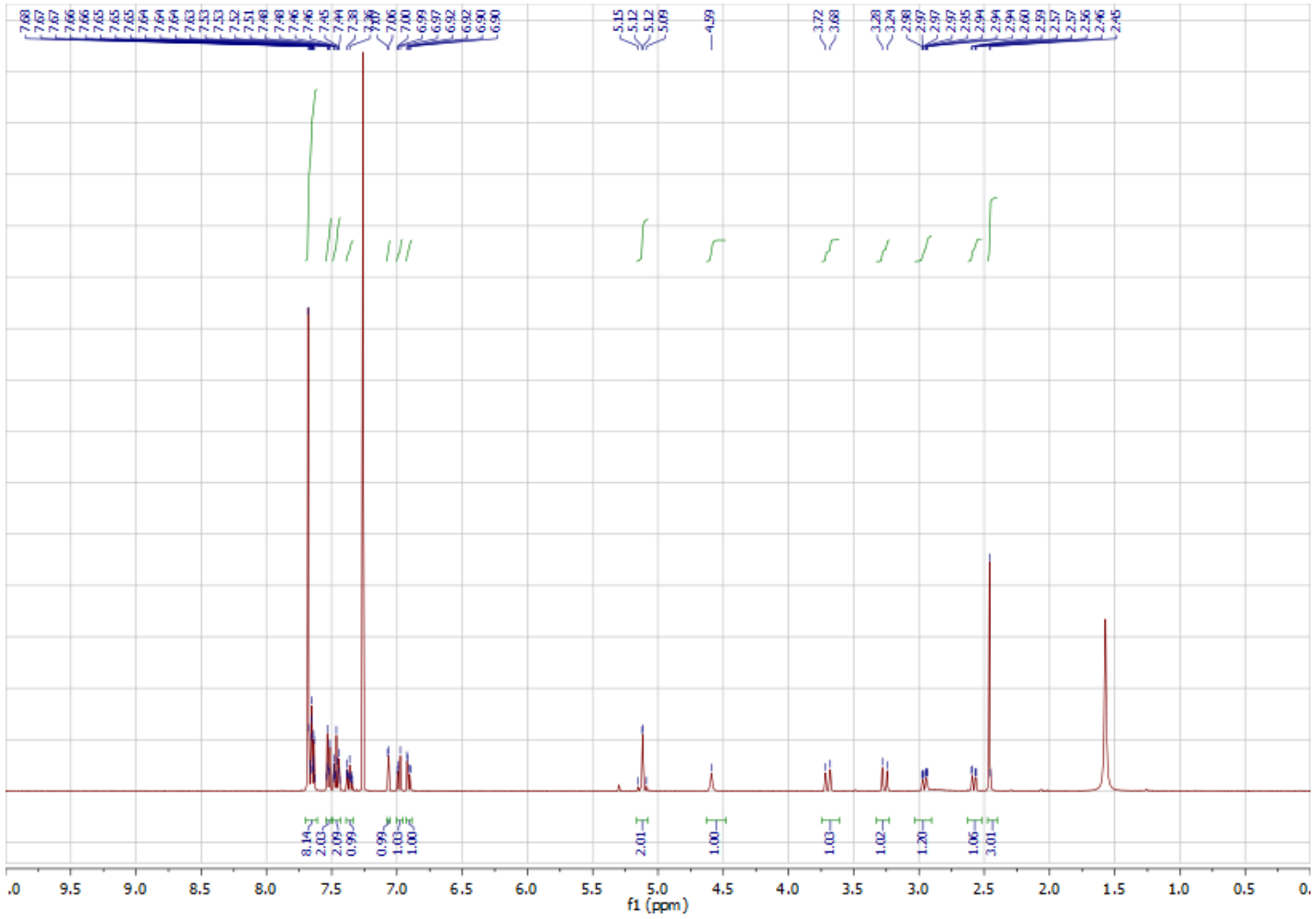


Figure A28 ^{1}H NMR spectra of **140** ($CDCl_3$).

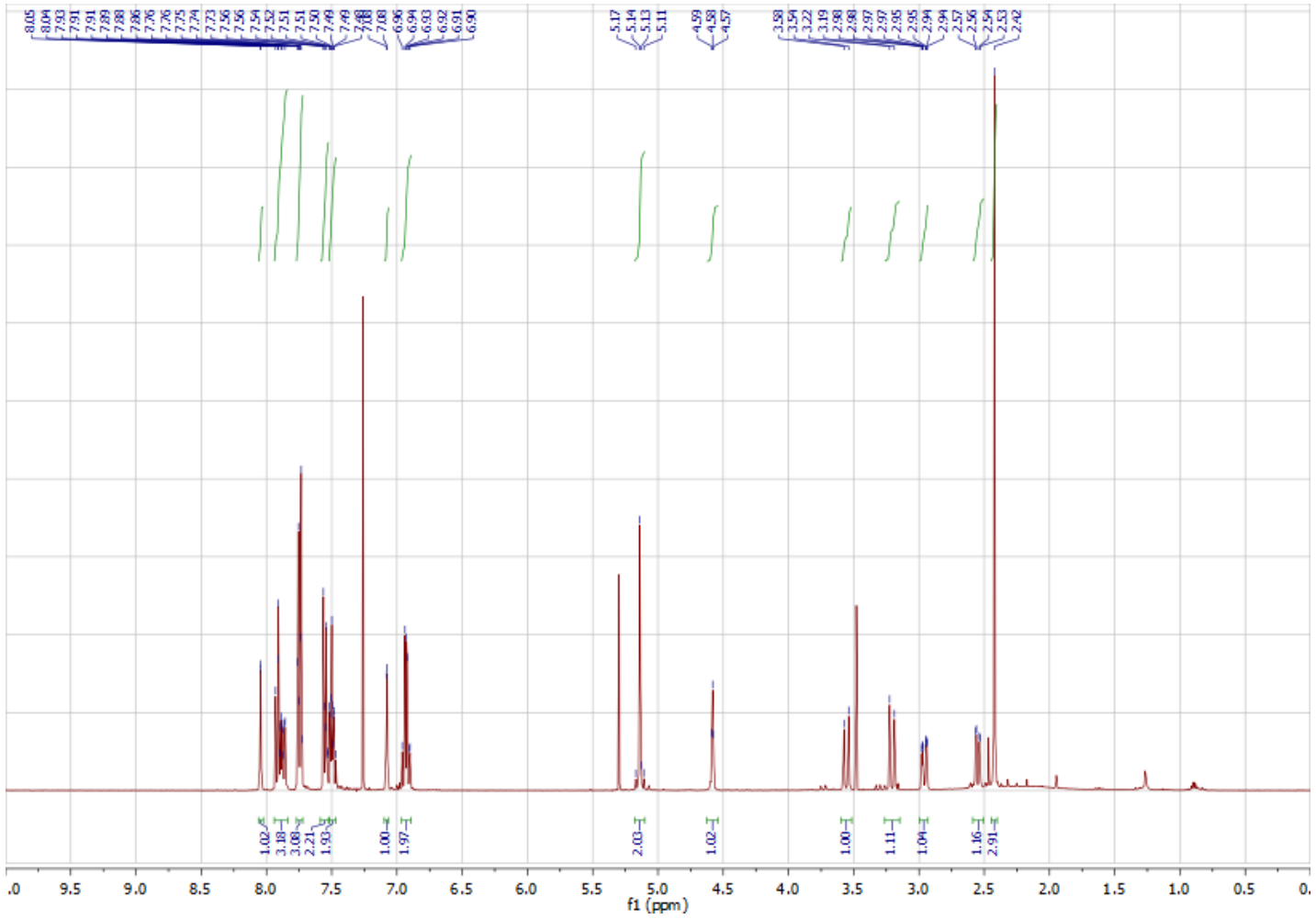


Figure A29 ^{1}H NMR spectra of **142** ($CDCl_3$).

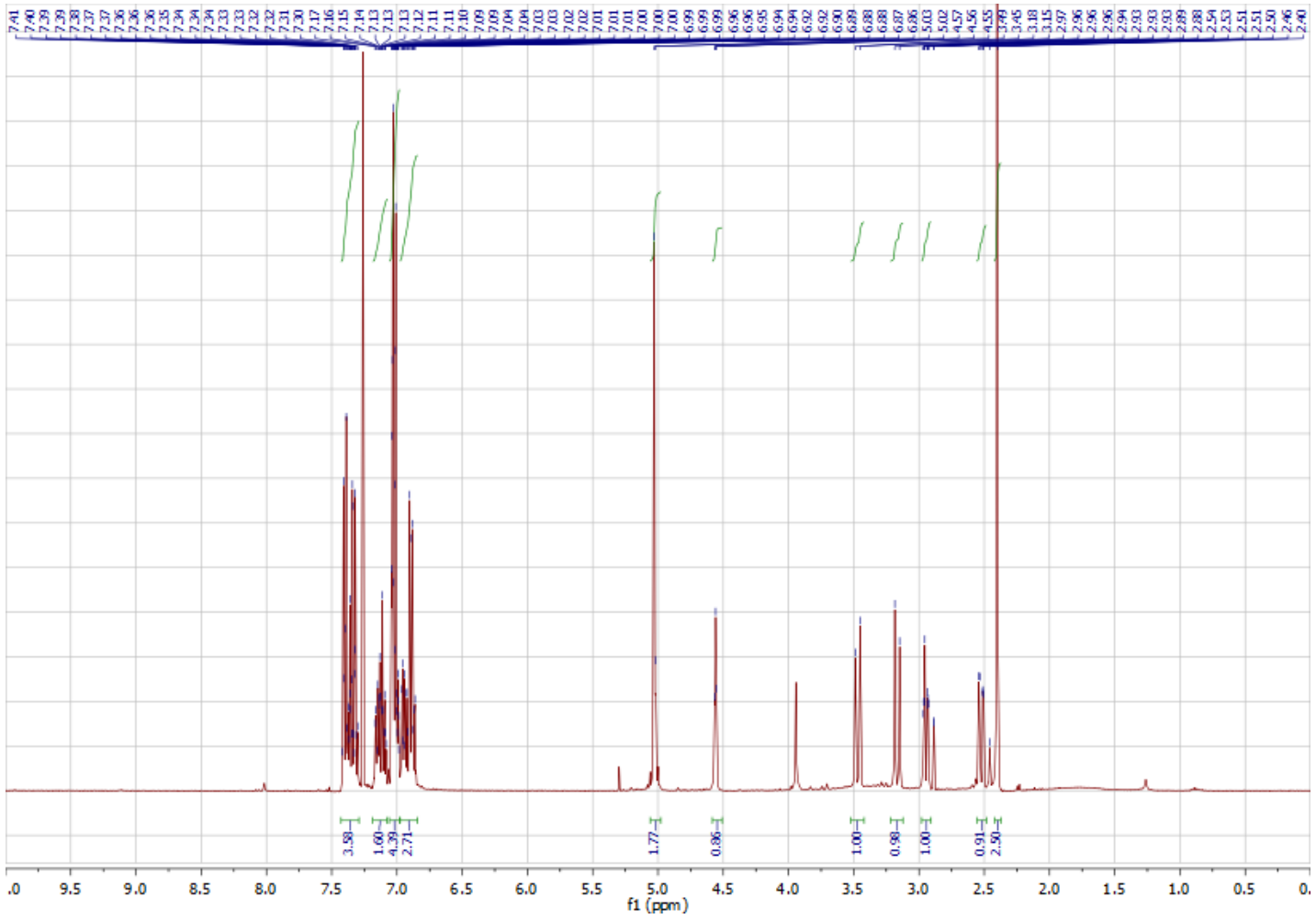


Figure A30 ^{1}H NMR spectra of **148** ($CDCl_3$).

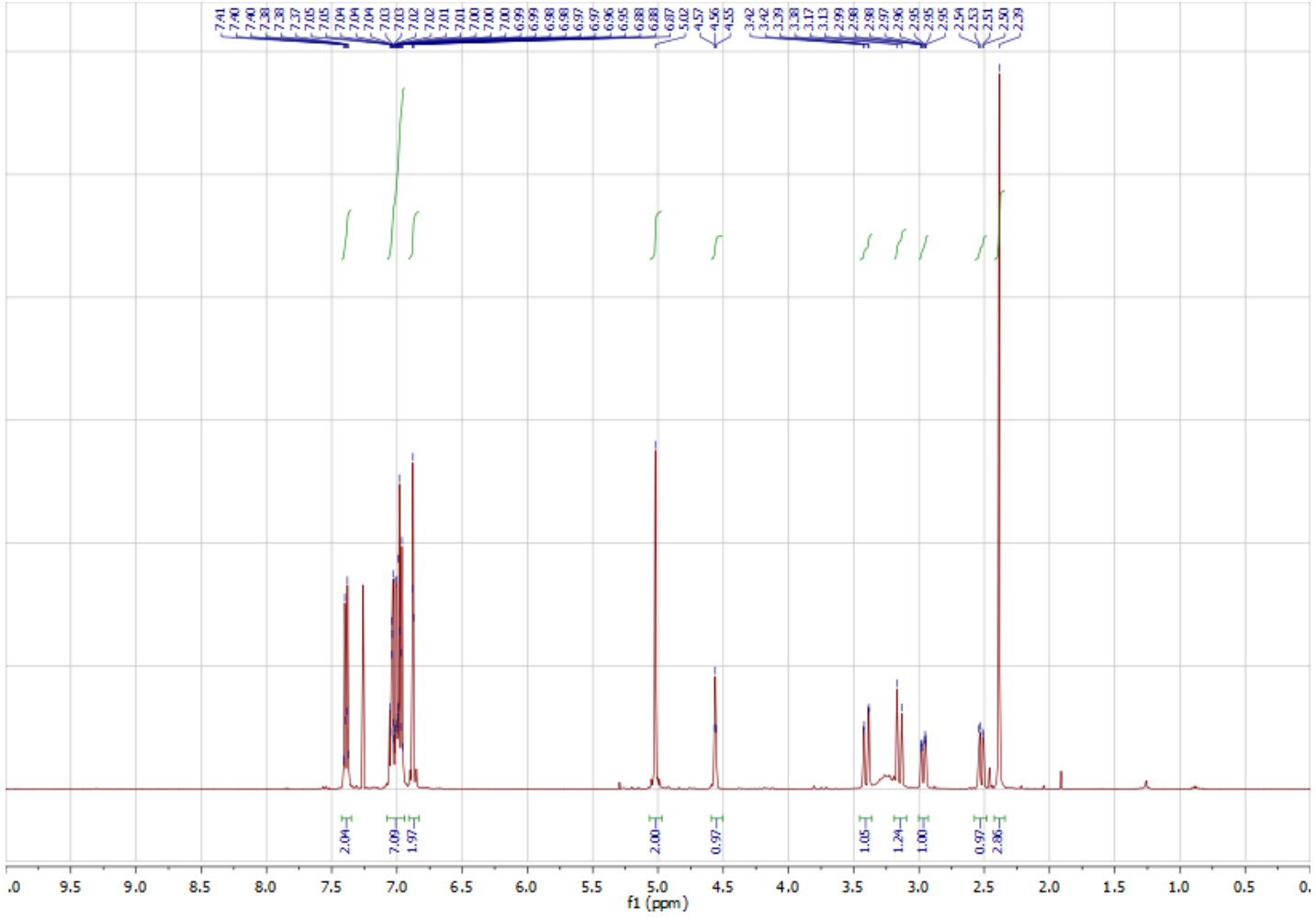


Figure A31 ^{1}H NMR spectra of **149** ($CDCl_3$).

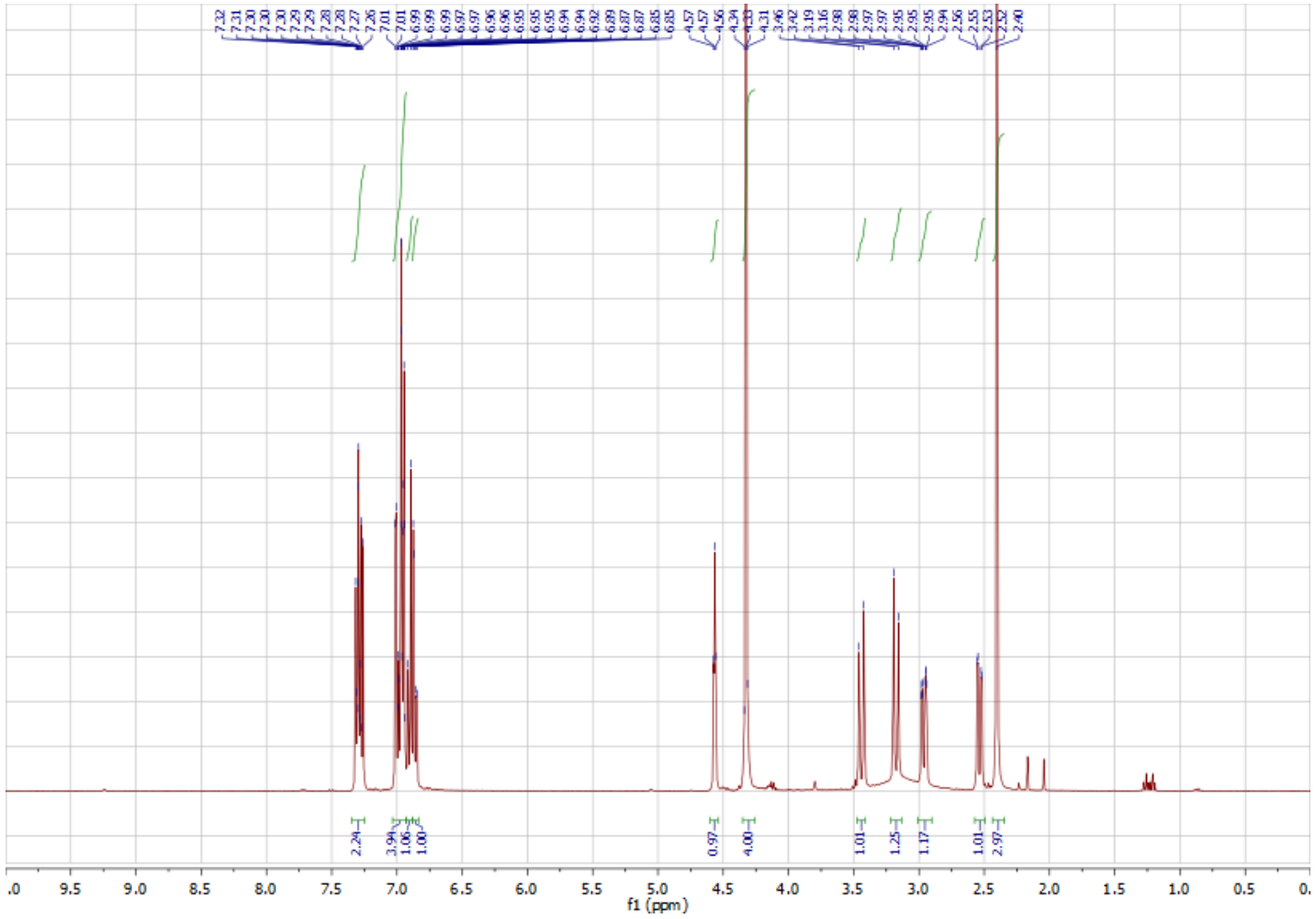


Figure A32 ^{1}H NMR spectra of **150** ($CDCl_3$).

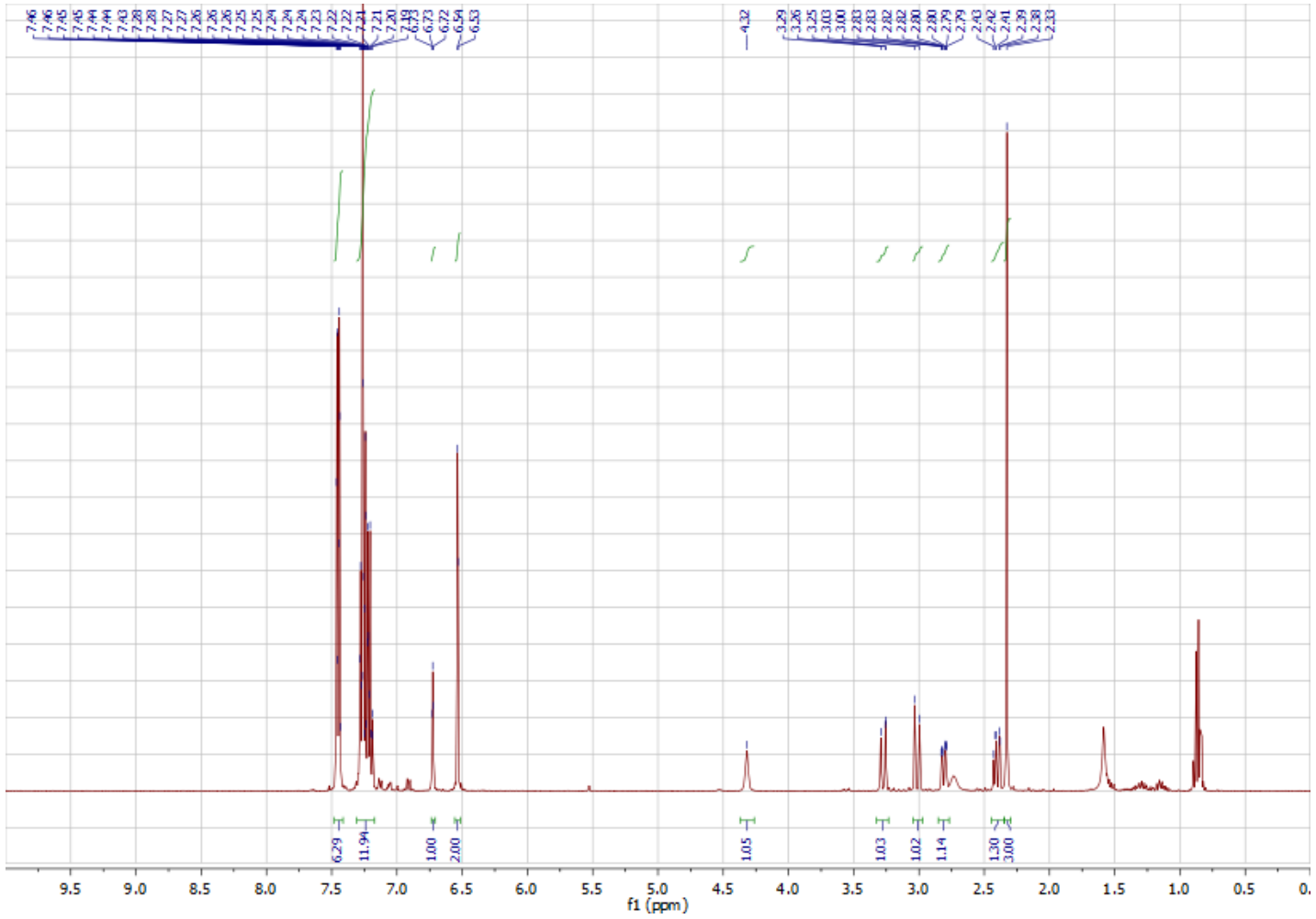


Figure A33 ^{1}H NMR spectra of **151** ($CDCl_3$).

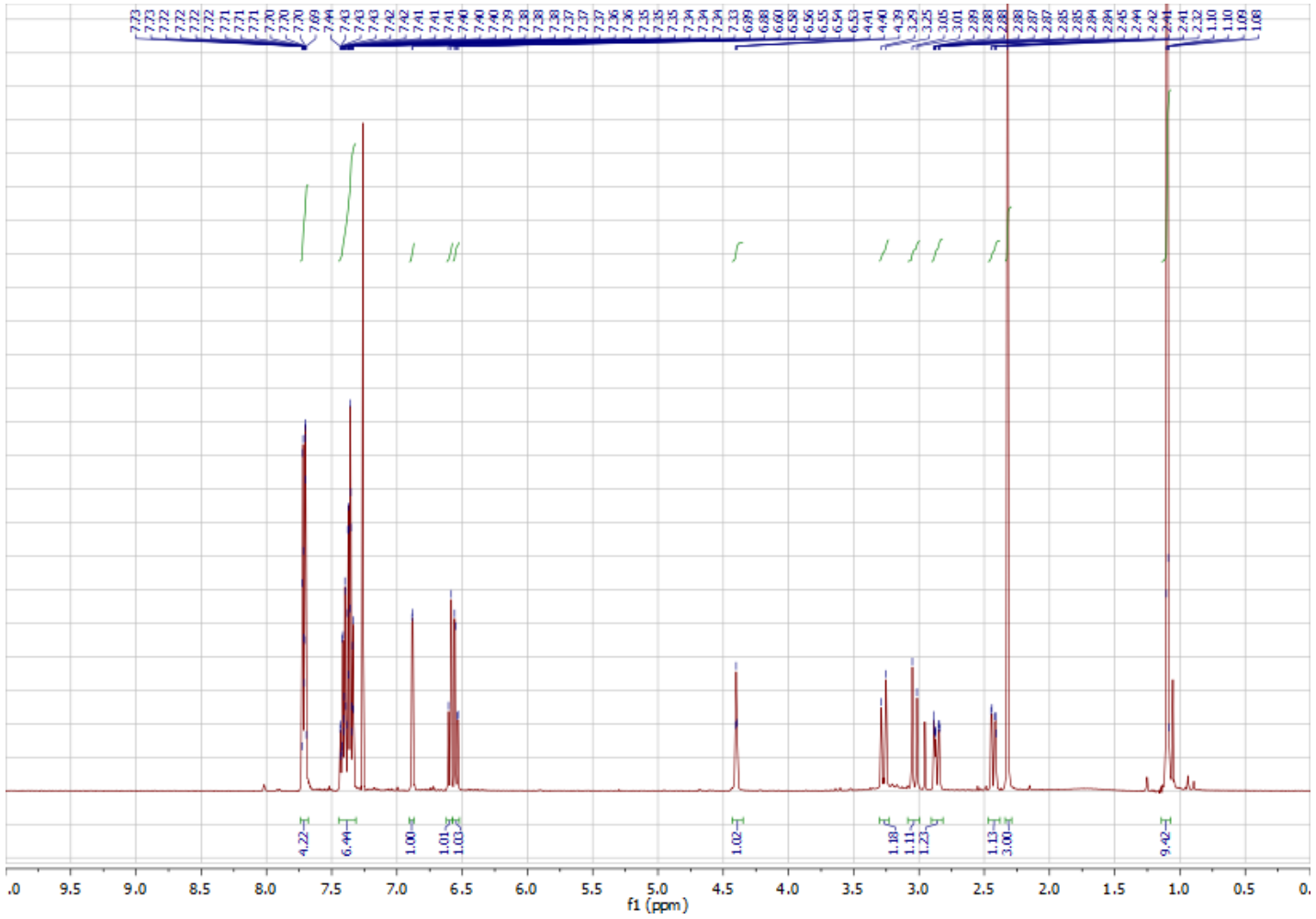


Figure A34 ^{1}H NMR spectra of **152** ($CDCl_3$).

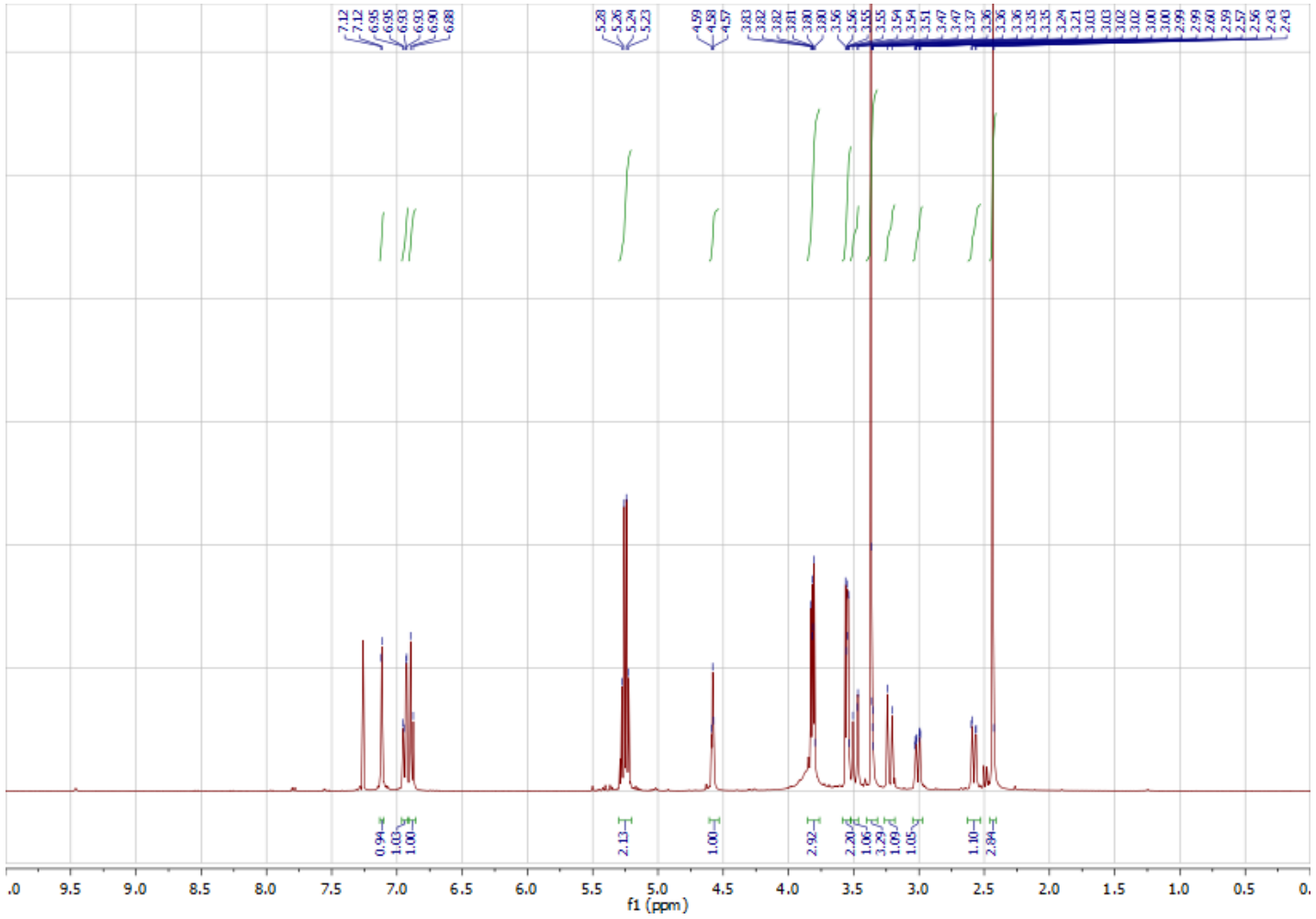


Figure A35 ^{1}H NMR spectra of **153** ($CDCl_3$).

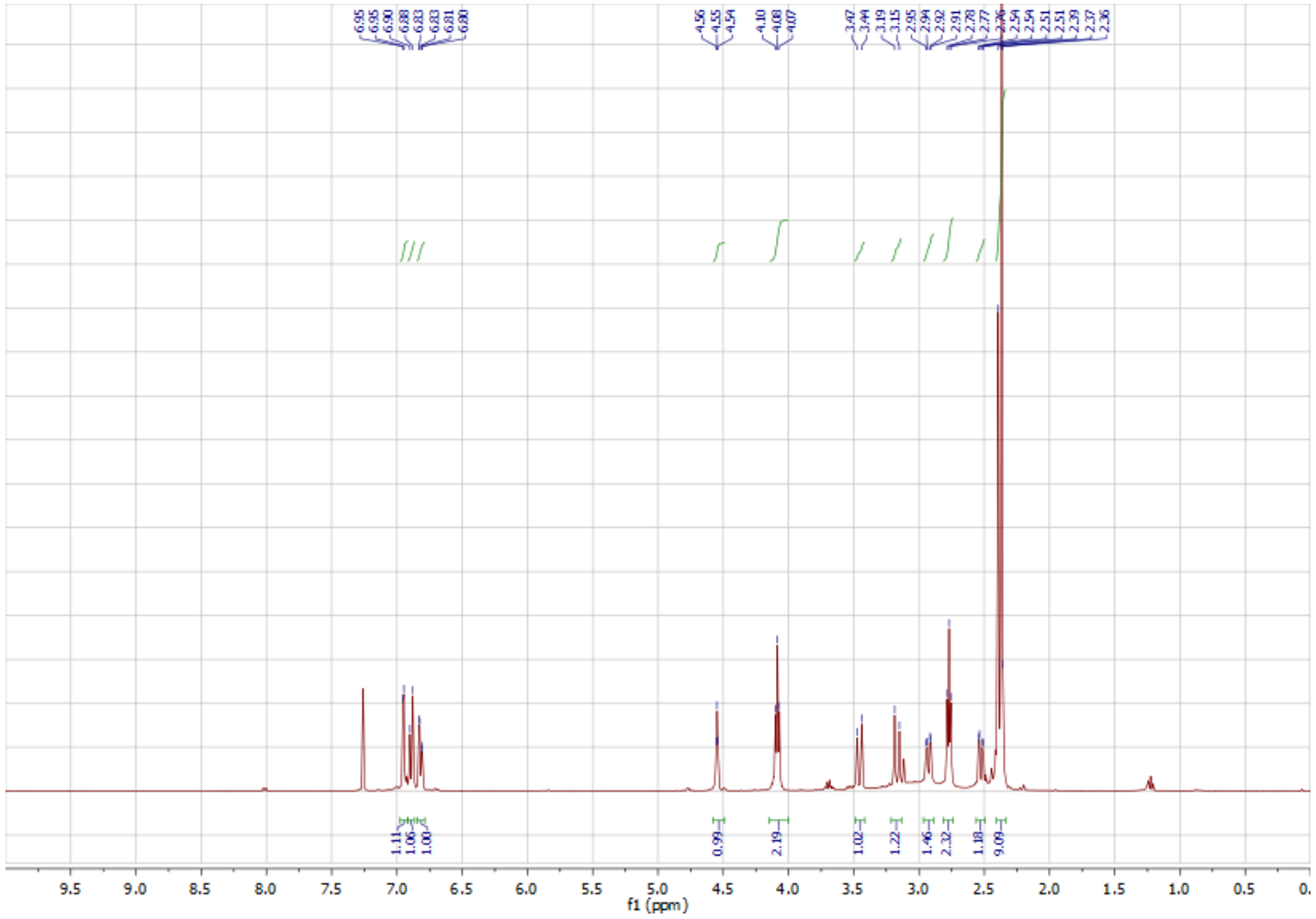


Figure A36 ^{1}H NMR spectra of **154** ($CDCl_3$).

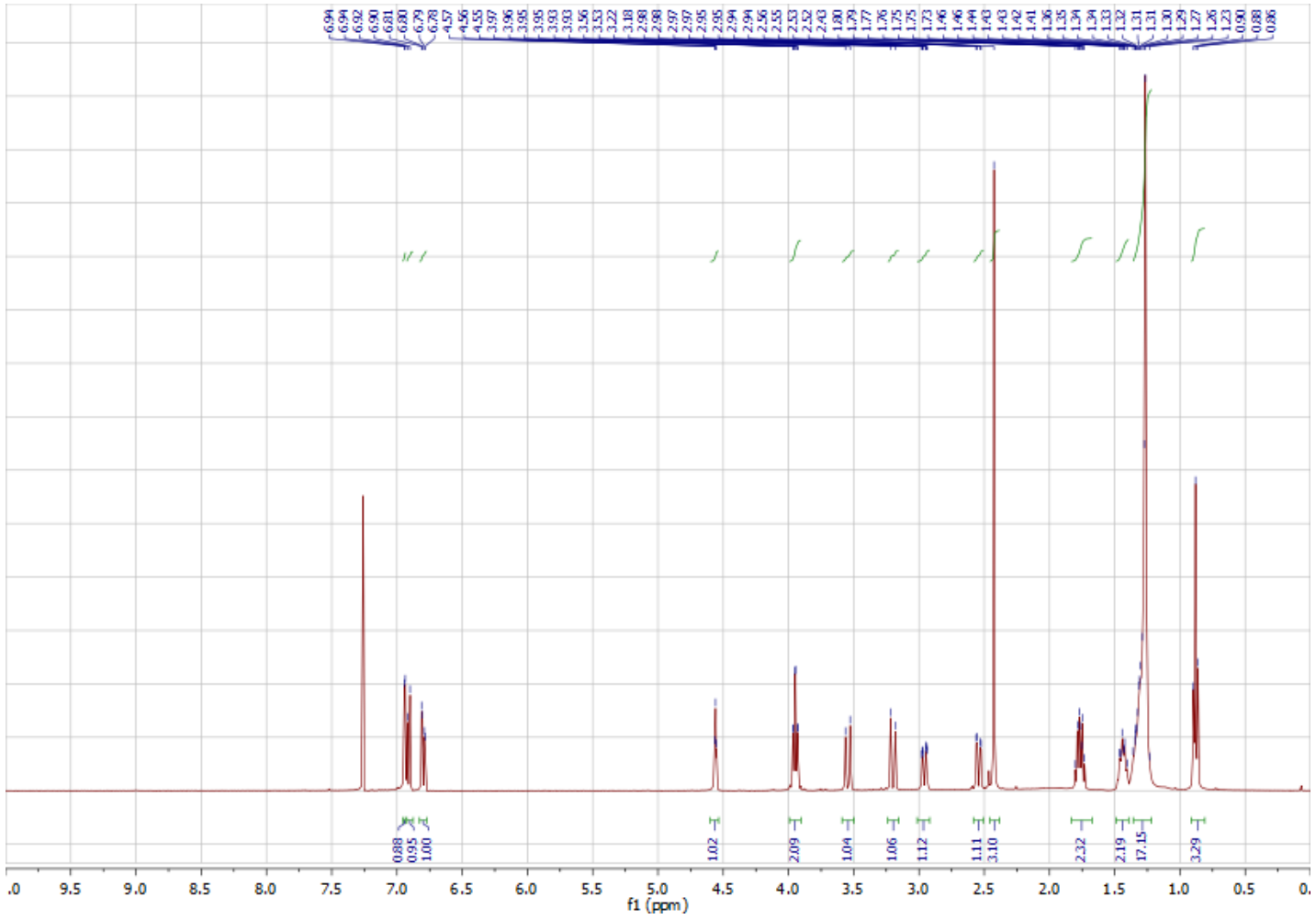


Figure A37 ^{1}H NMR spectra of **155** ($CDCl_3$).

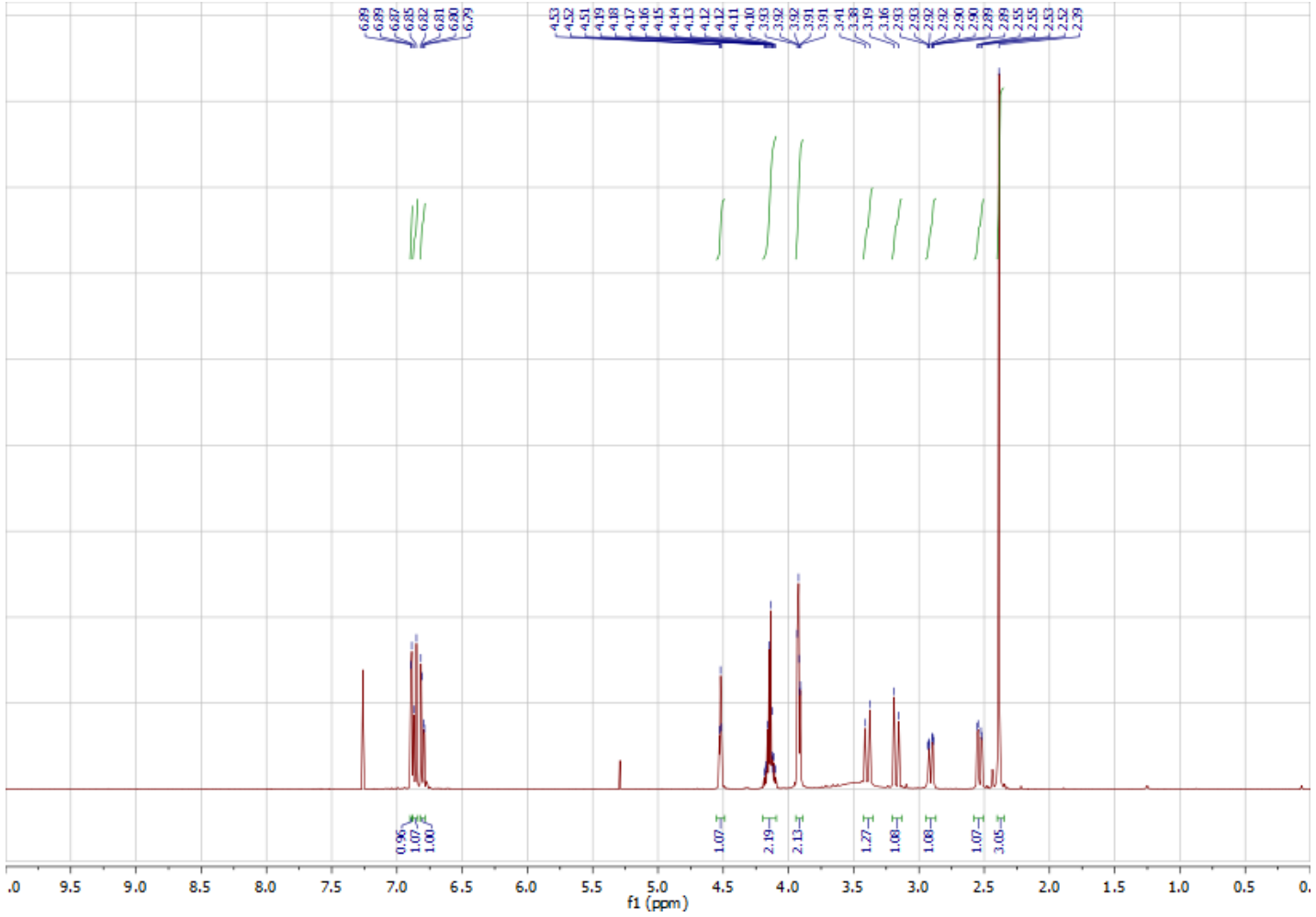


Figure A38 ^{1}H NMR spectra of **157** ($CDCl_3$).

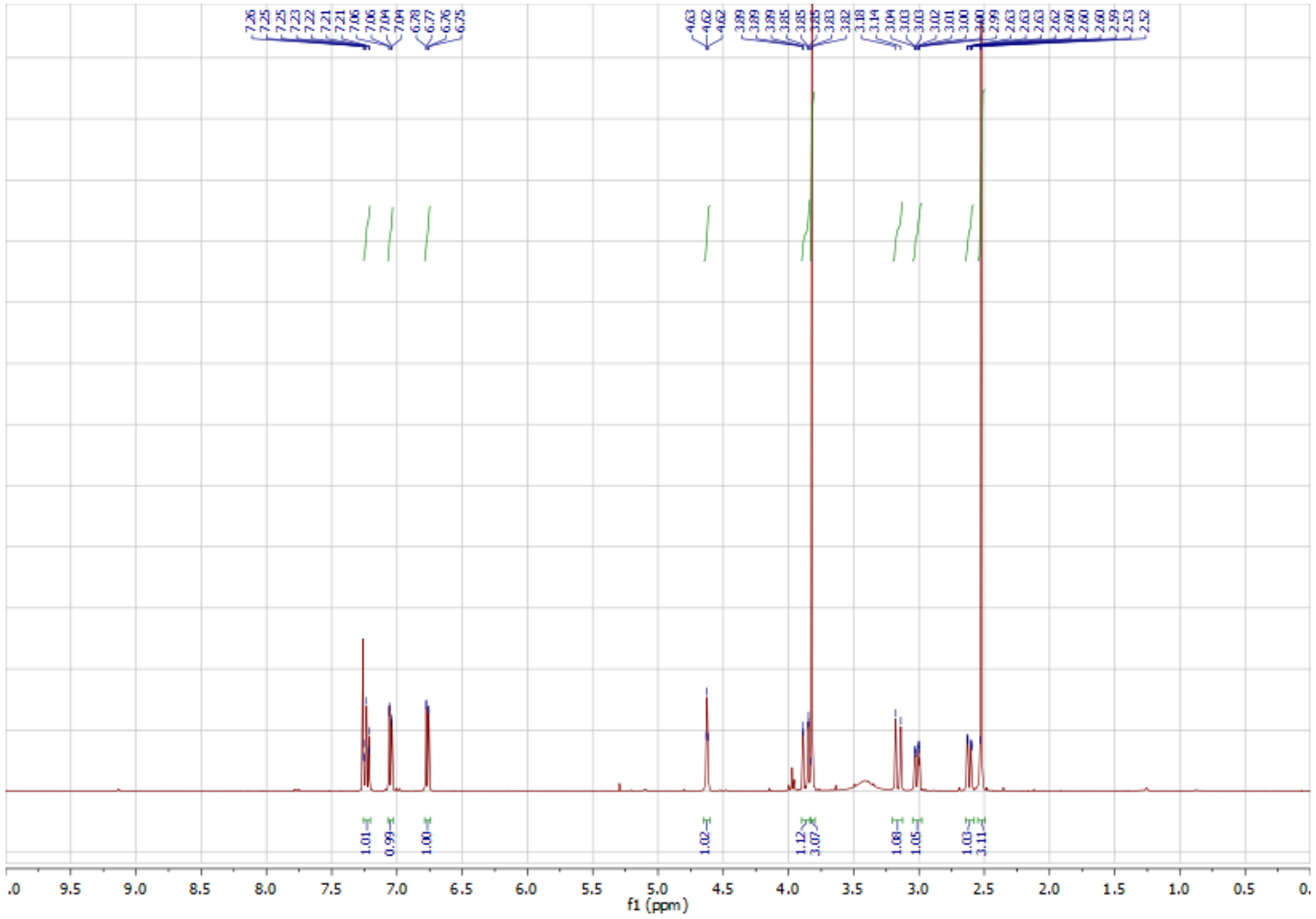


Figure A39 ^{1}H NMR spectra of **158** ($CDCl_3$).

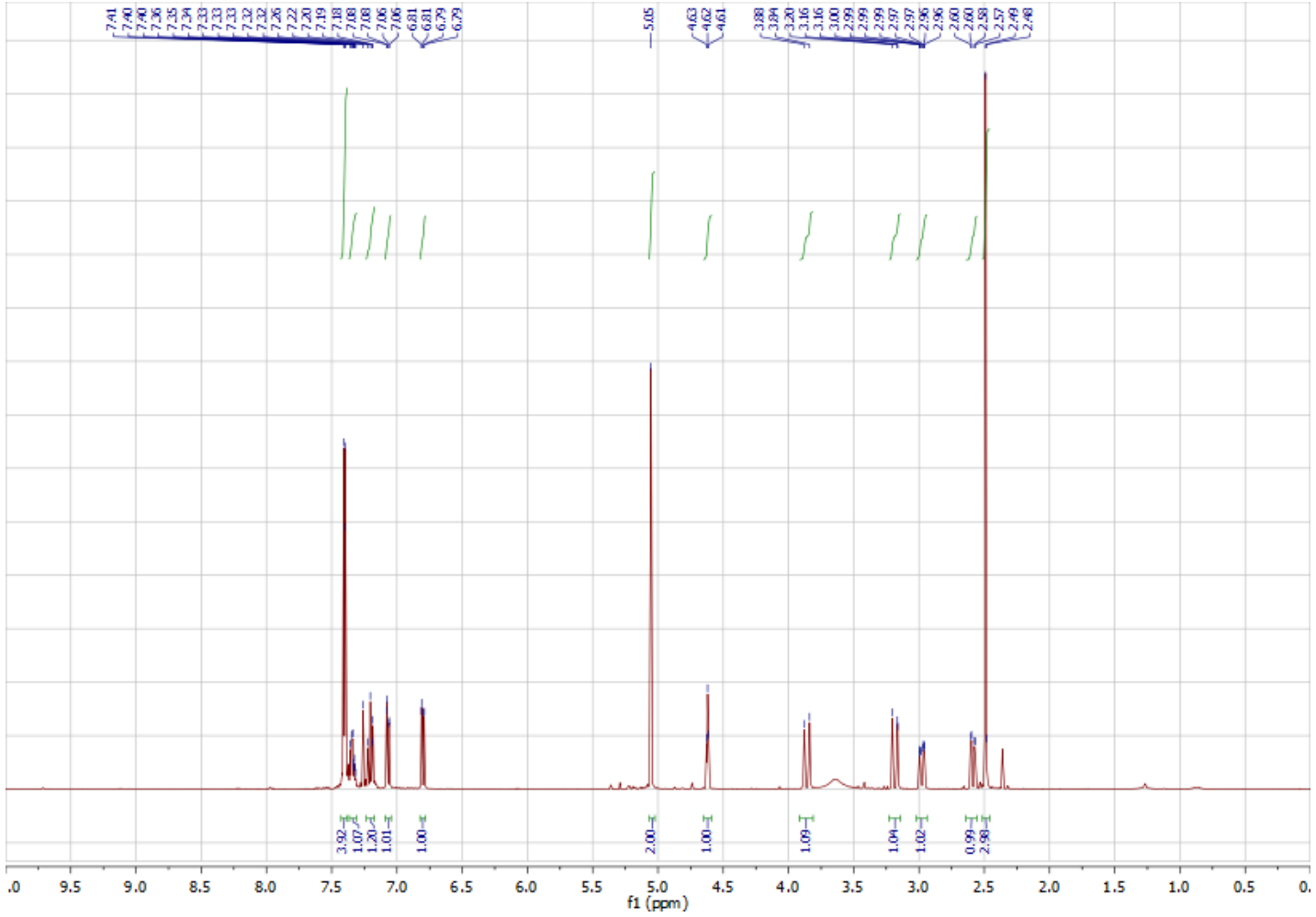


Figure A40 ^{1}H NMR spectra of **159** ($CDCl_3$).

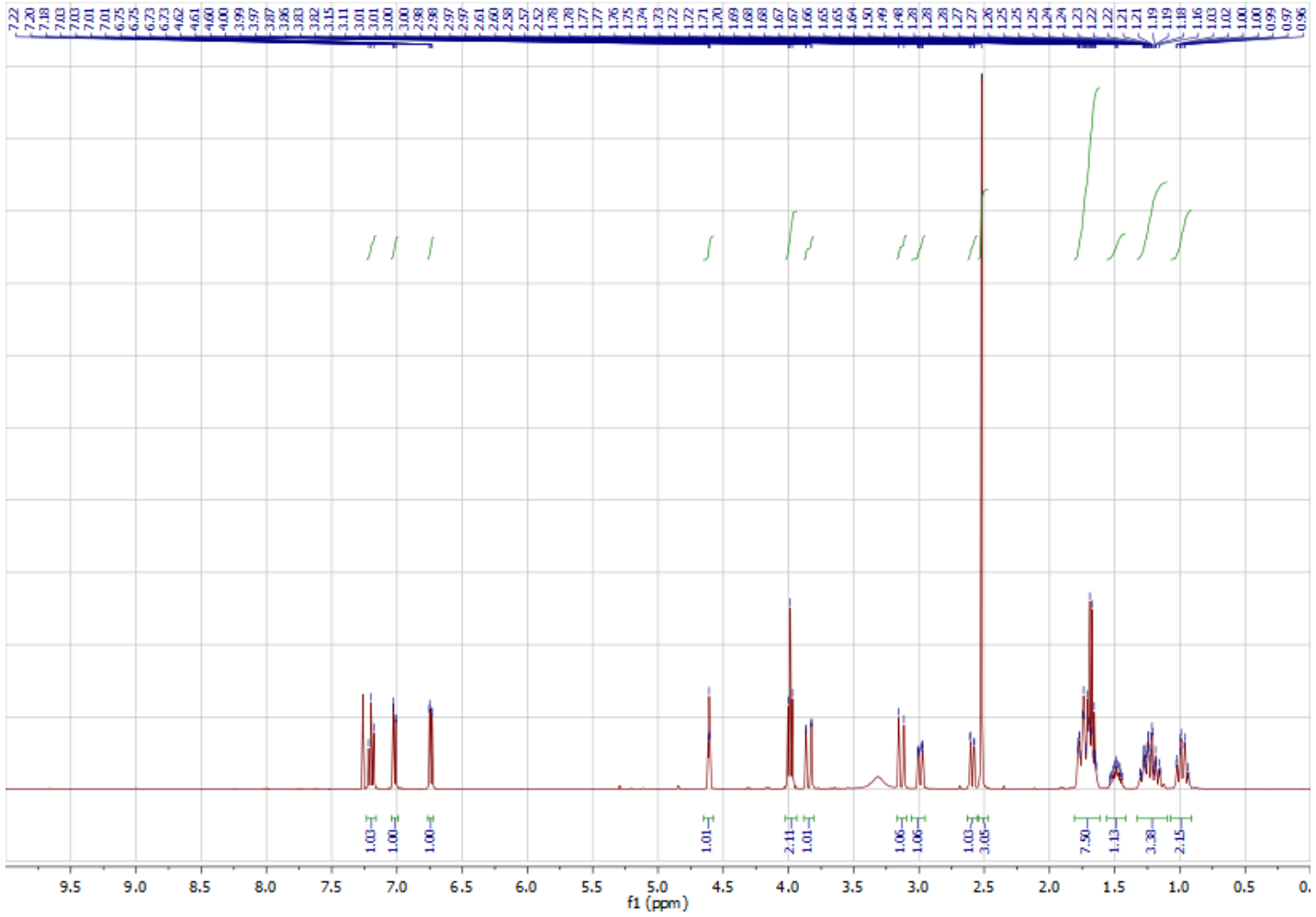


Figure A41 ^{1}H NMR spectra of **160** ($CDCl_3$).

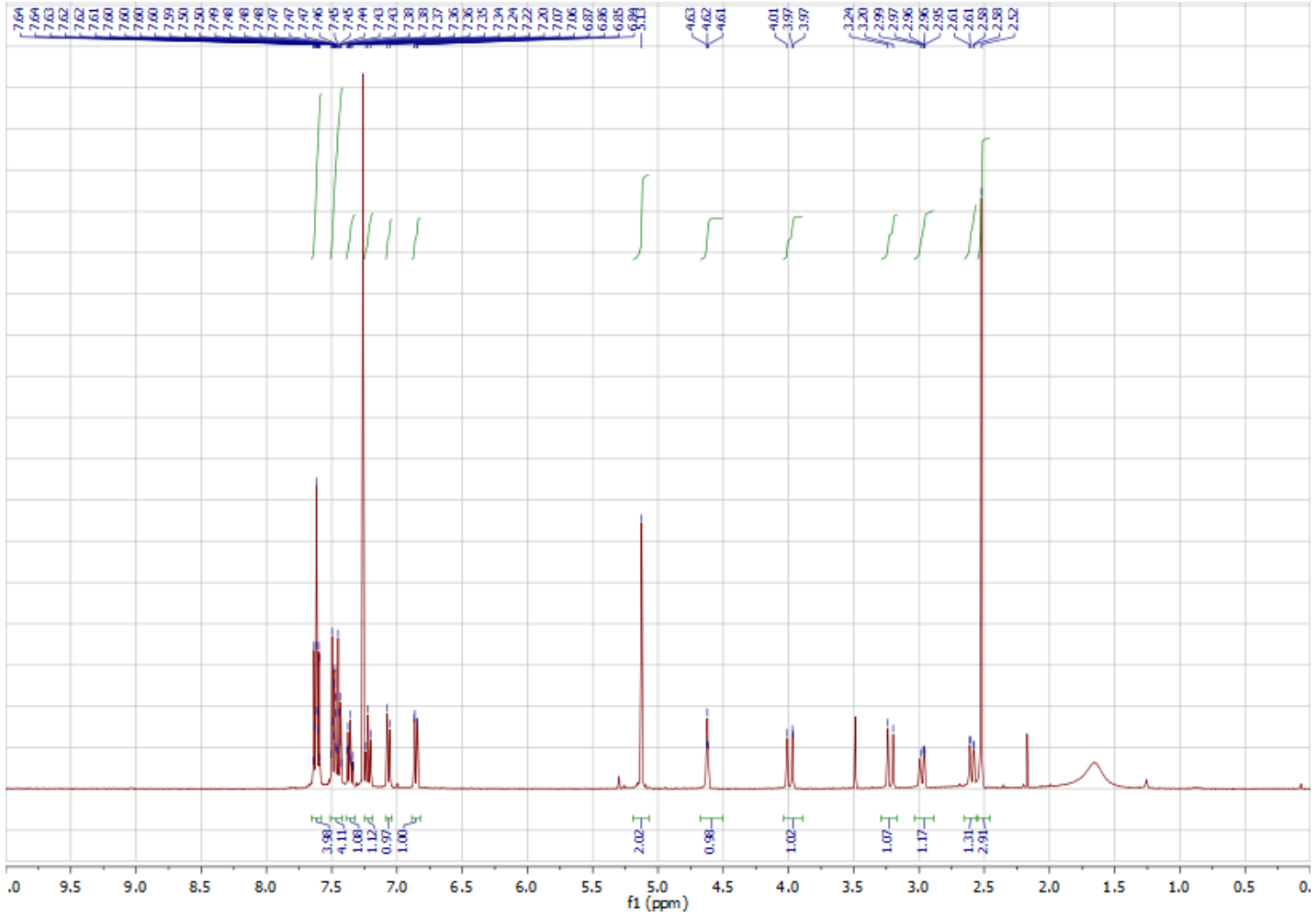


Figure A42 ^{1}H NMR spectra of **161** ($CDCl_3$).

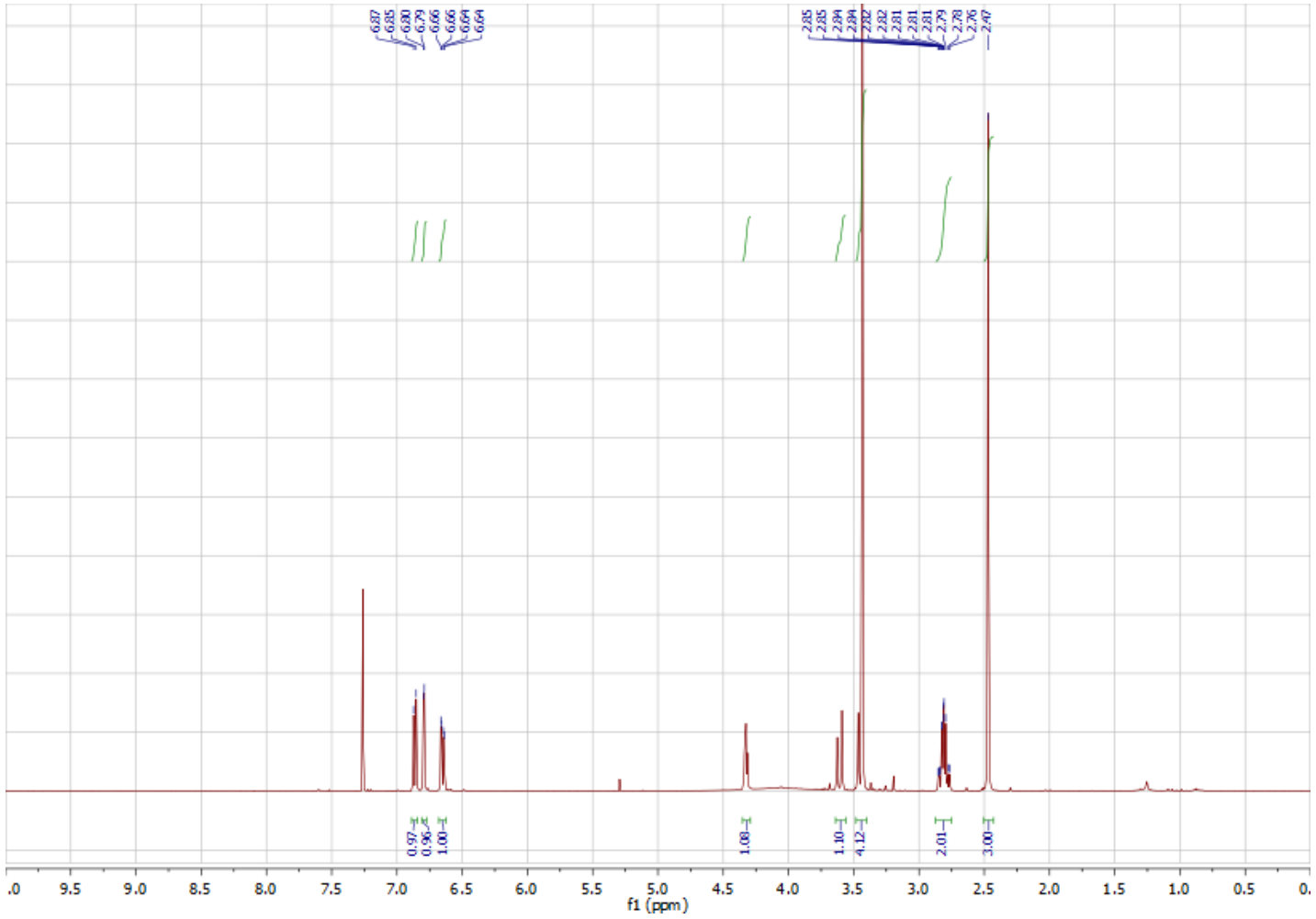


Figure A43 ^{1}H NMR spectra of **162** ($CDCl_3$).

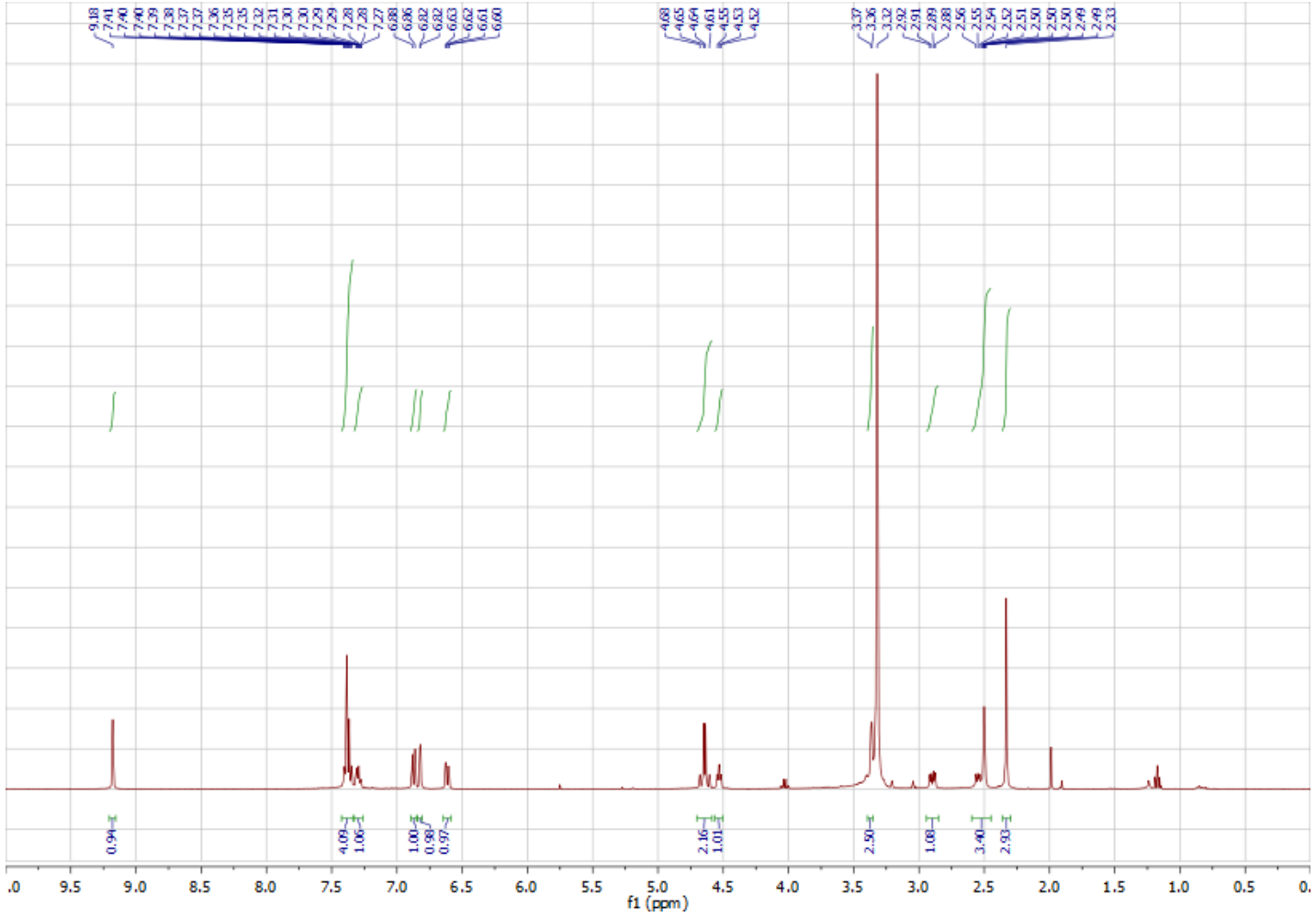


Figure A44 ^{1}H NMR spectra of **166** (DMSO-d_6).

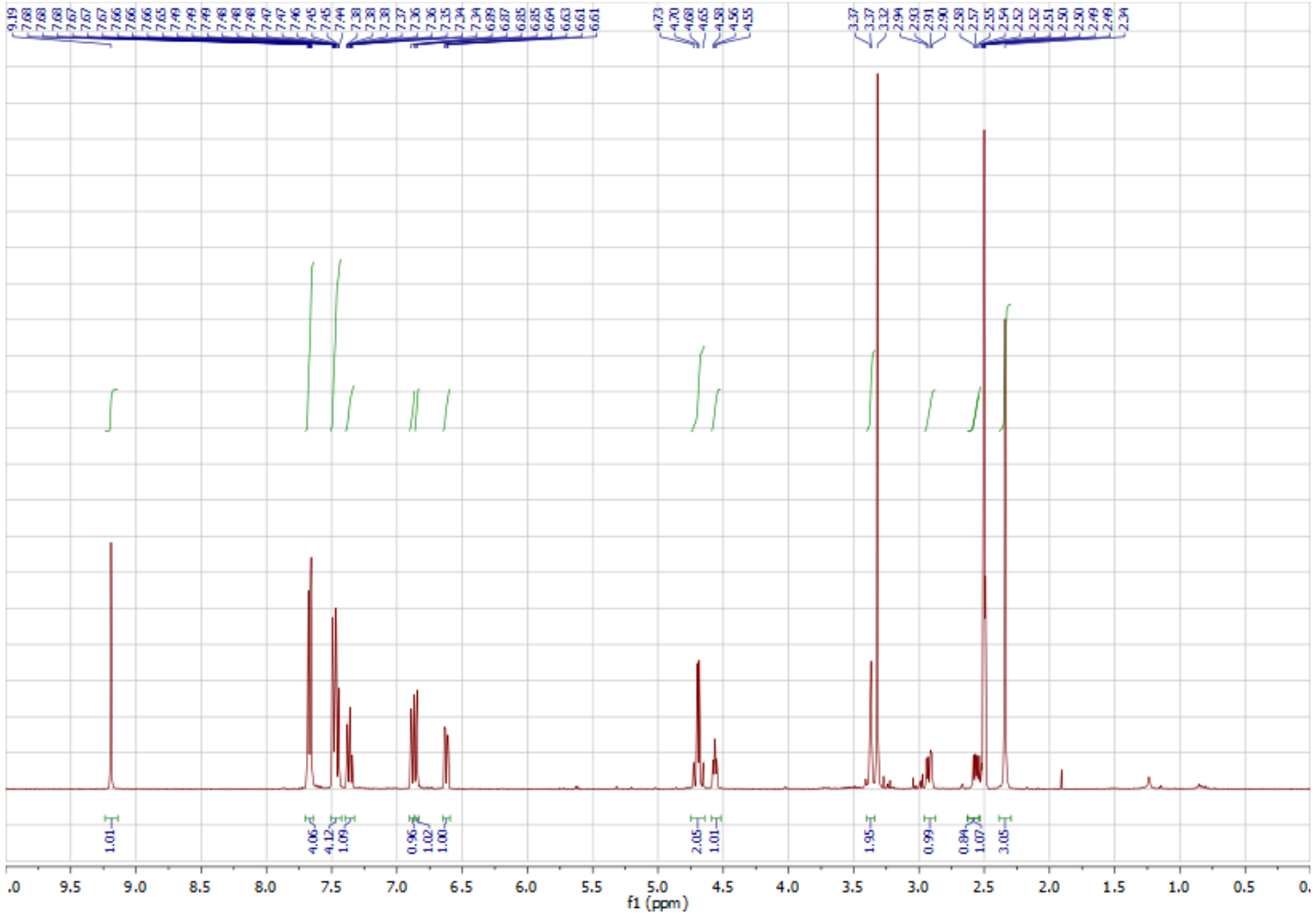


Figure A45 ^{1}H NMR spectra of **167** (DMSO-d_6).

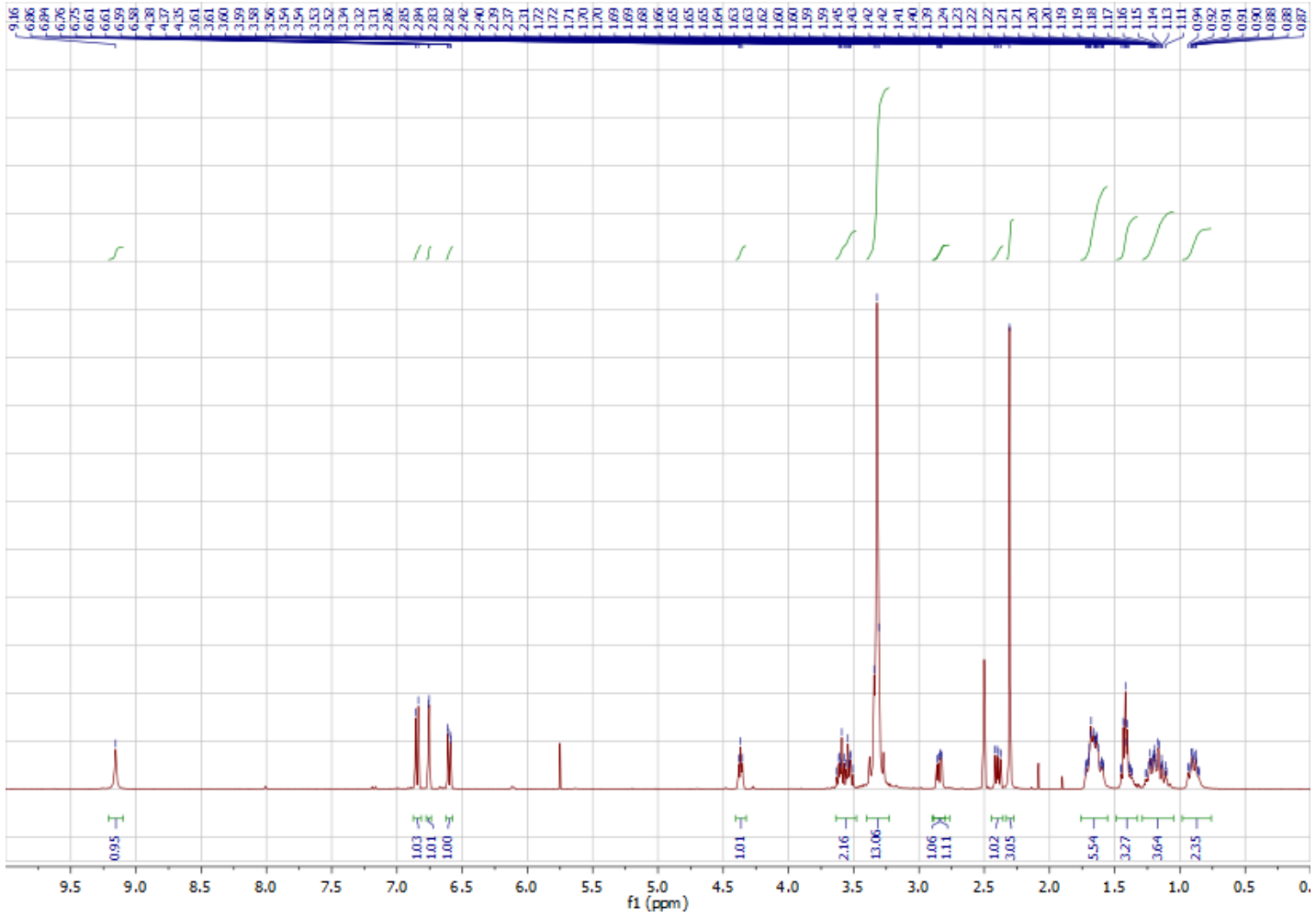


Figure A46 ^{1}H NMR spectra of **168** (DMSO-d_6).

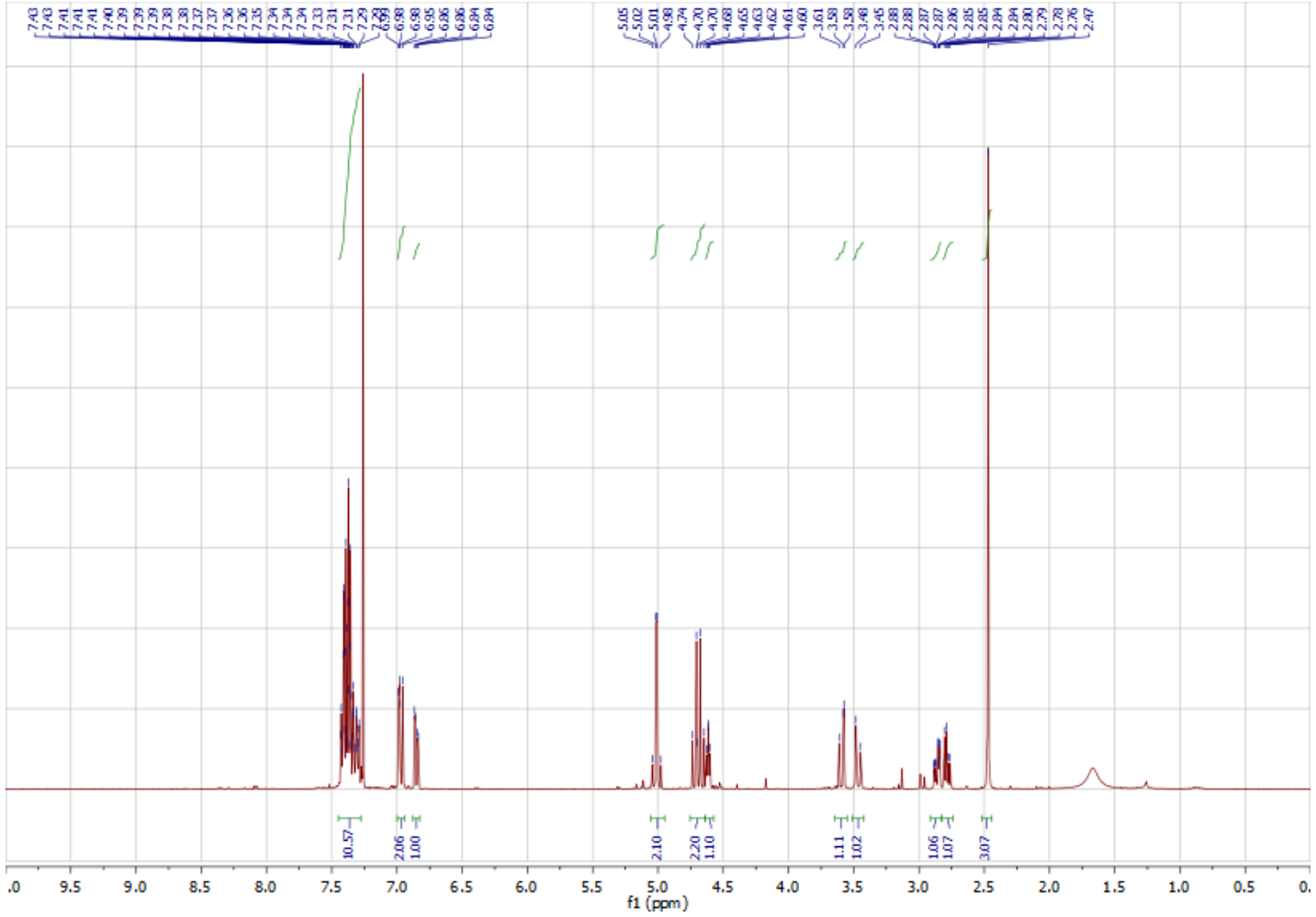


Figure A47 ^{1}H NMR spectra of **169** ($CDCl_3$).

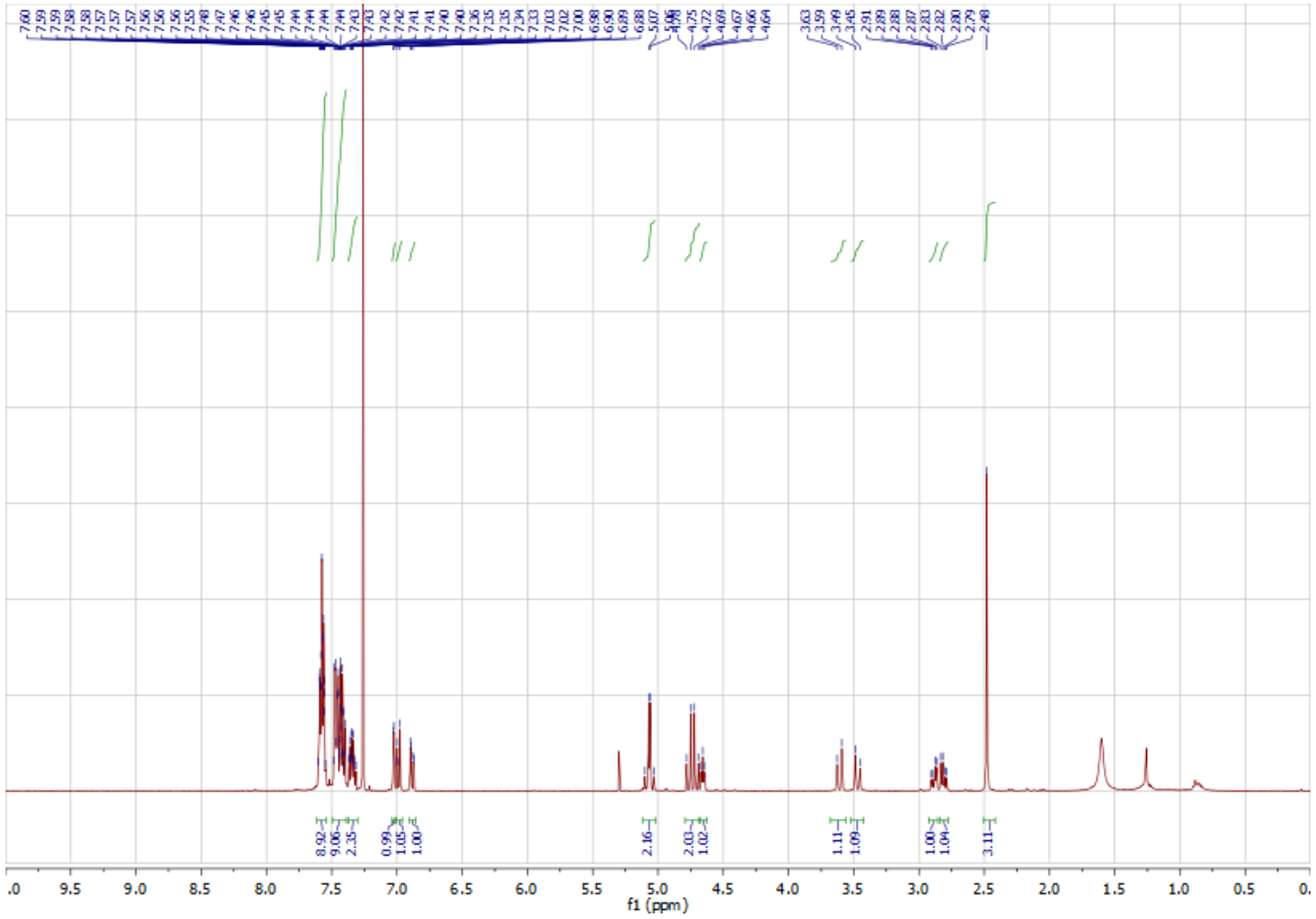


Figure A48 ^{1}H NMR spectra of **170** ($CDCl_3$).

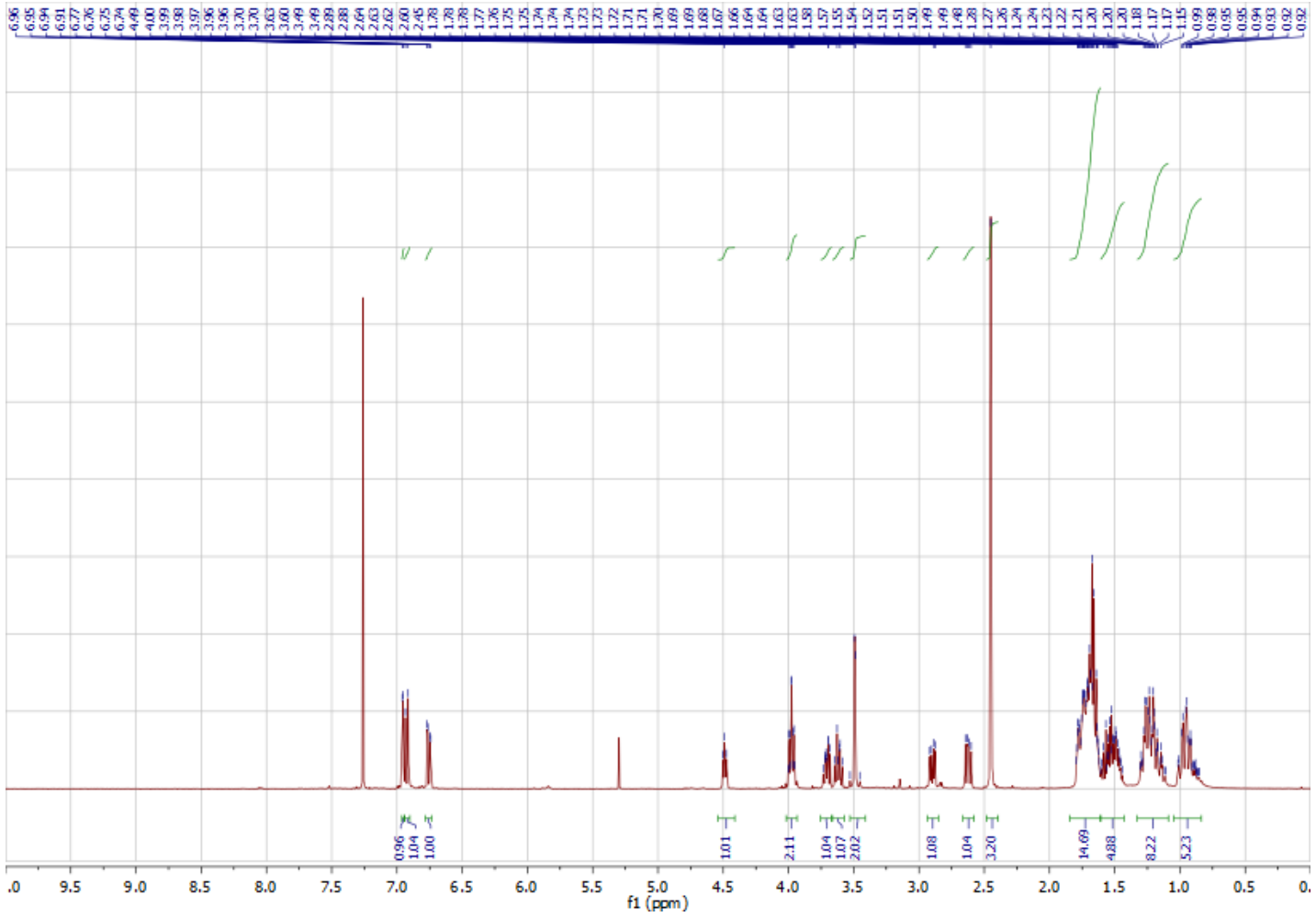


Figure A49 ^{1}H NMR spectra of **172** ($CDCl_3$).

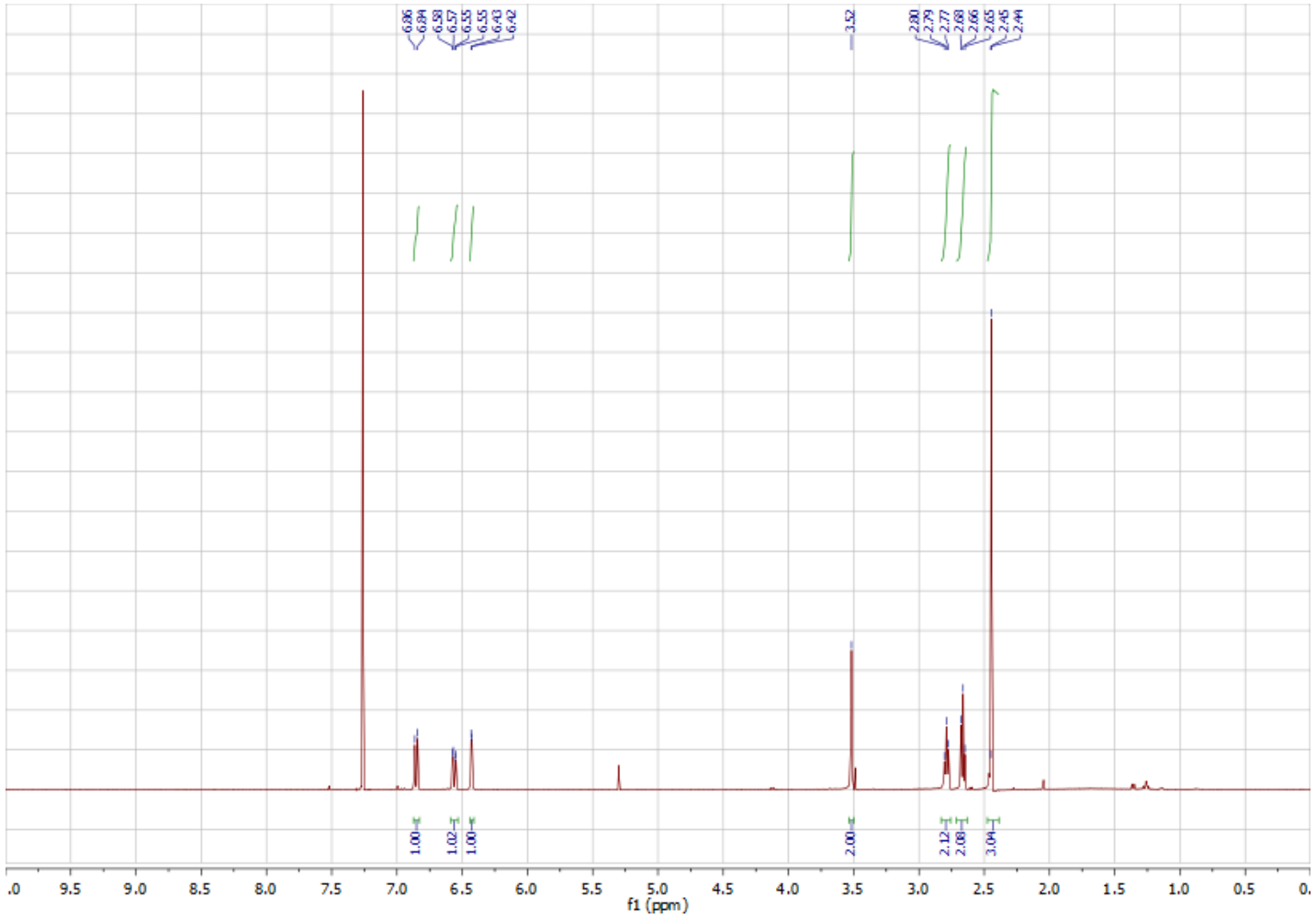


Figure A50 ^{1}H NMR spectra of **175** ($CDCl_3$).

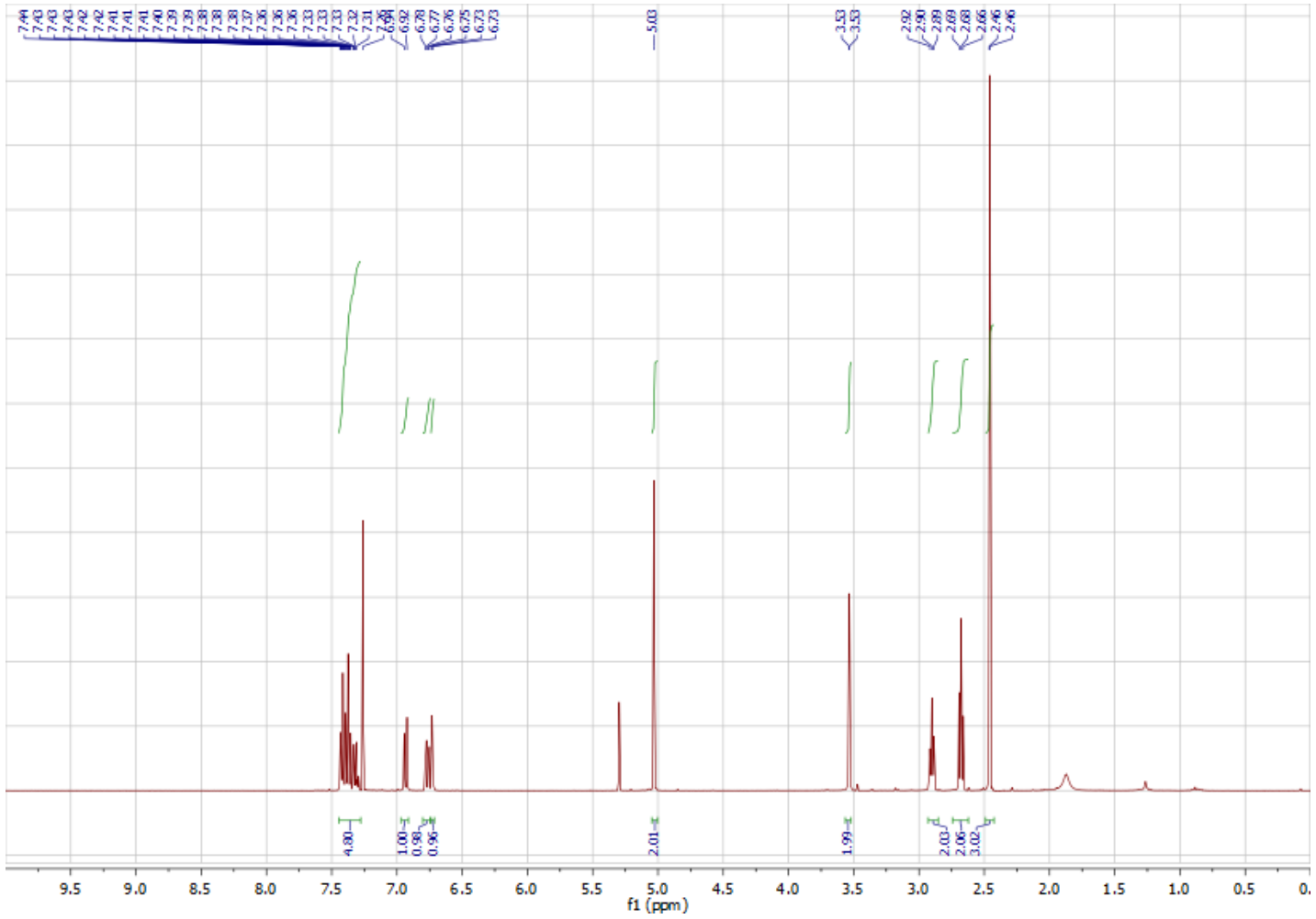


Figure A51 ^{1}H NMR spectra of **176** ($CDCl_3$).

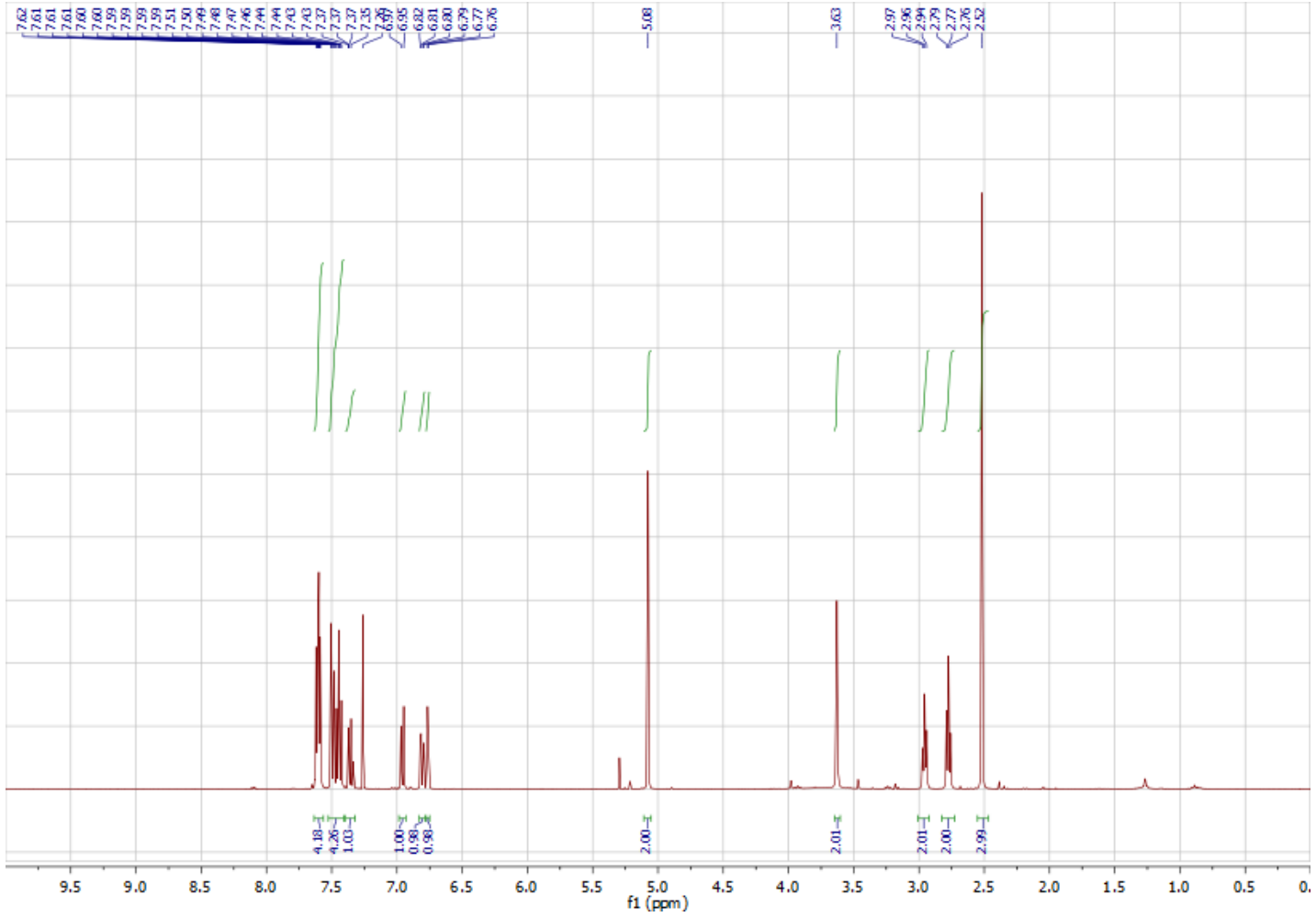


Figure A52 ^{1}H NMR spectra of **177** ($CDCl_3$).

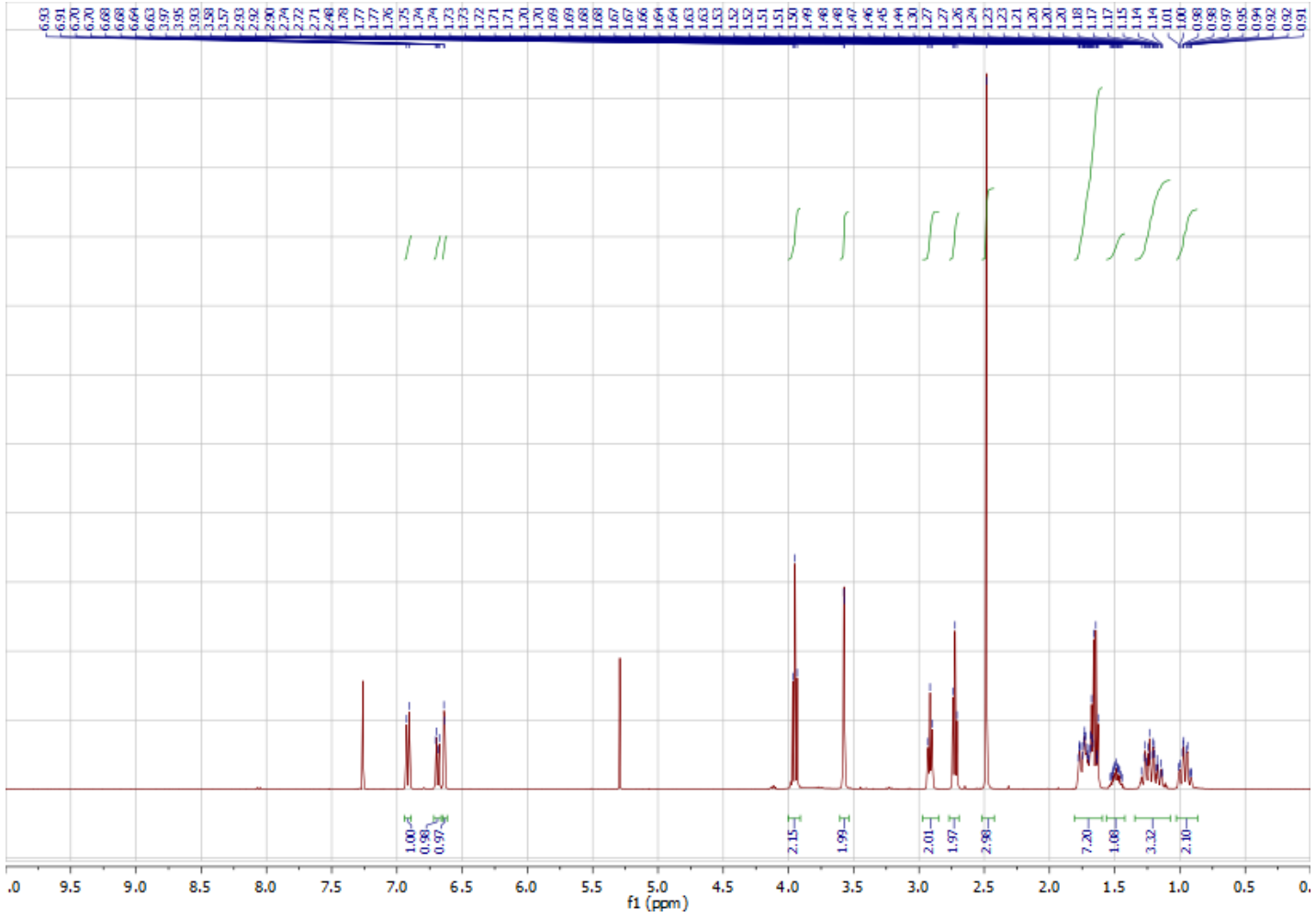


Figure A53 ^{1}H NMR spectra of **178** ($CDCl_3$).

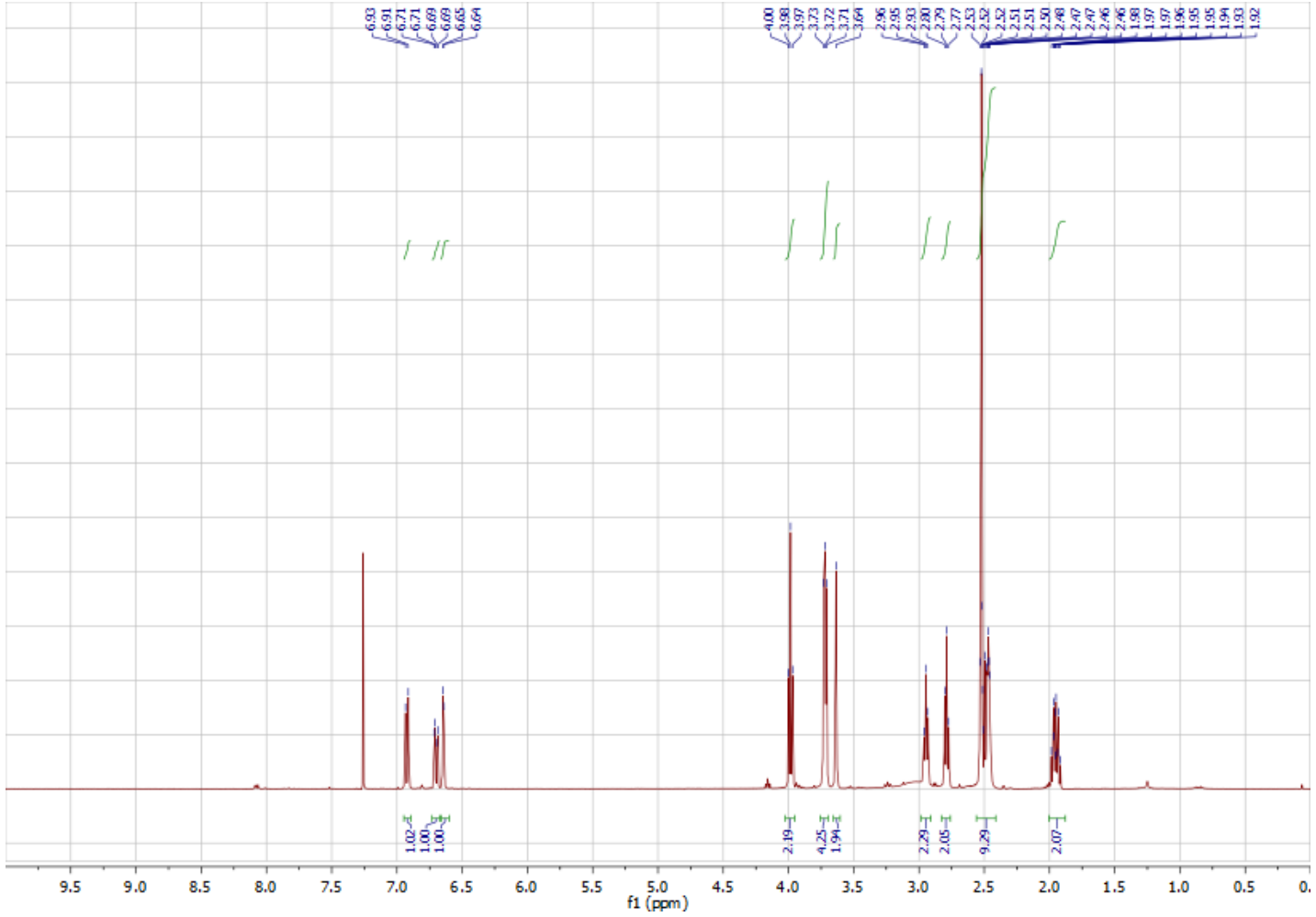


Figure A54 ^{1}H NMR spectra of **179** ($CDCl_3$).

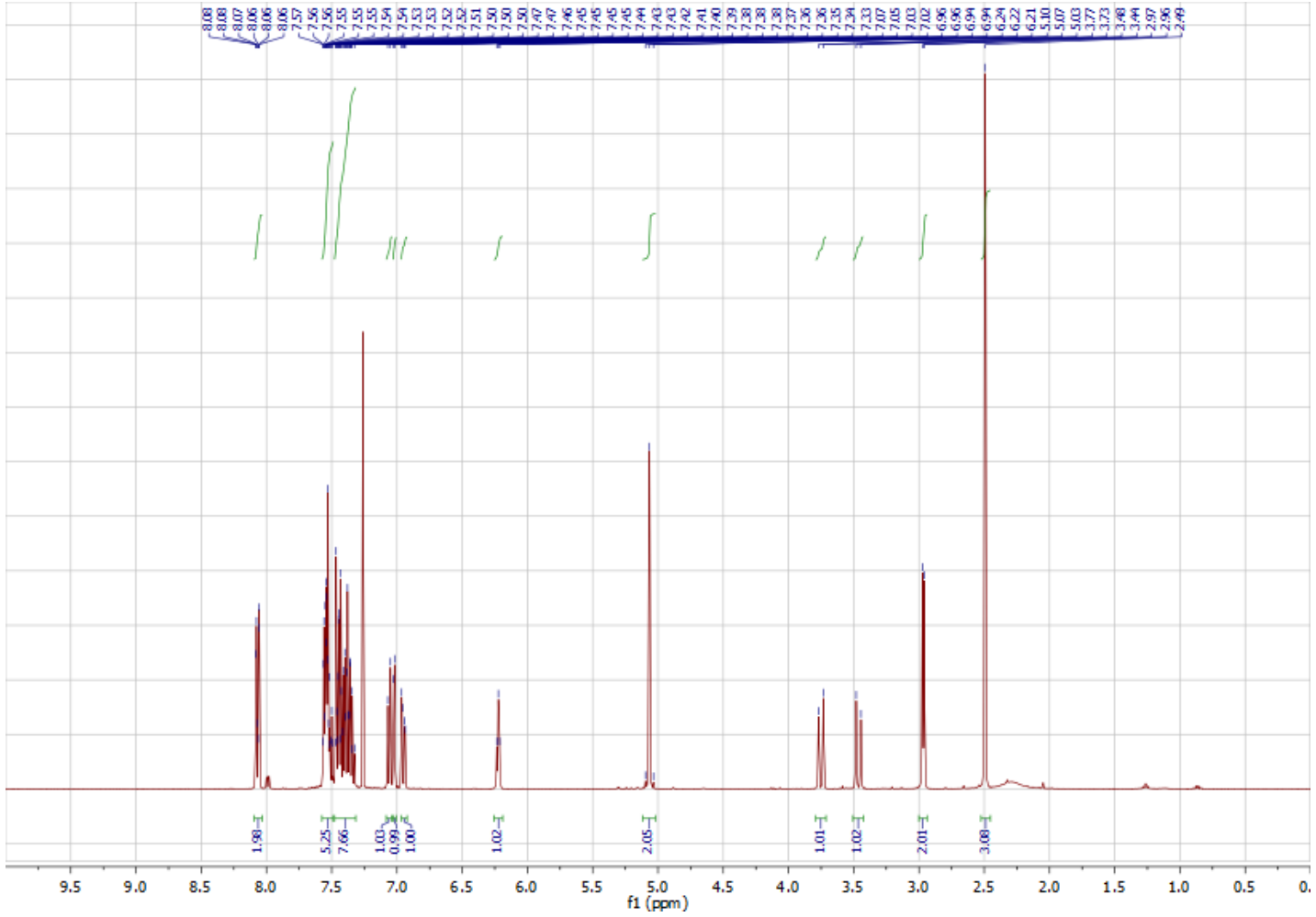


Figure A55 ^{1}H NMR spectra of **180** ($CDCl_3$).

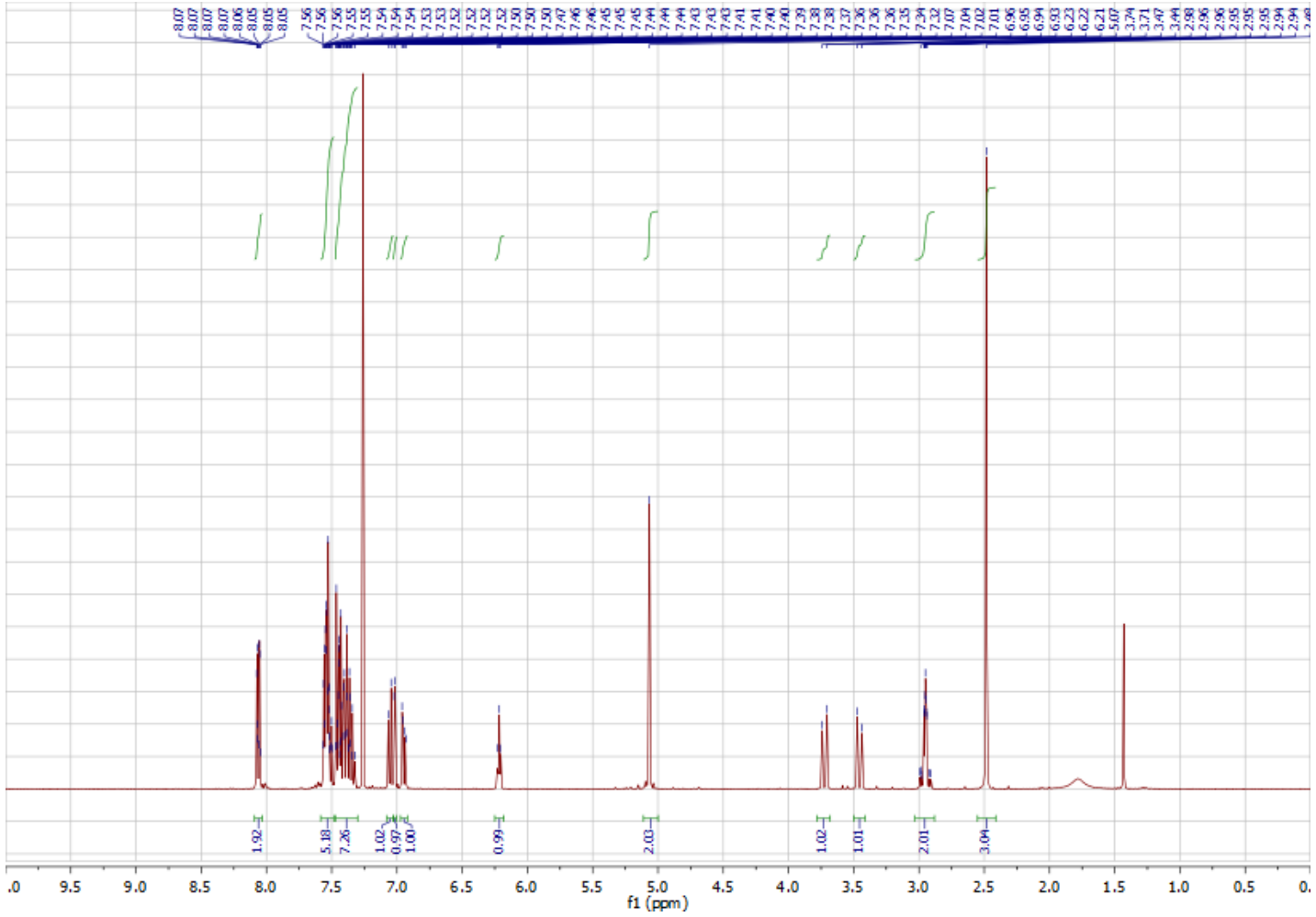


Figure A56 ^{1}H NMR spectra of **181** ($CDCl_3$).

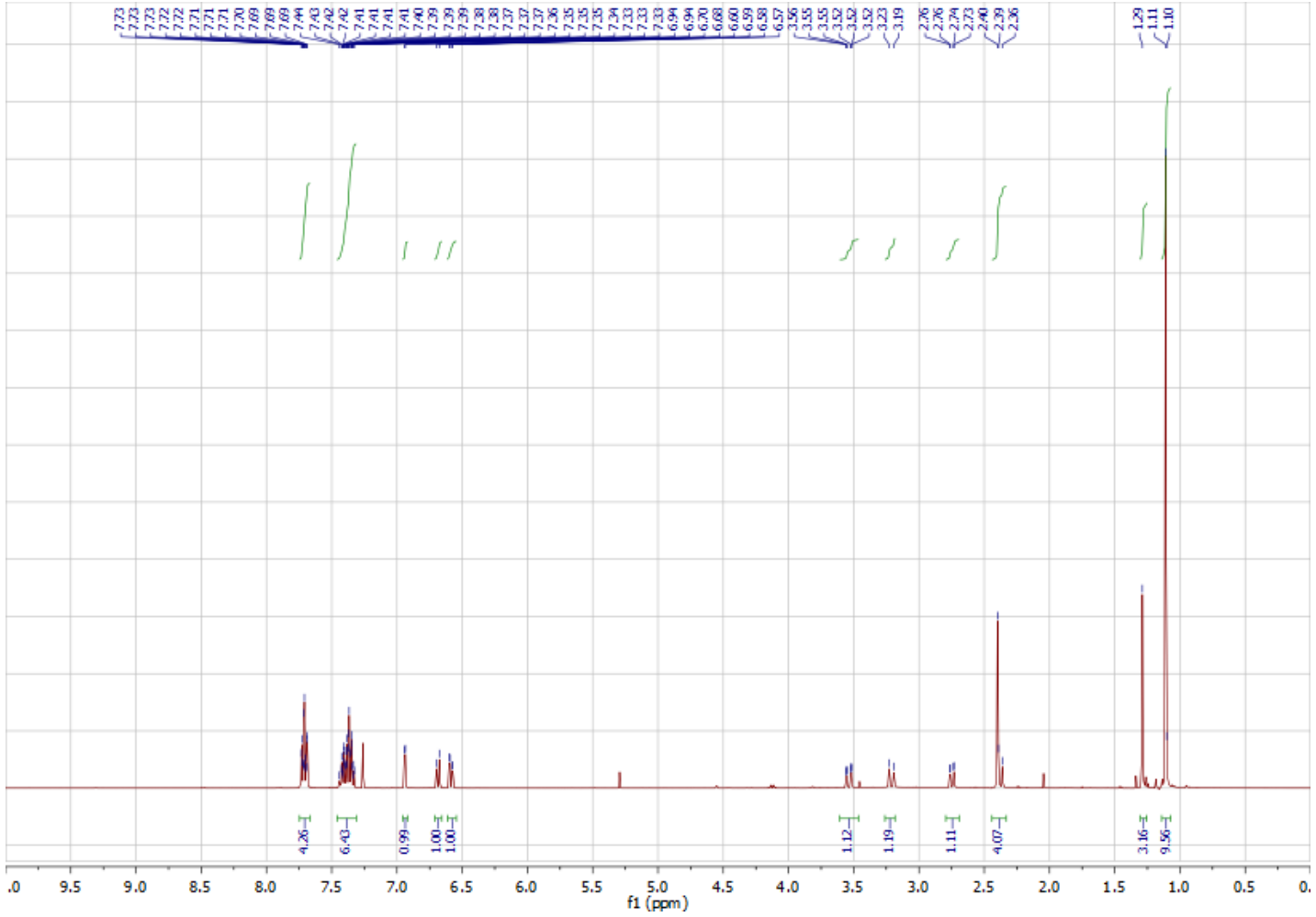


Figure A57 ^{1}H NMR spectra of **188** ($CDCl_3$).

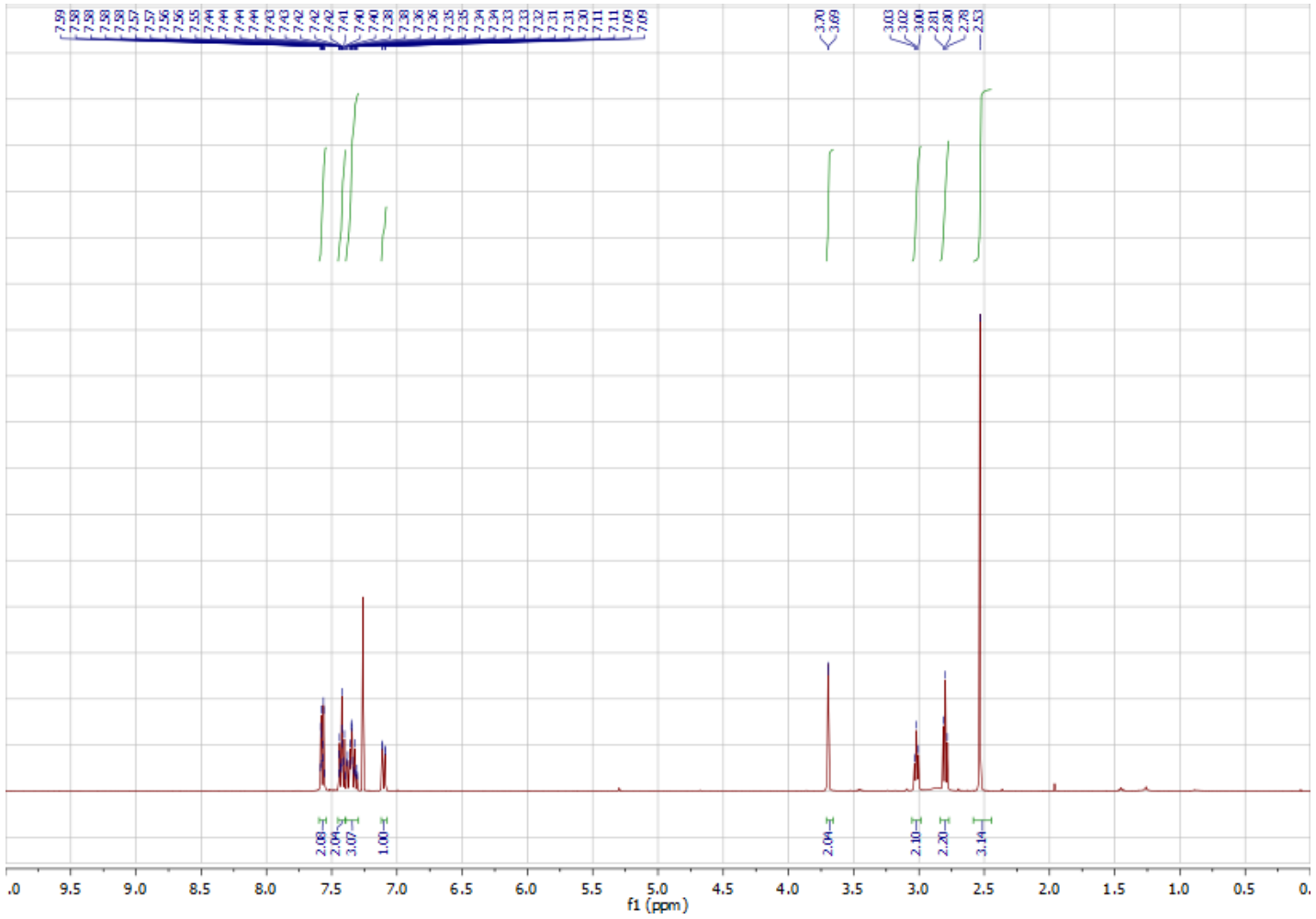


Figure A58 ^{1}H NMR spectra of **190** ($CDCl_3$).

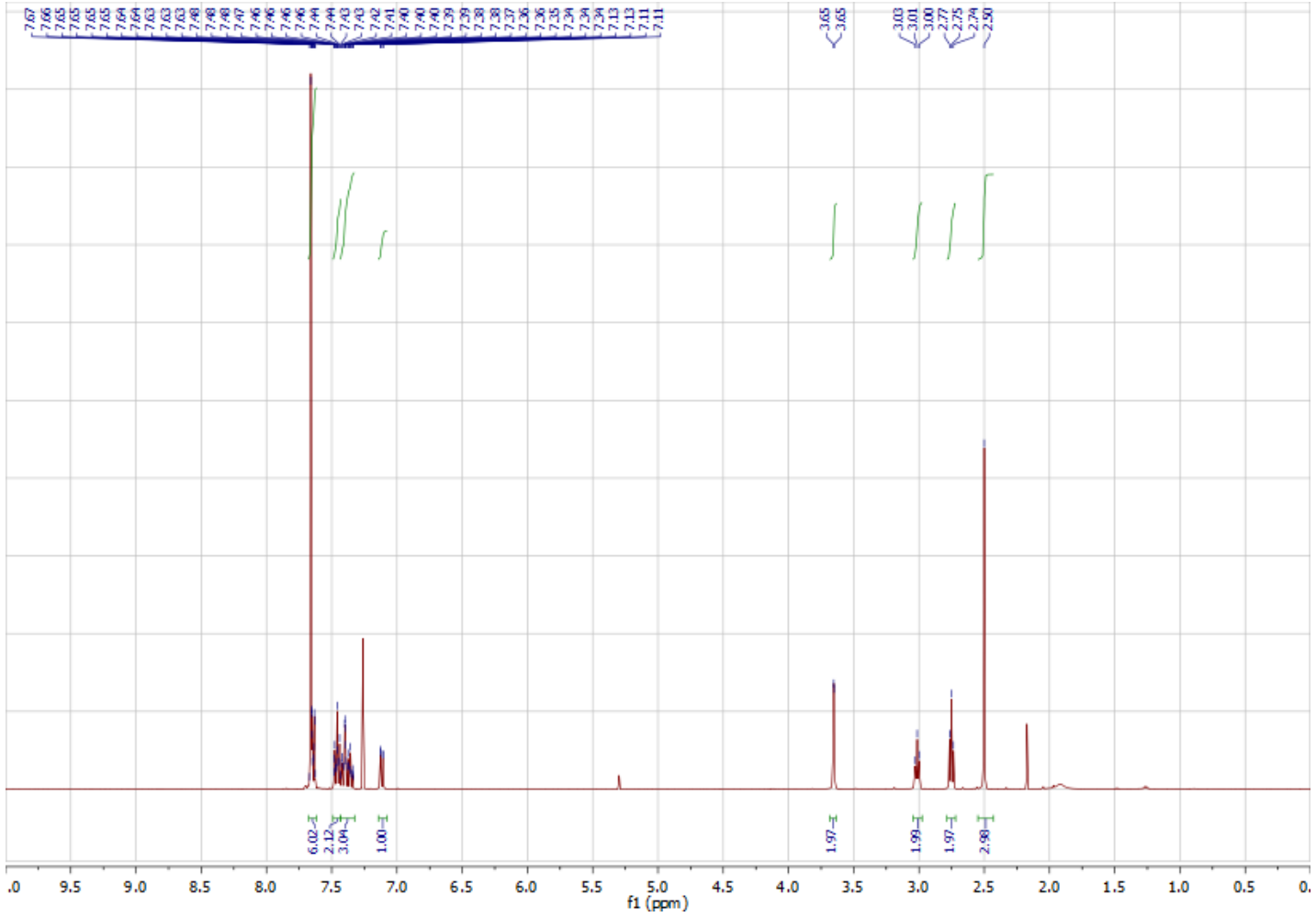


Figure A59 ^{1}H NMR spectra of **191** ($CDCl_3$).

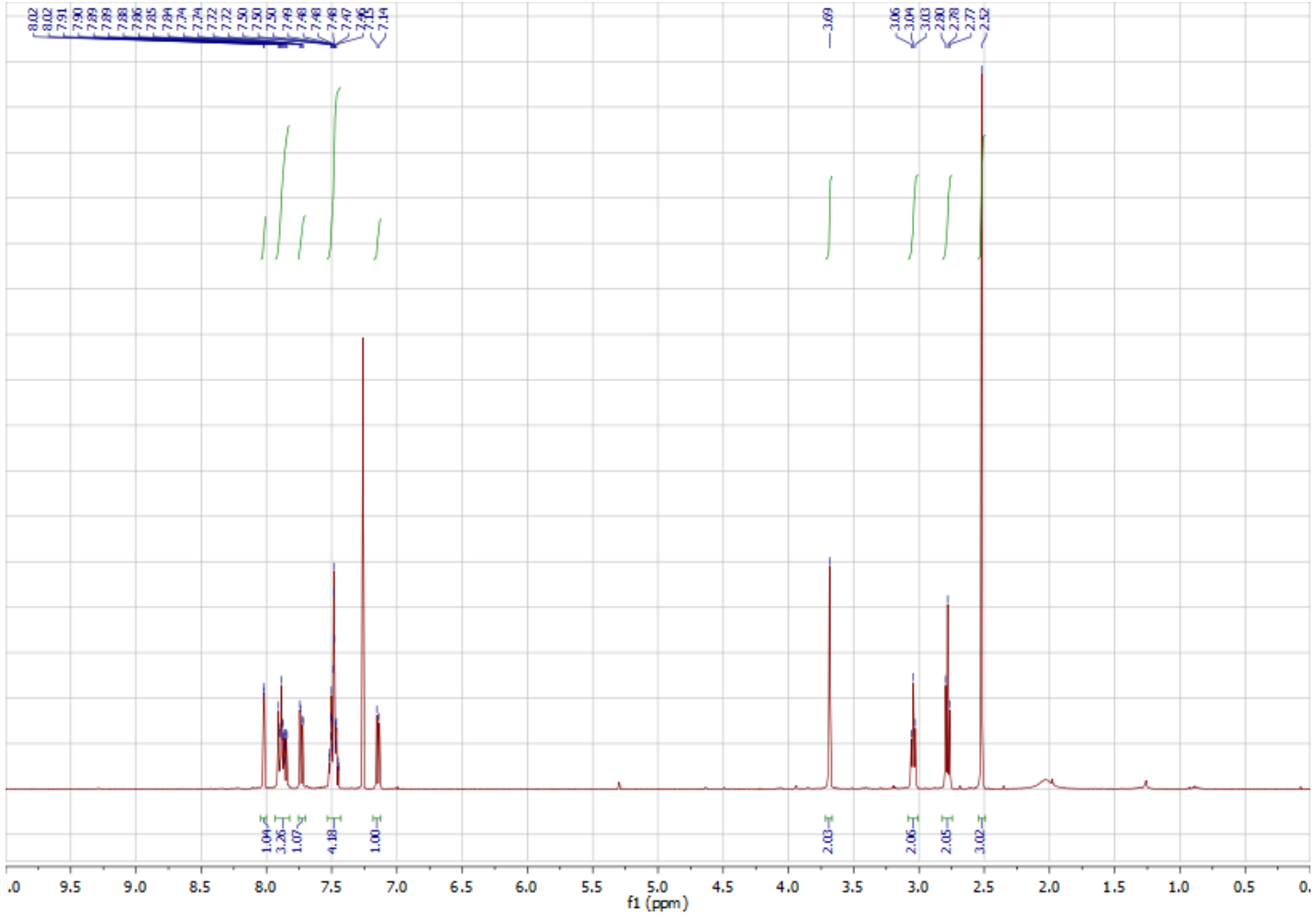


Figure A60 ^{1}H NMR spectra of **192** ($CDCl_3$).

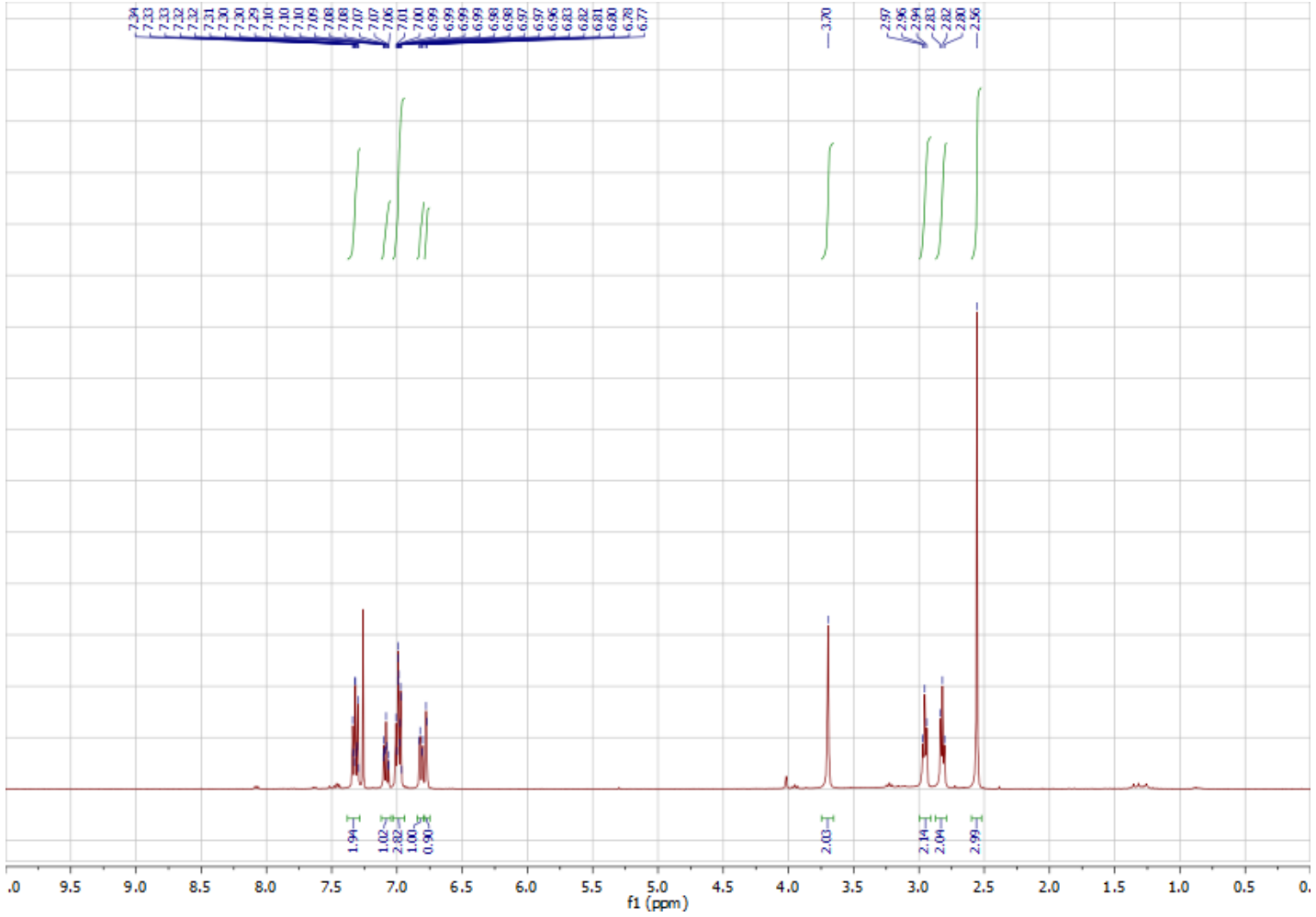


Figure A61 ^{1}H NMR spectra of **195** ($CDCl_3$).

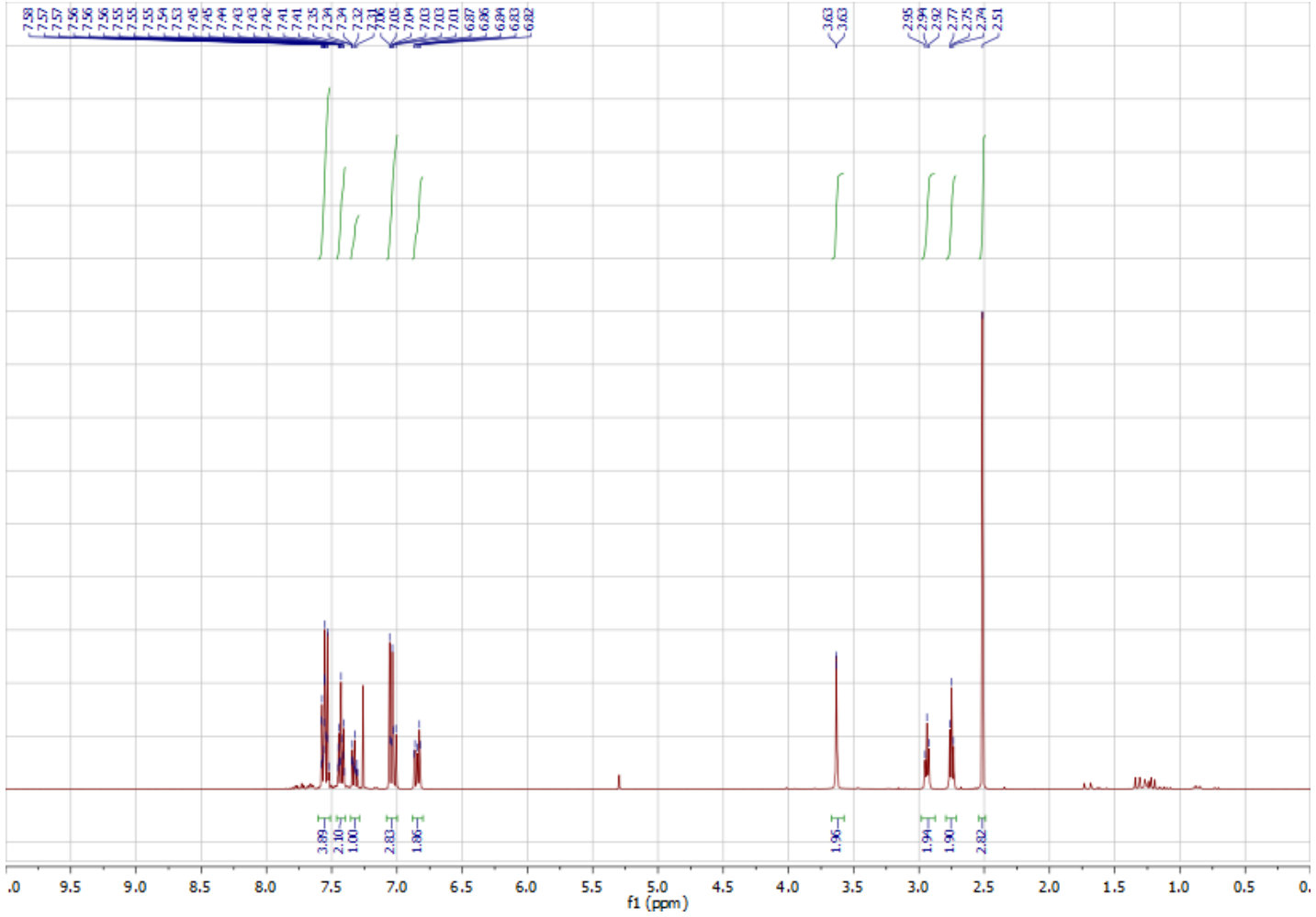


Figure A62 ^{1}H NMR spectra of **197** ($CDCl_3$).

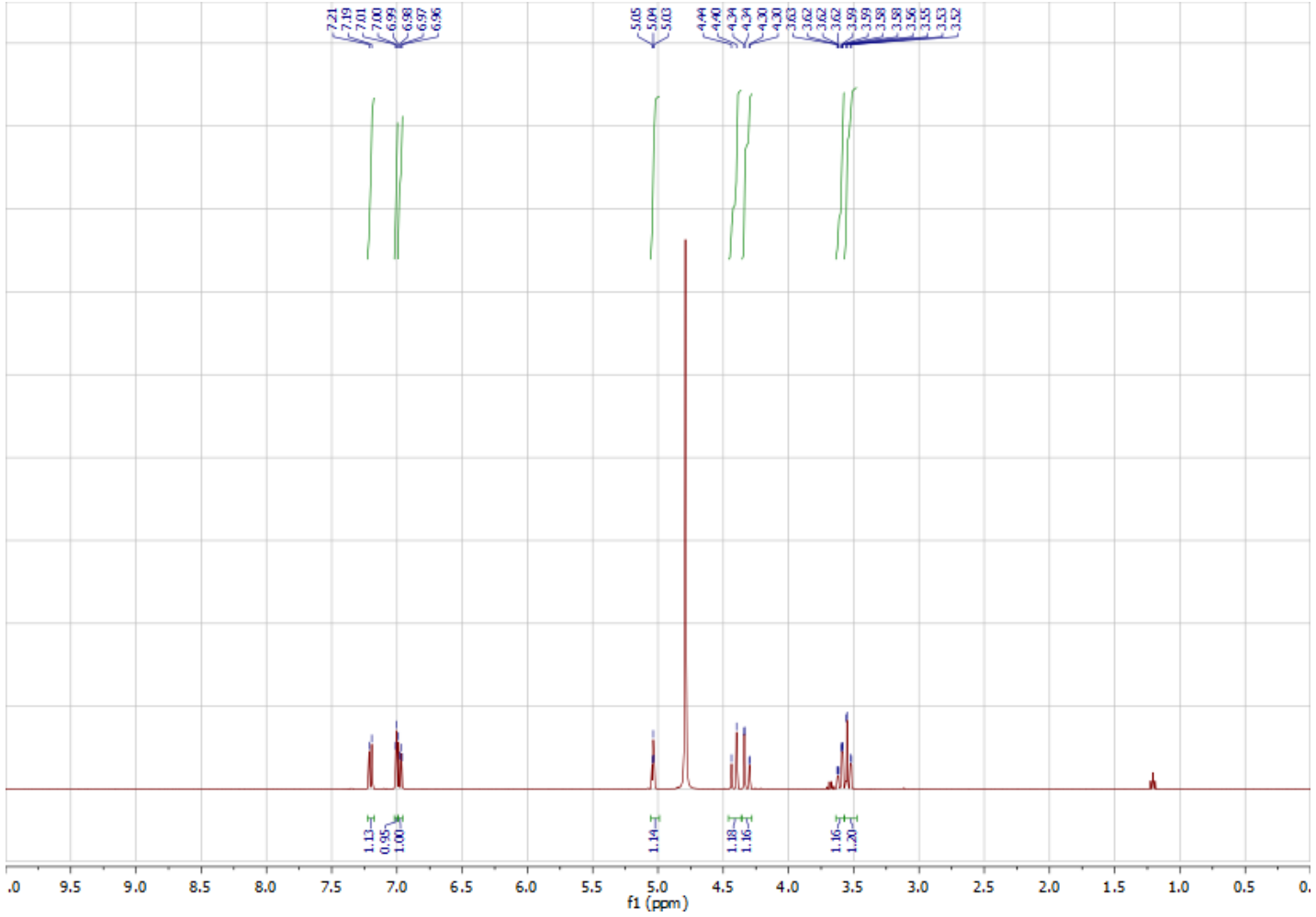


Figure A63 ^{1}H NMR spectra of **200** (D_2O).

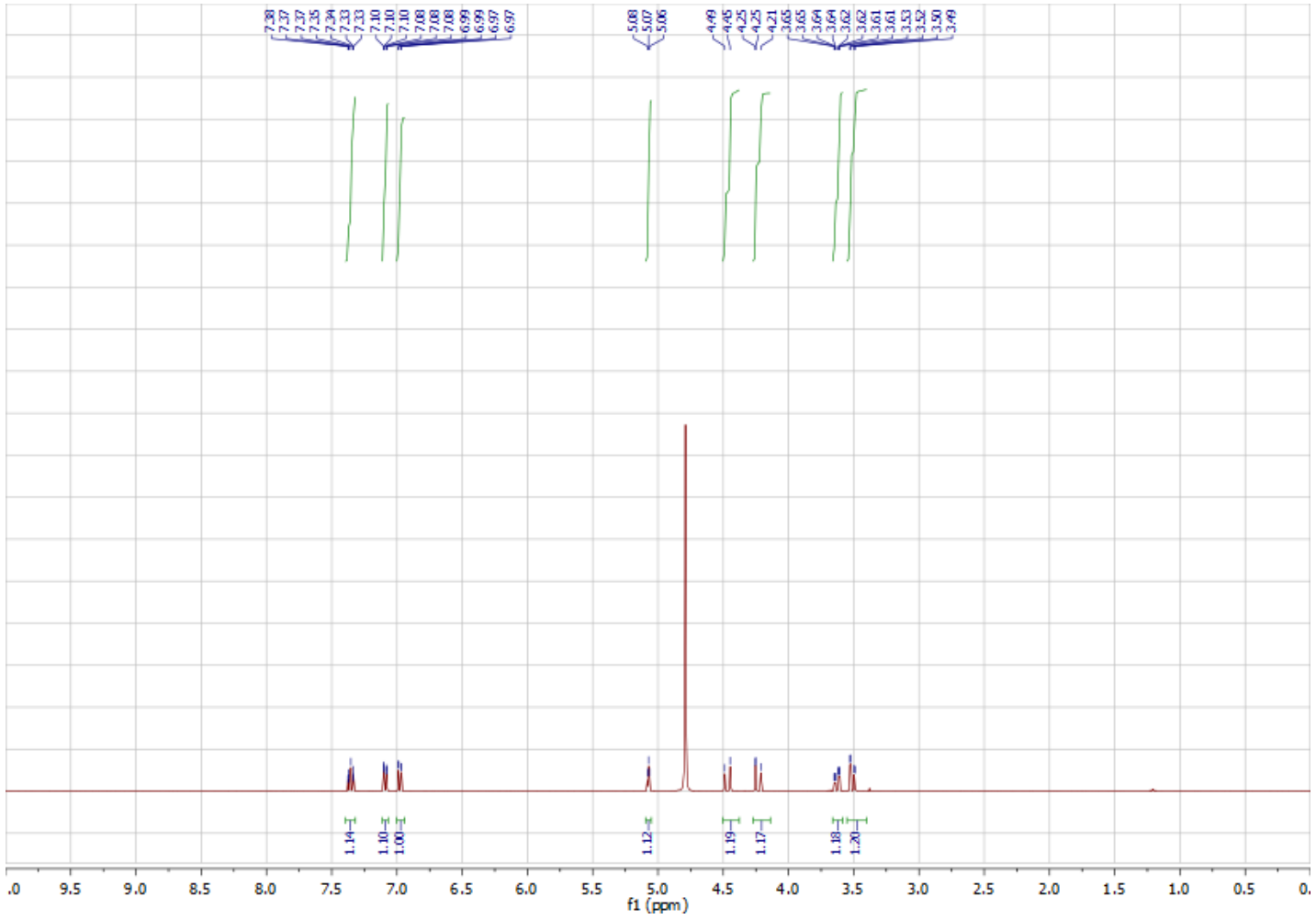


Figure A64 ^{1}H NMR spectra of **201** (D_2O).

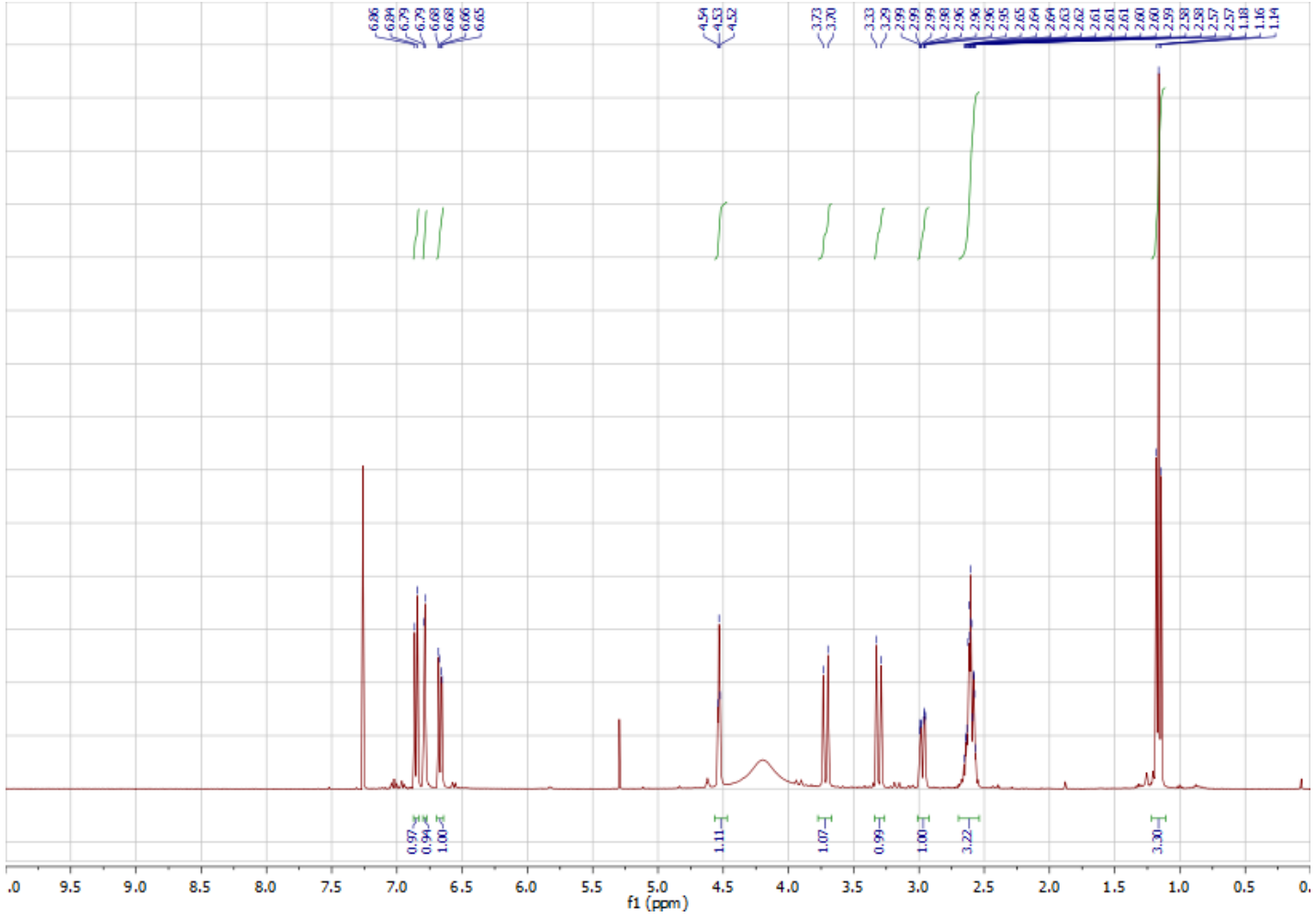


Figure A65 ^{1}H NMR spectra of **202** ($CDCl_3$).

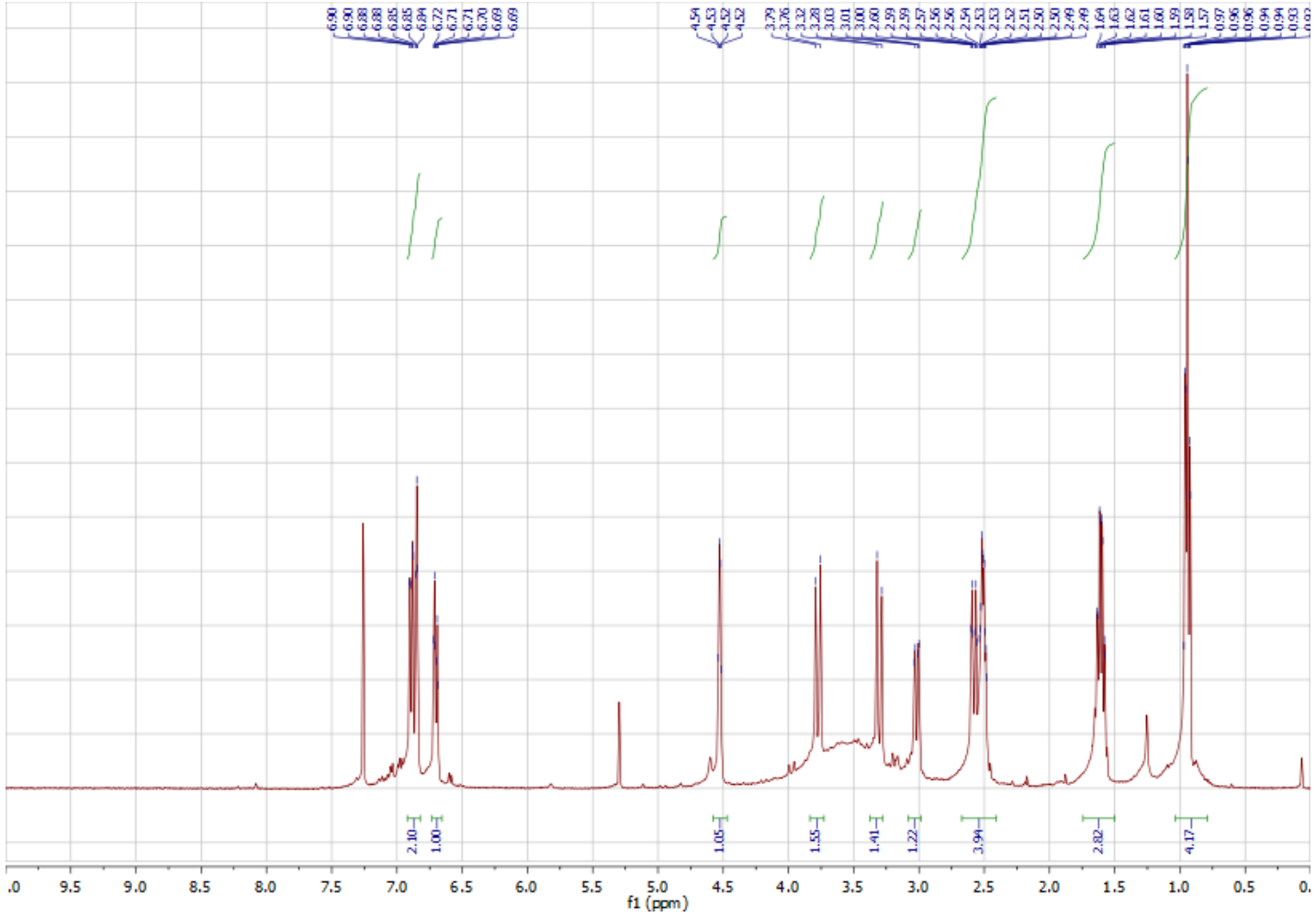


Figure A66 ^{1}H NMR spectra of **203** ($CDCl_3$).

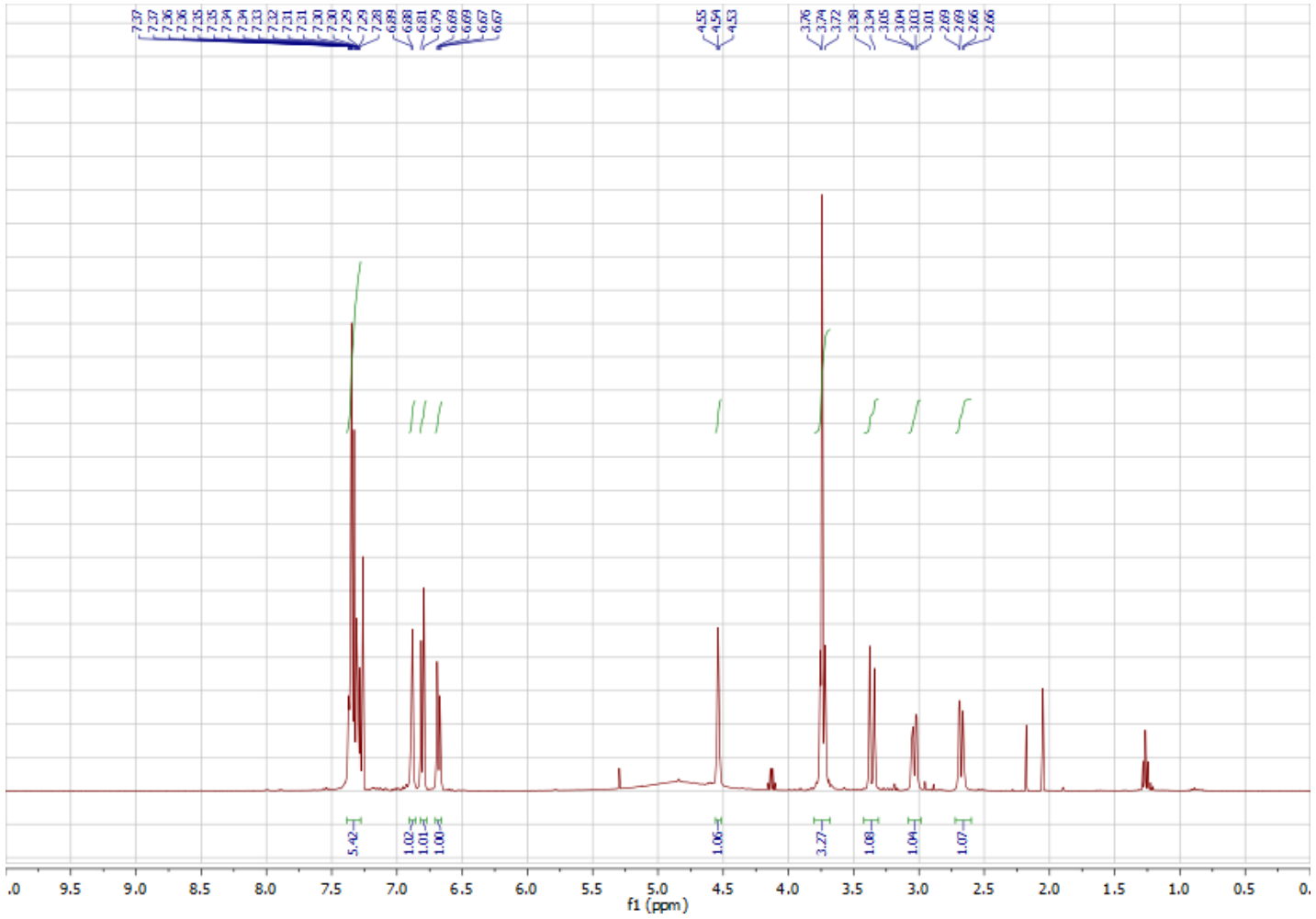


Figure A67 ^{1}H NMR spectra of **204** ($CDCl_3$).

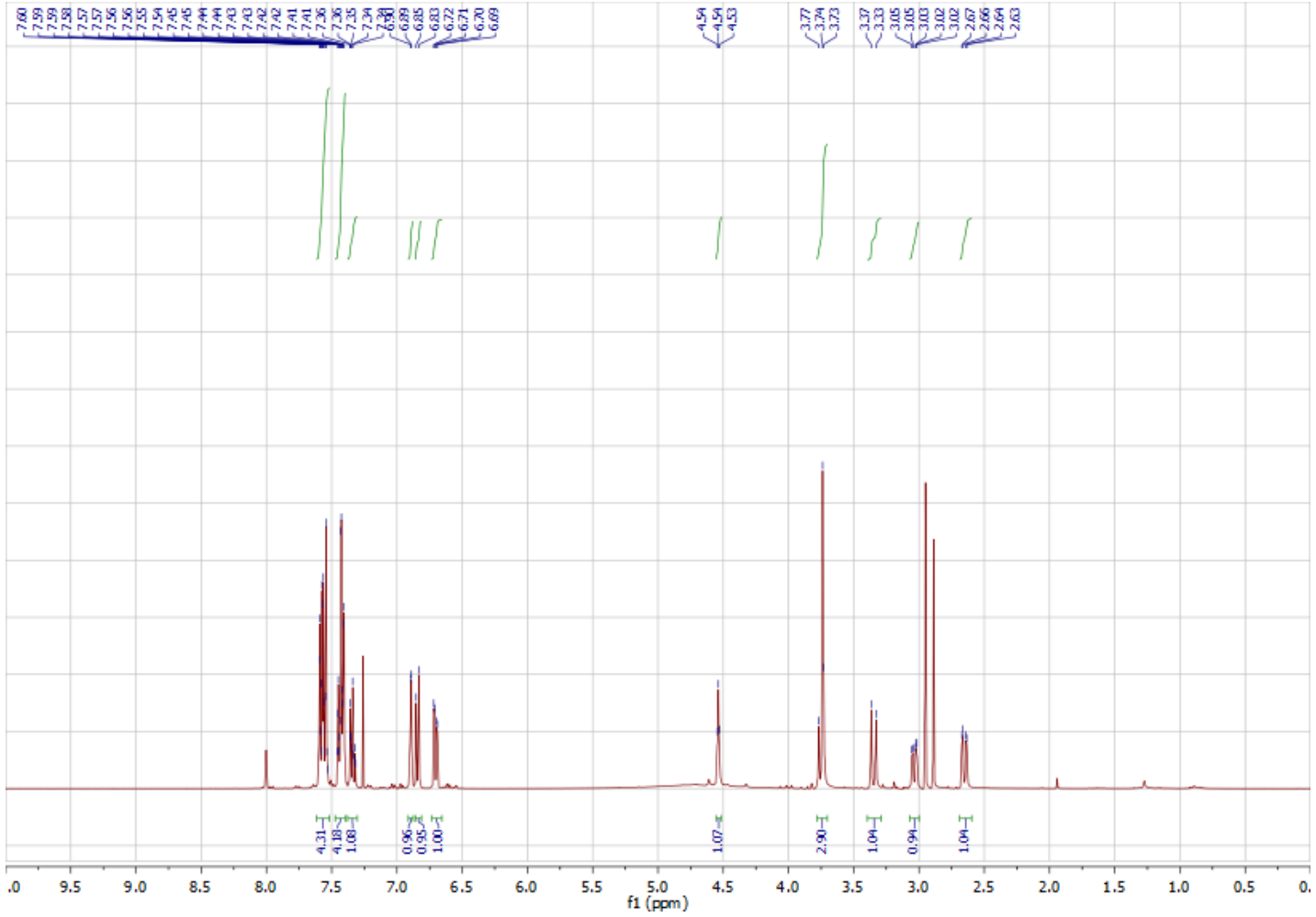


Figure A68 ^{1}H NMR spectra of **205** ($CDCl_3$).

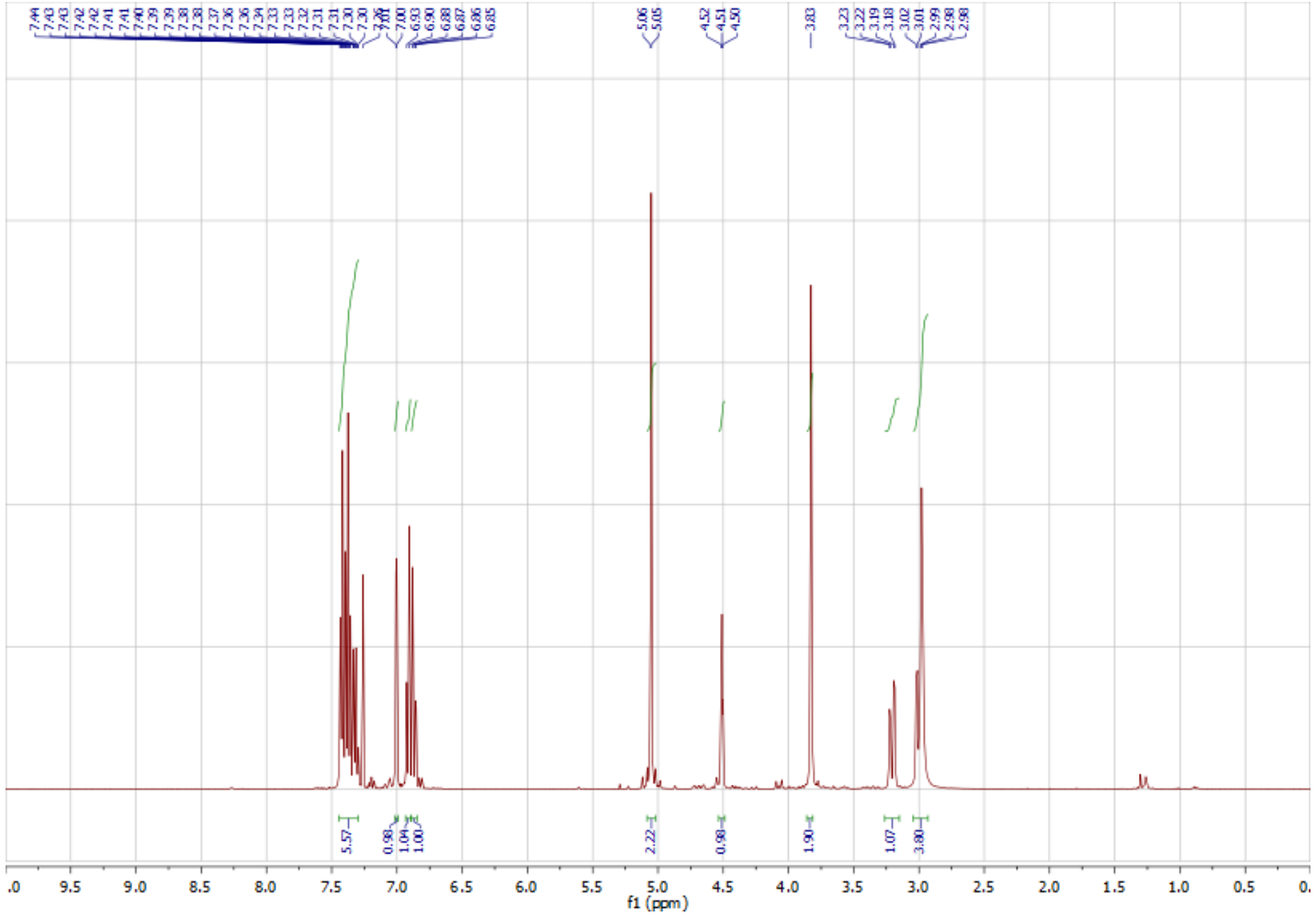


Figure A69 ^{1}H NMR spectra of **210** ($CDCl_3$).

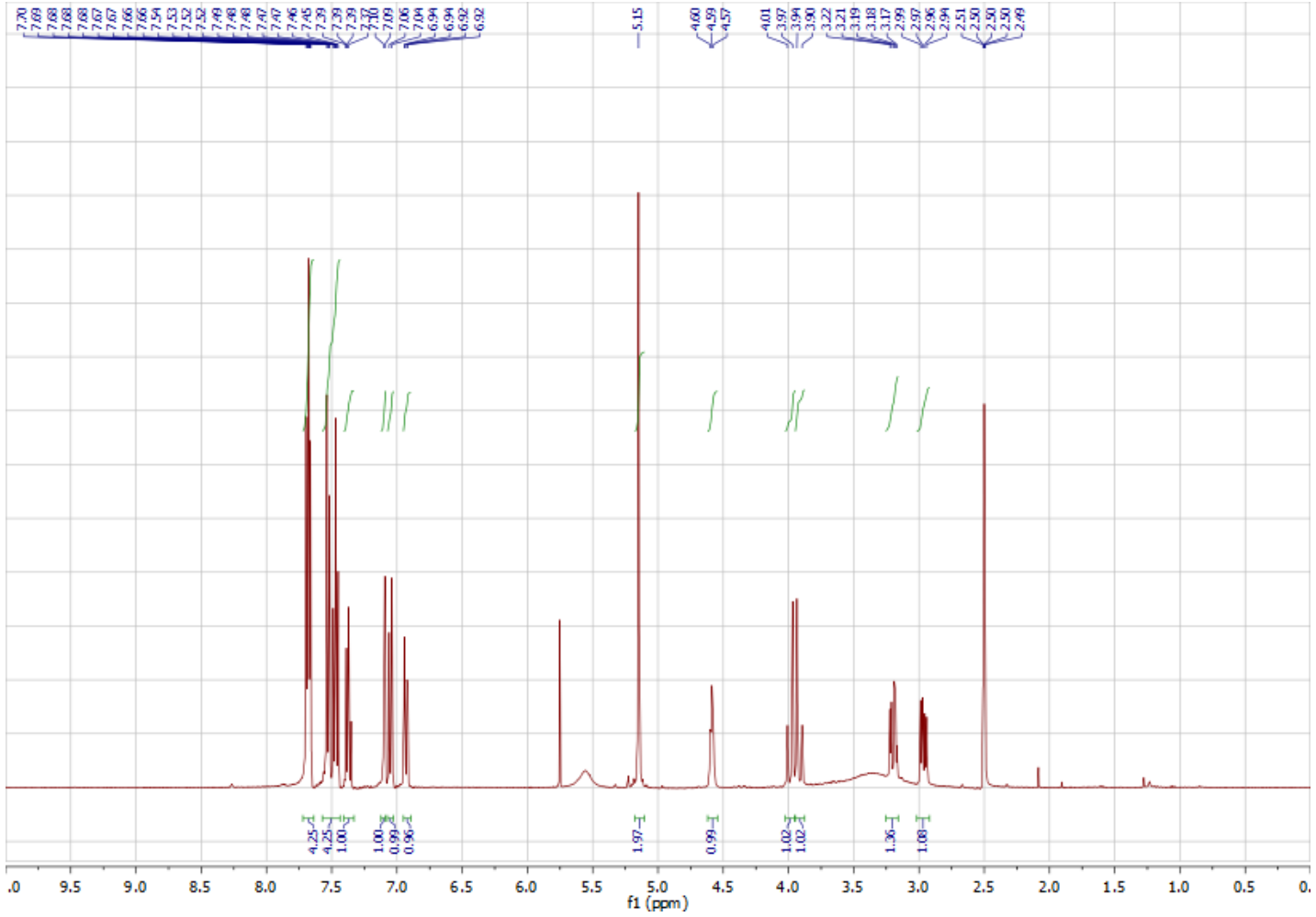


Figure A70 ^{1}H NMR spectra of **211** (DMSO-d_6).

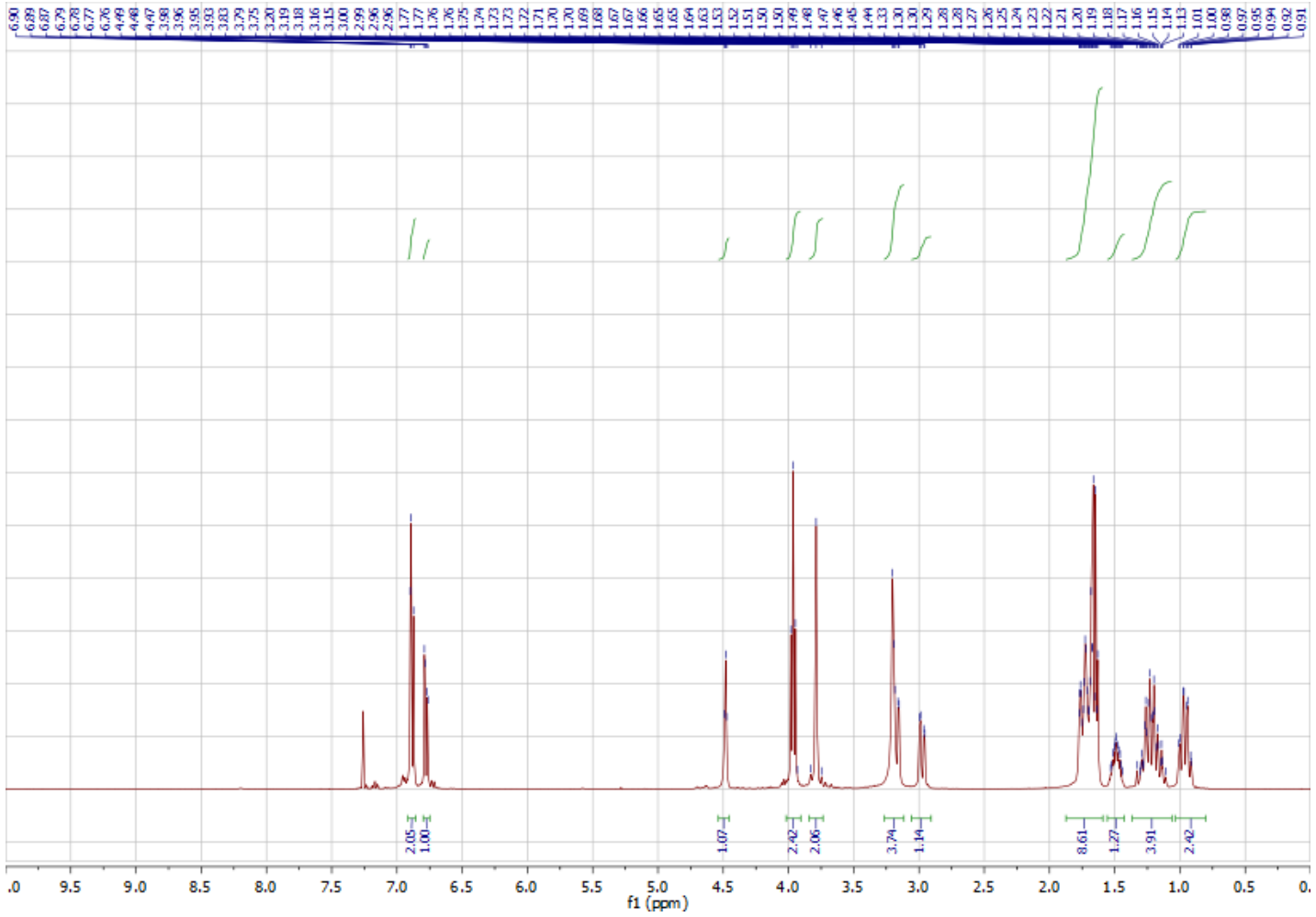


Figure A71 ^{1}H NMR spectra of **212** ($CDCl_3$).

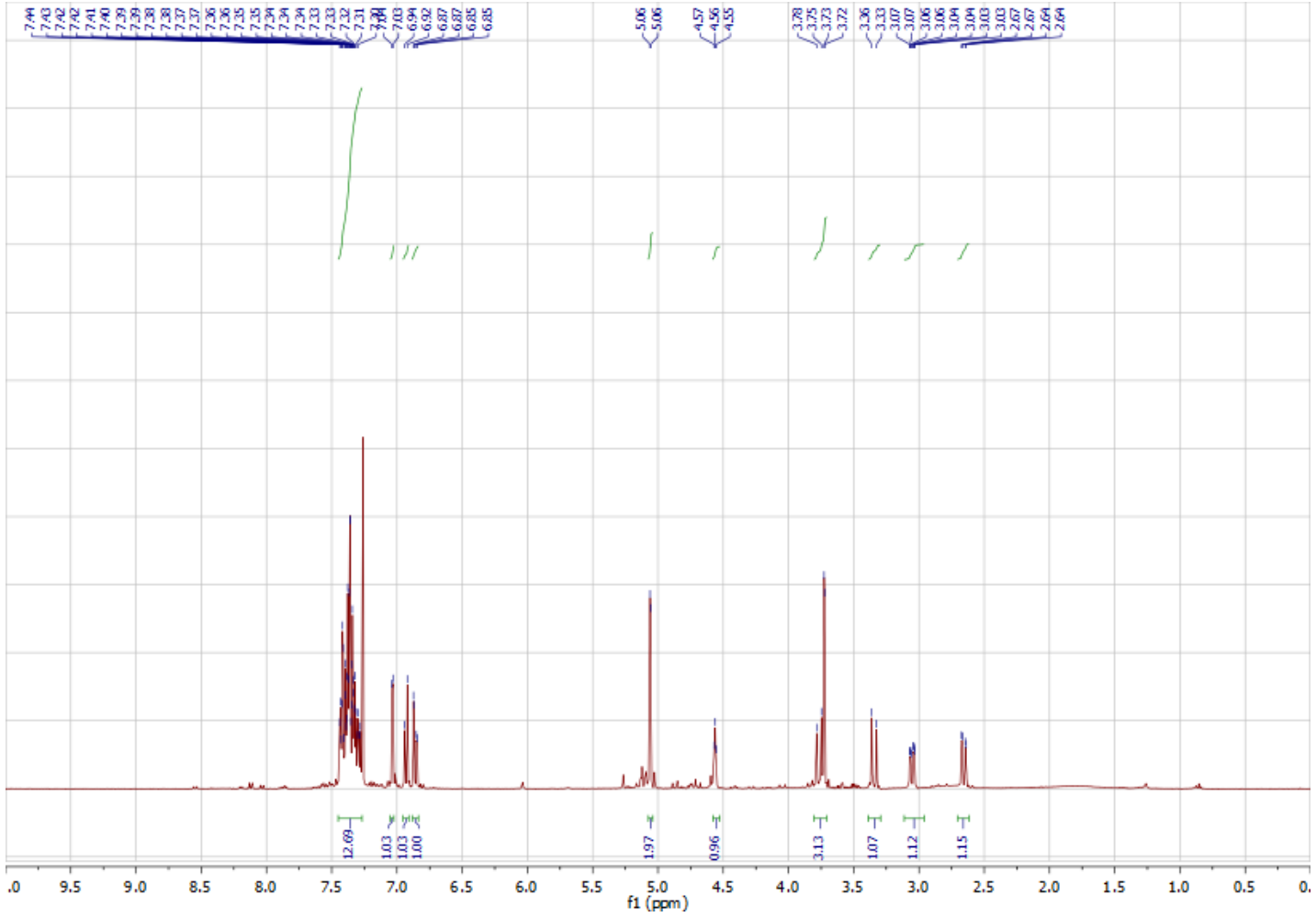


Figure A72 ^{1}H NMR spectra of **213** ($CDCl_3$).

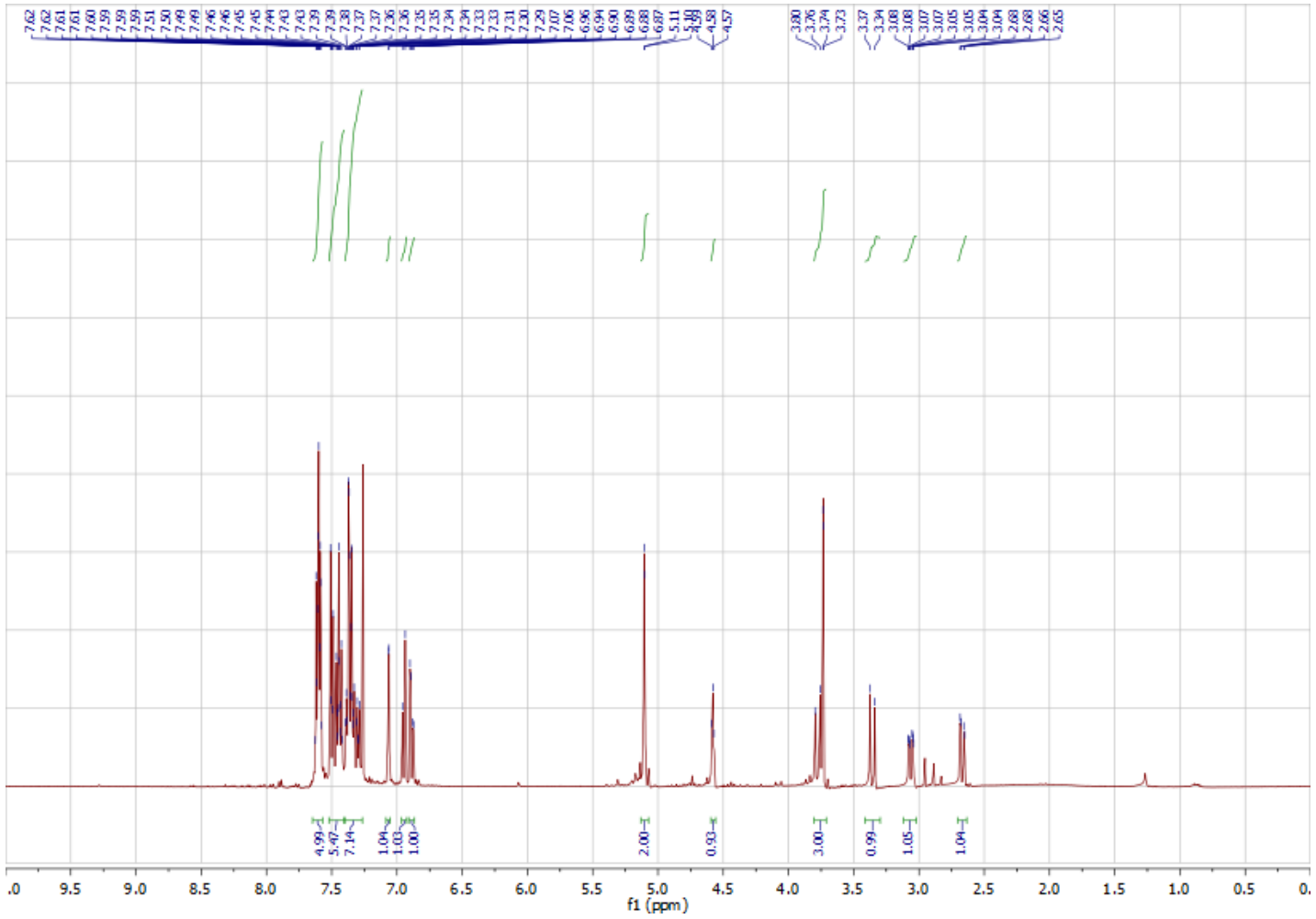


Figure A73 ^{1}H NMR spectra of **214** ($CDCl_3$).

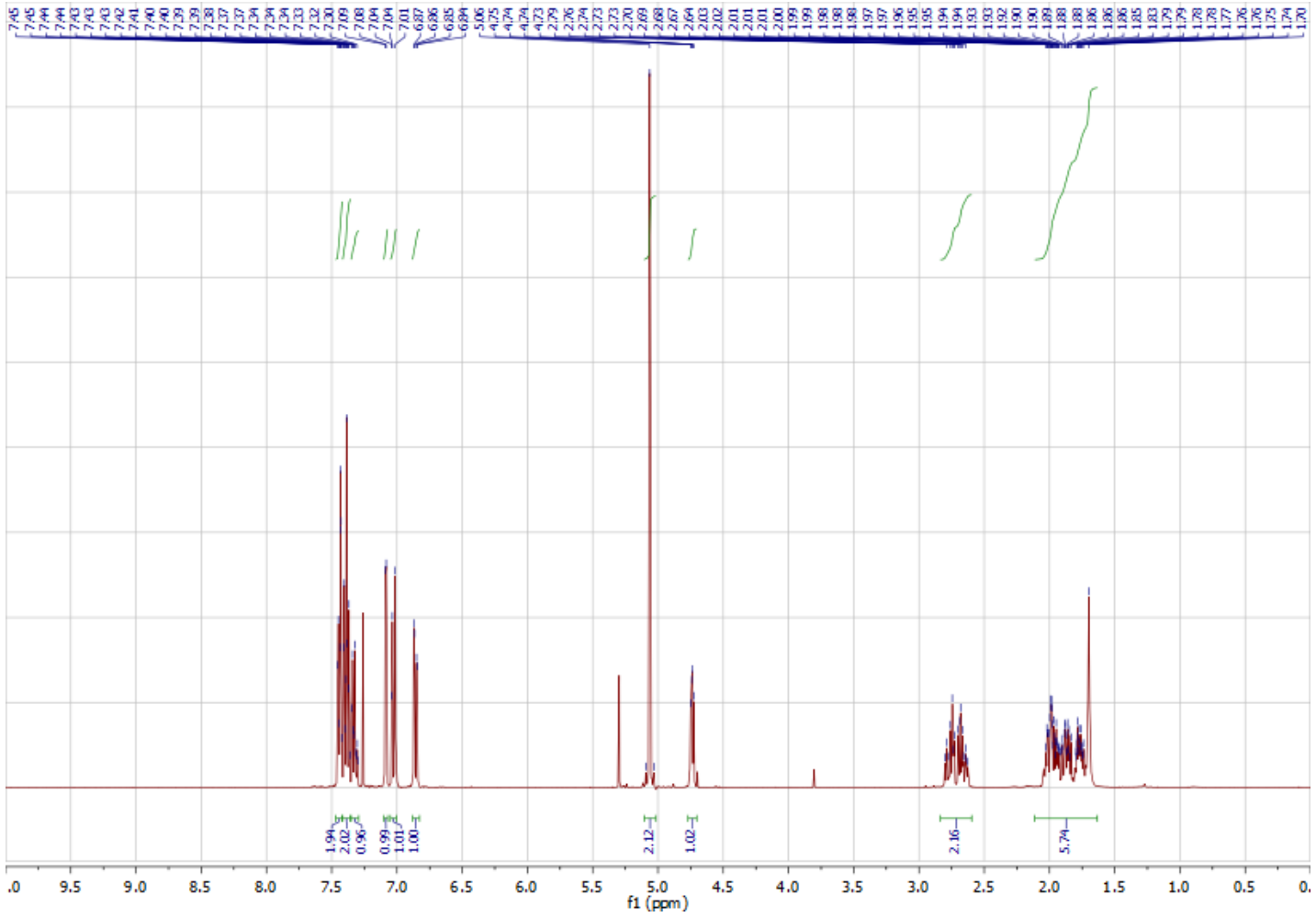


Figure A74 ^{1}H NMR spectra of **218** ($CDCl_3$).

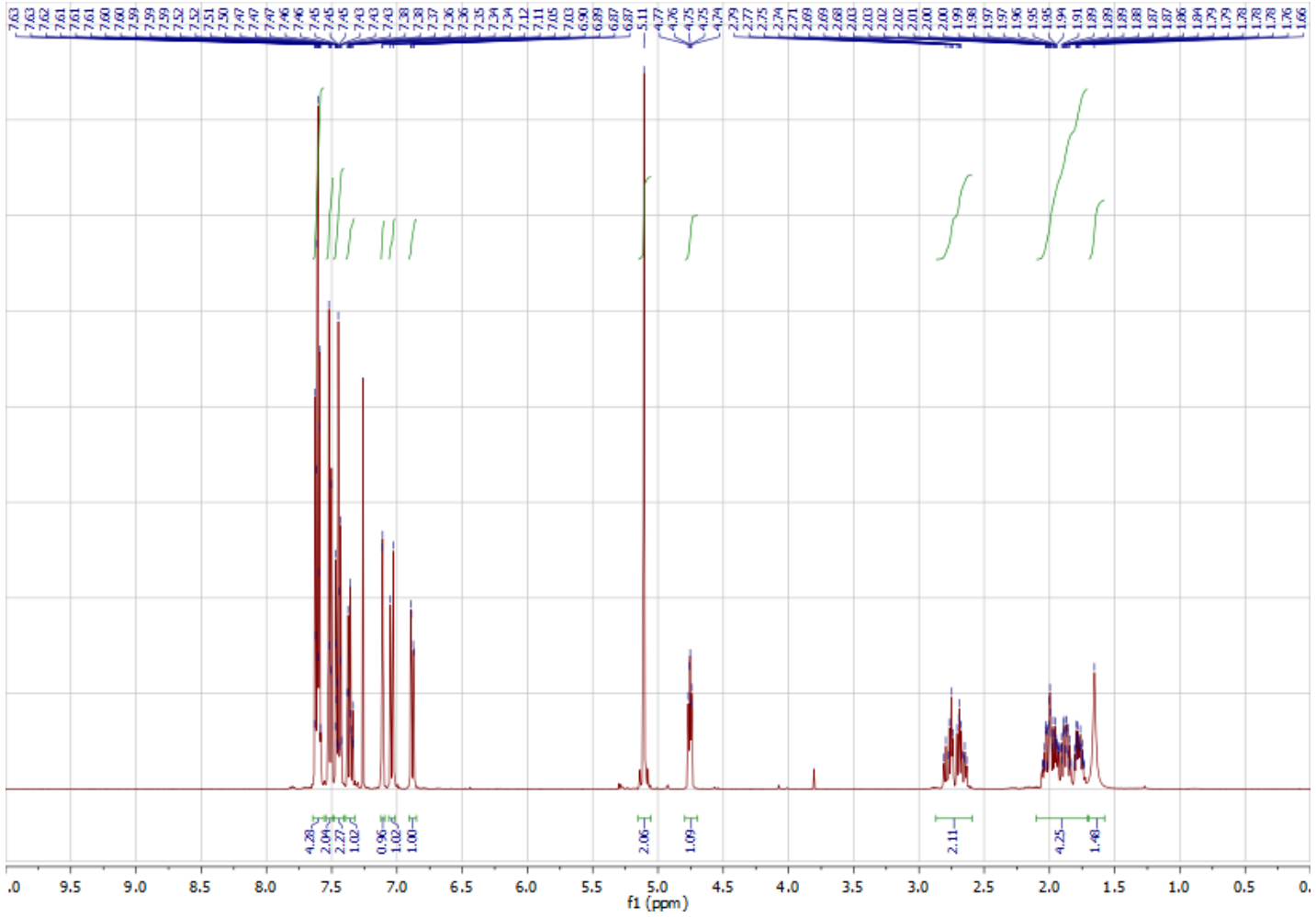


Figure A75 ^{1}H NMR spectra of **219** ($CDCl_3$).

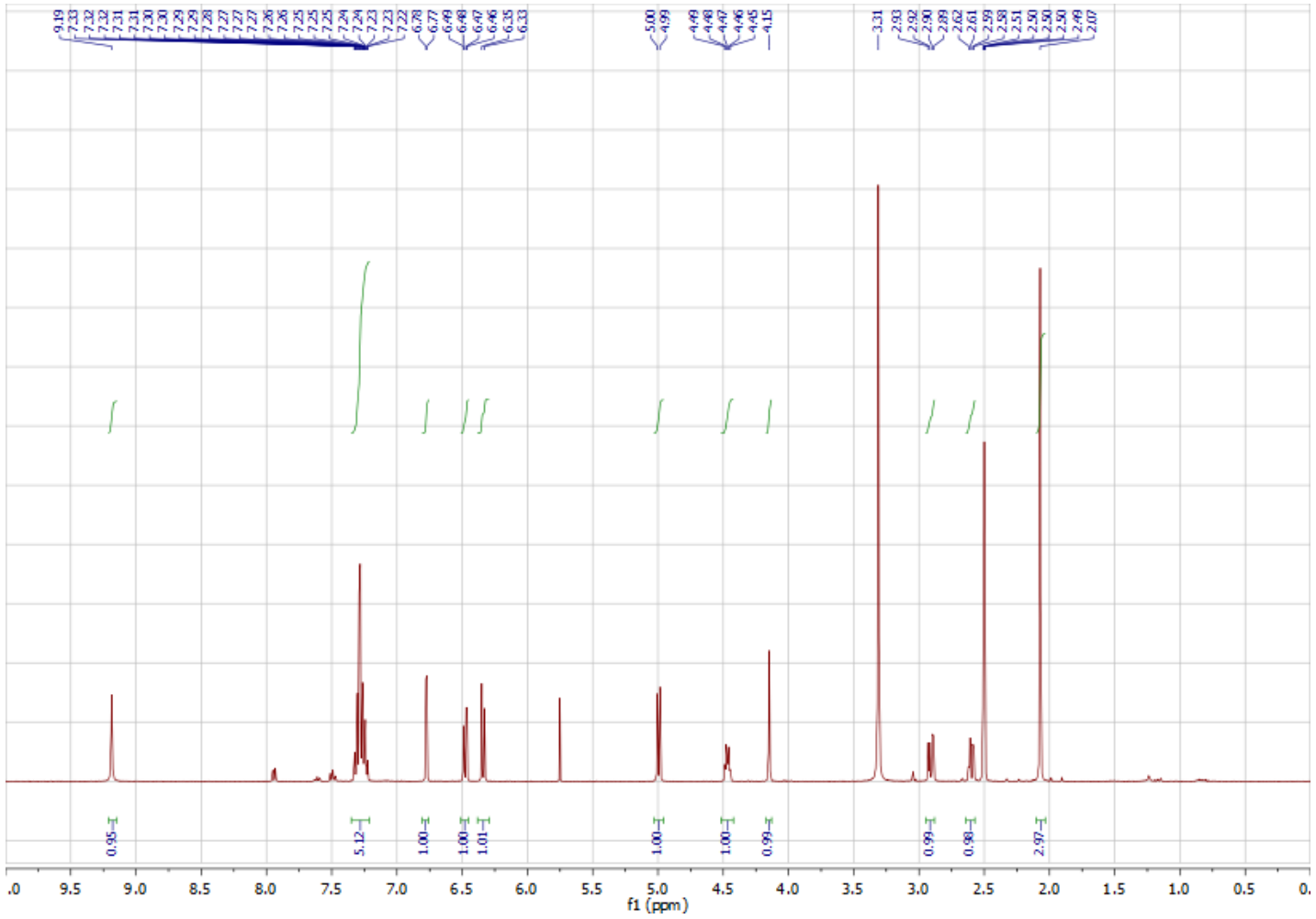


Figure A76 ^{1}H NMR spectra of **220A** (DMSO-d_6).

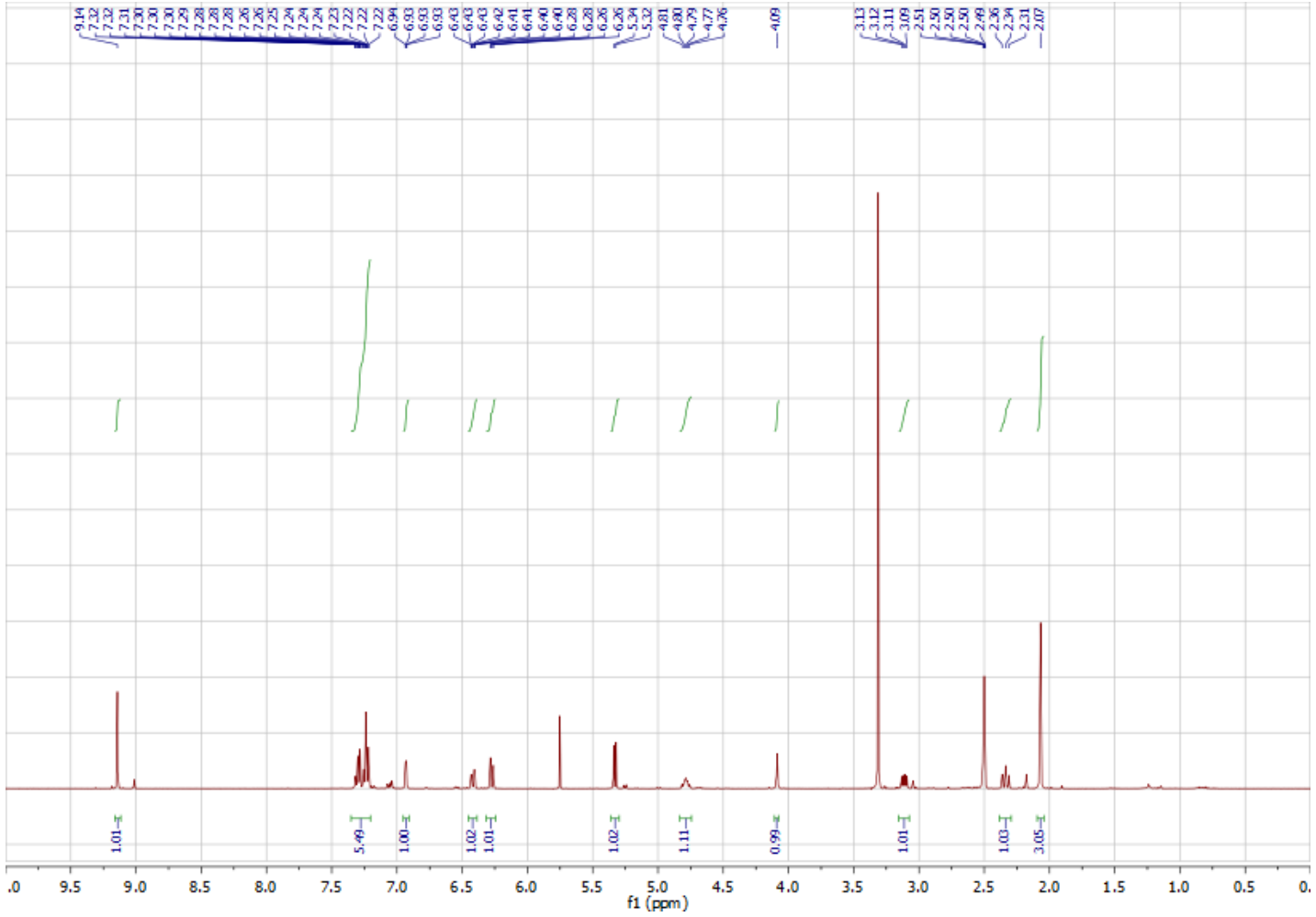


Figure A77 ^{1}H NMR spectra of **220B** (DMSO-d_6).

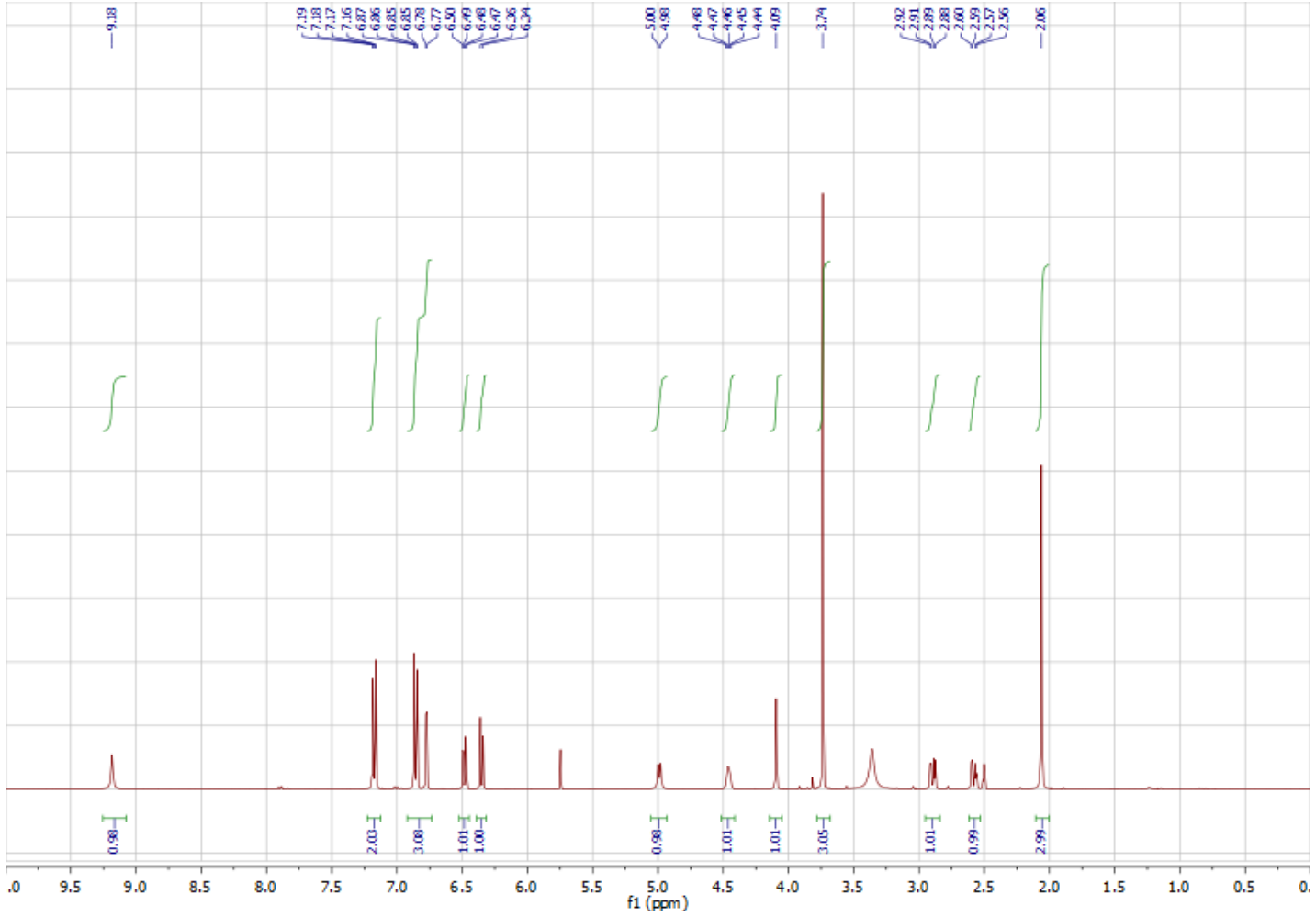


Figure A78 ^{1}H NMR spectra of **221A** (DMSO-d_6).

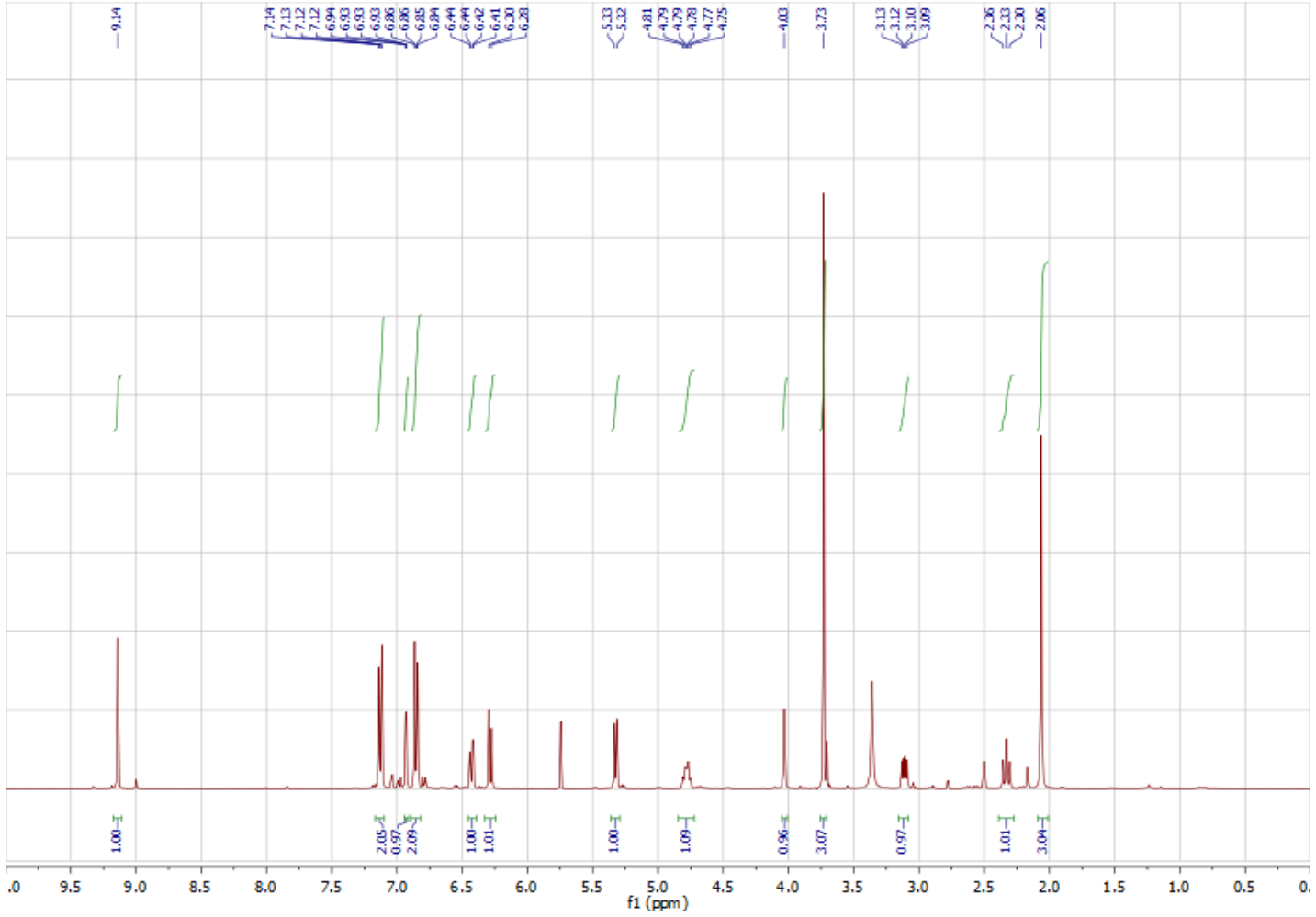


Figure A79 ^{1}H NMR spectra of **221B** (DMSO-d_6).

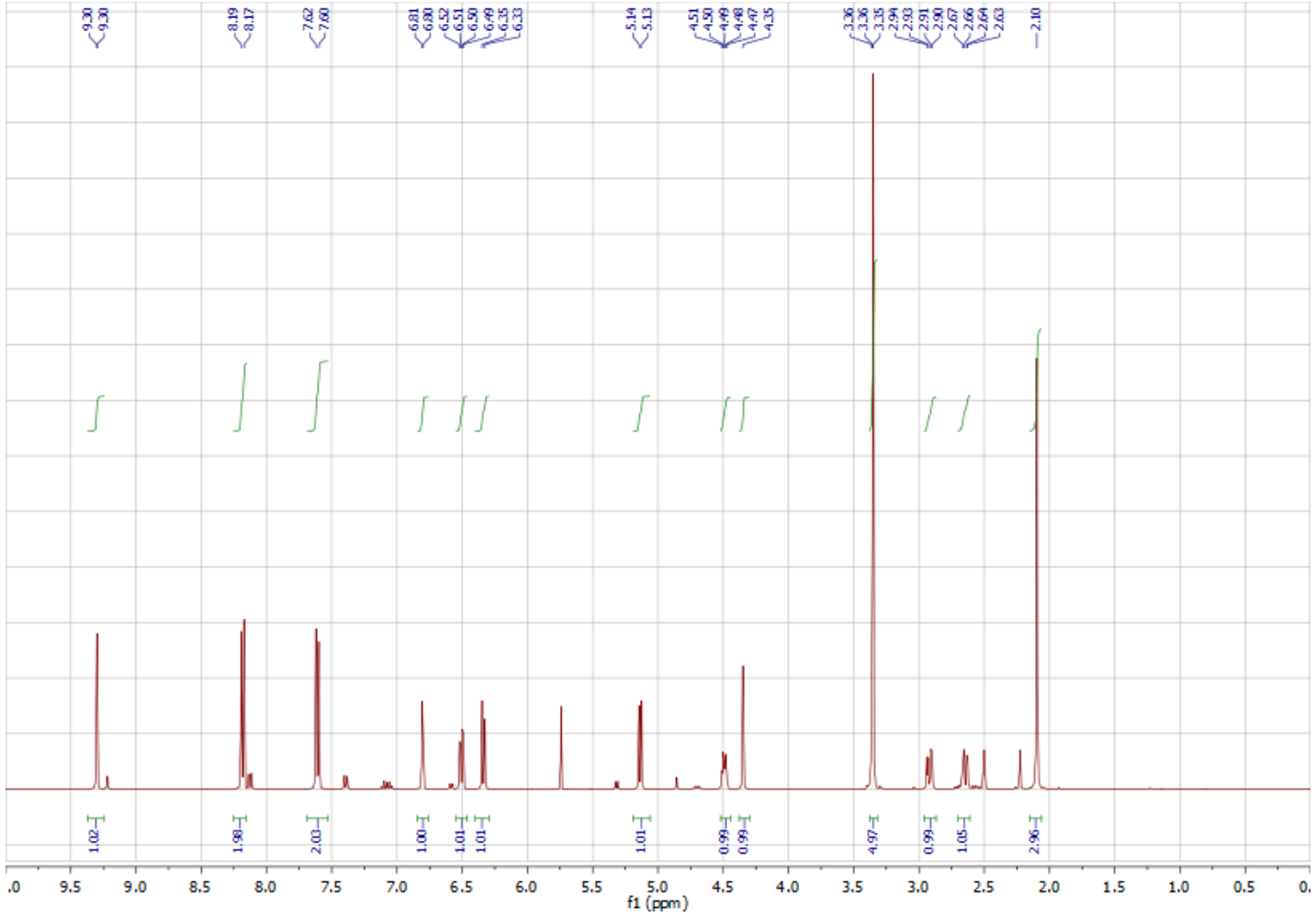


Figure A80 ^{1}H NMR spectra of **222A** (DMSO-d_6).

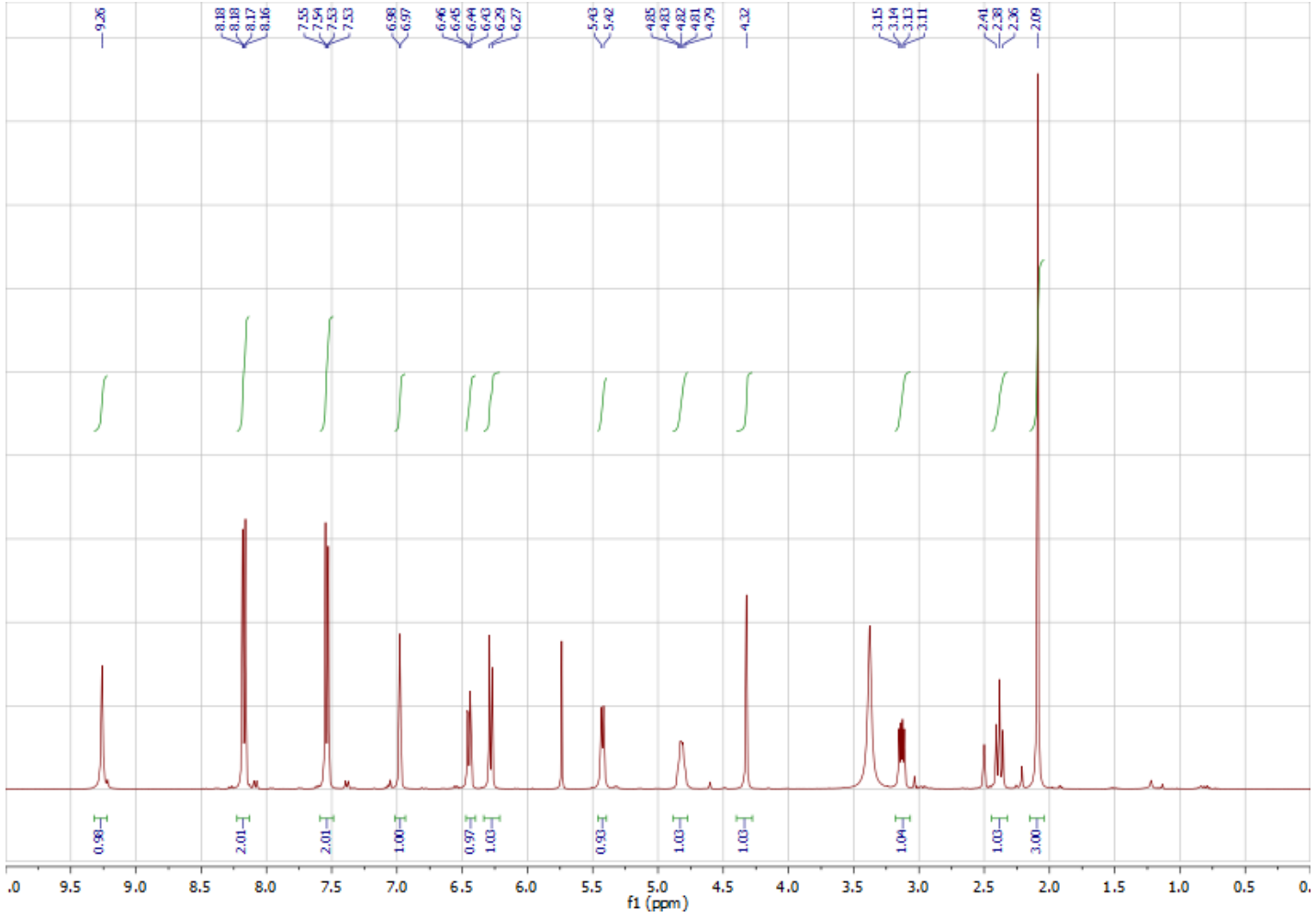


Figure A81 ^{1}H NMR spectra of **222B** (DMSO-d_6).

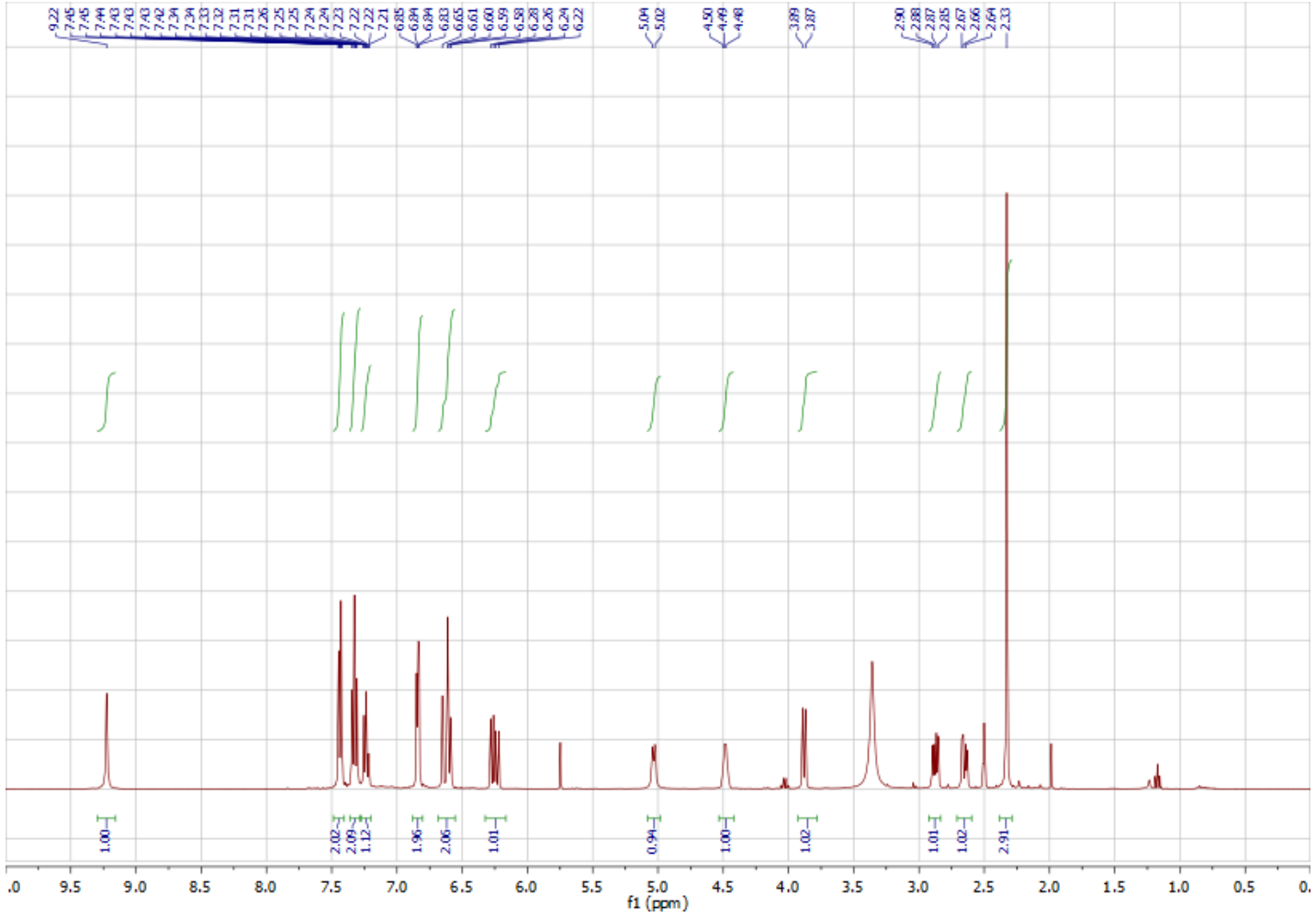


Figure A82 ^{1}H NMR spectra of **223A** (DMSO-d_6).

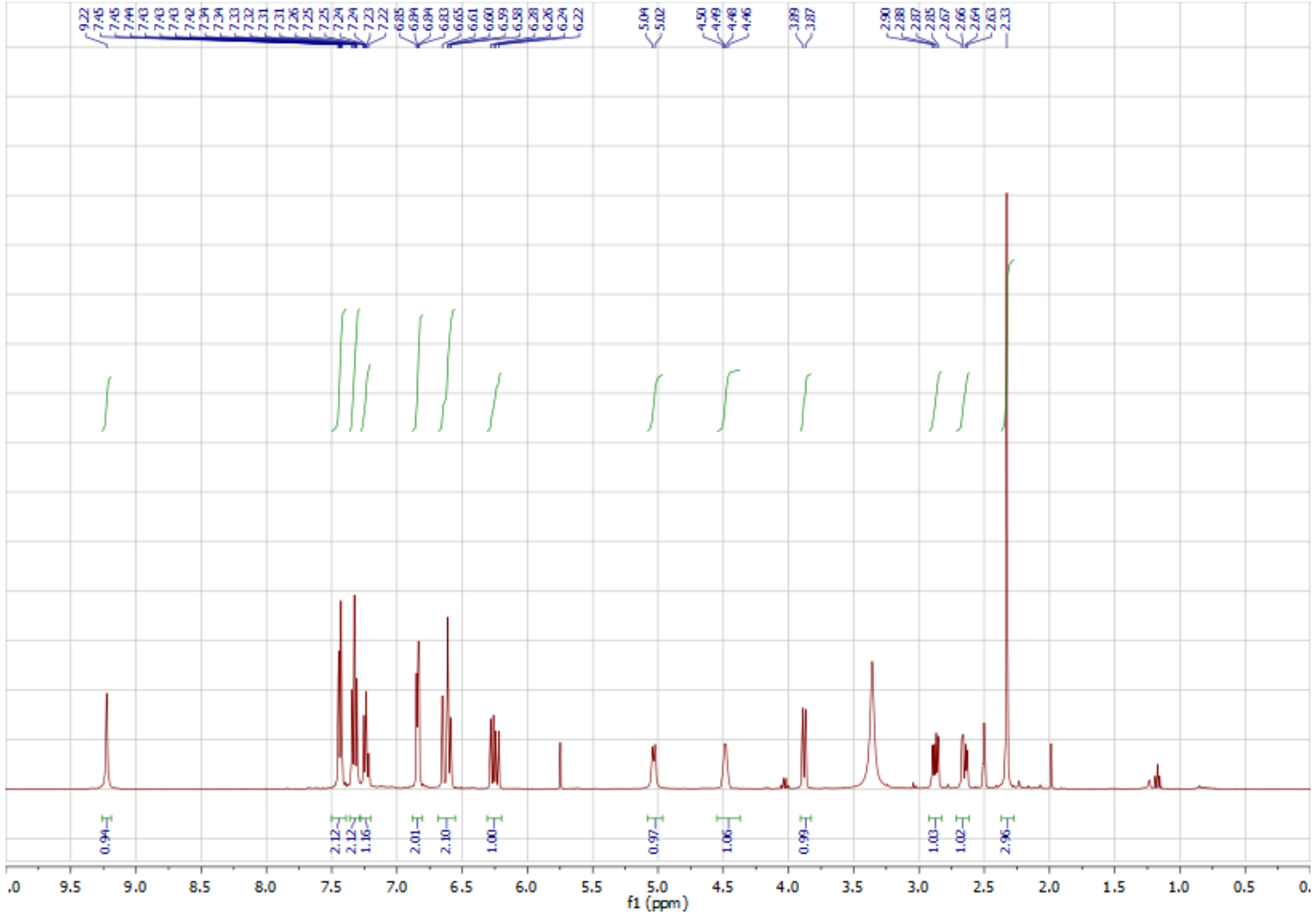


Figure A83 ^{1}H NMR spectra of **223B** (DMSO-d_6).

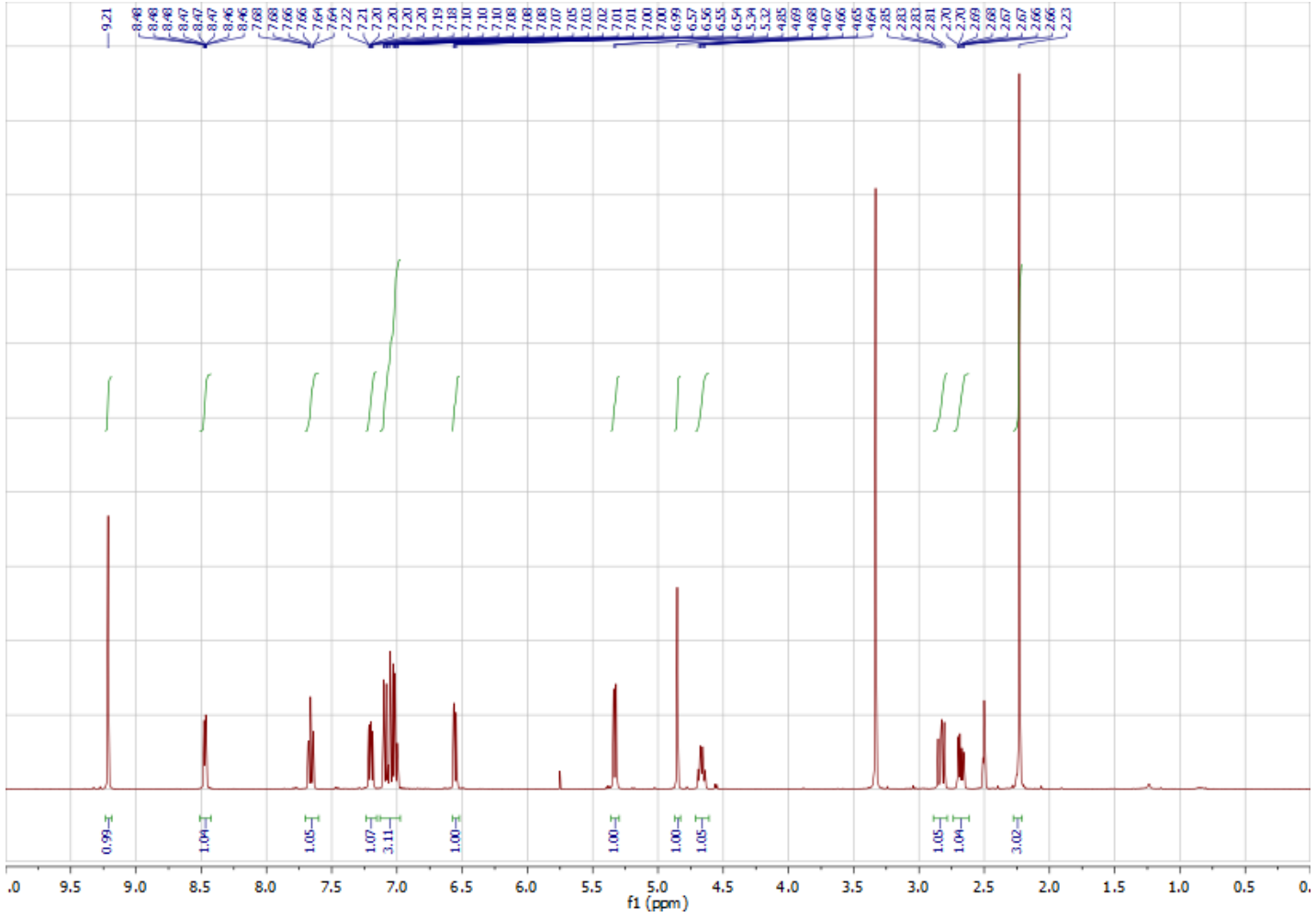


Figure A84 ^{1}H NMR spectra of **224A** (DMSO-d_6).

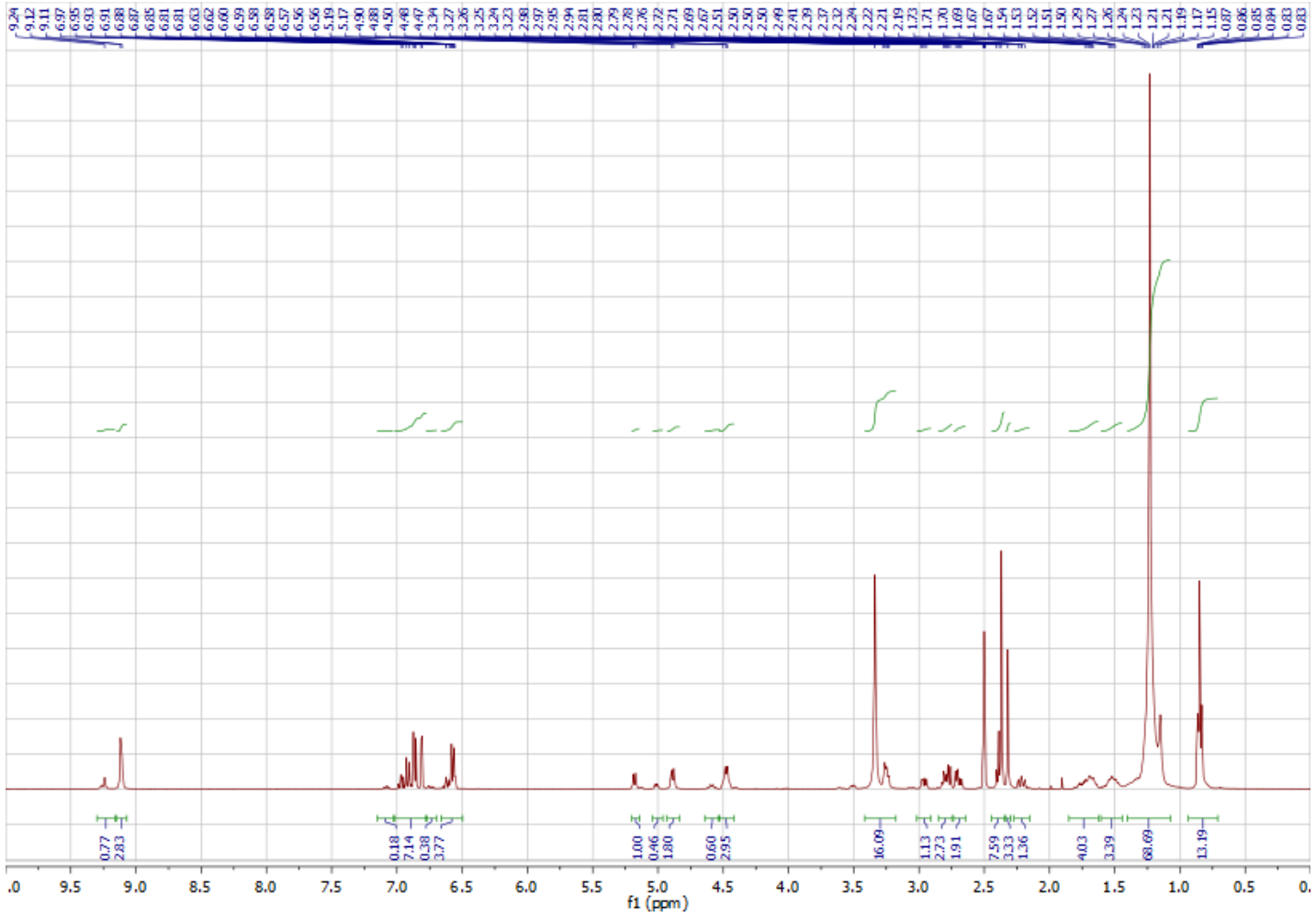


Figure A85 ^{1}H NMR spectra of **225** (DMSO-d_6).

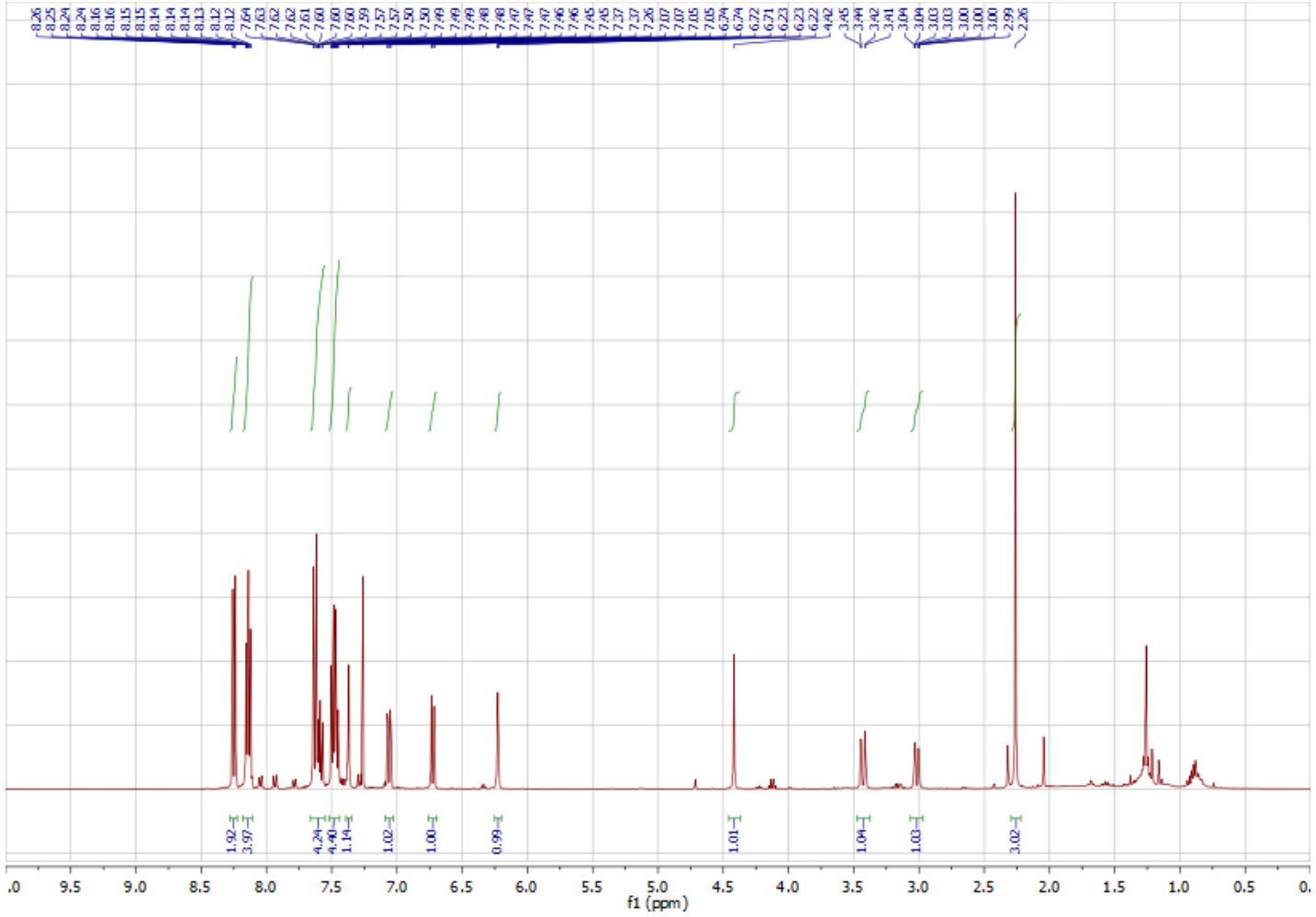


Figure A86 ^{1}H NMR spectra of **226** ($CDCl_3$).

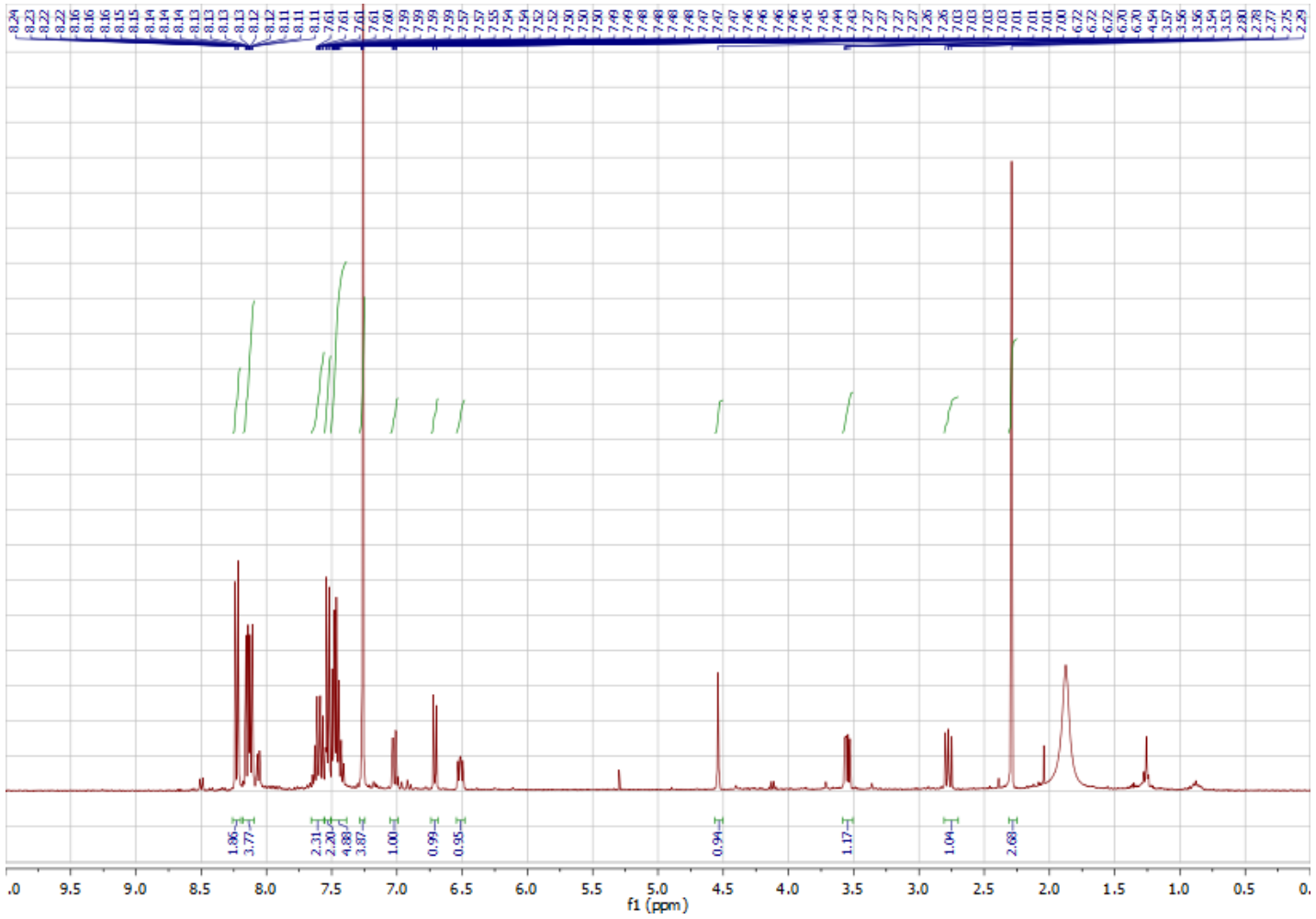


Figure A87 ^{1}H NMR spectra of **227** ($CDCl_3$).

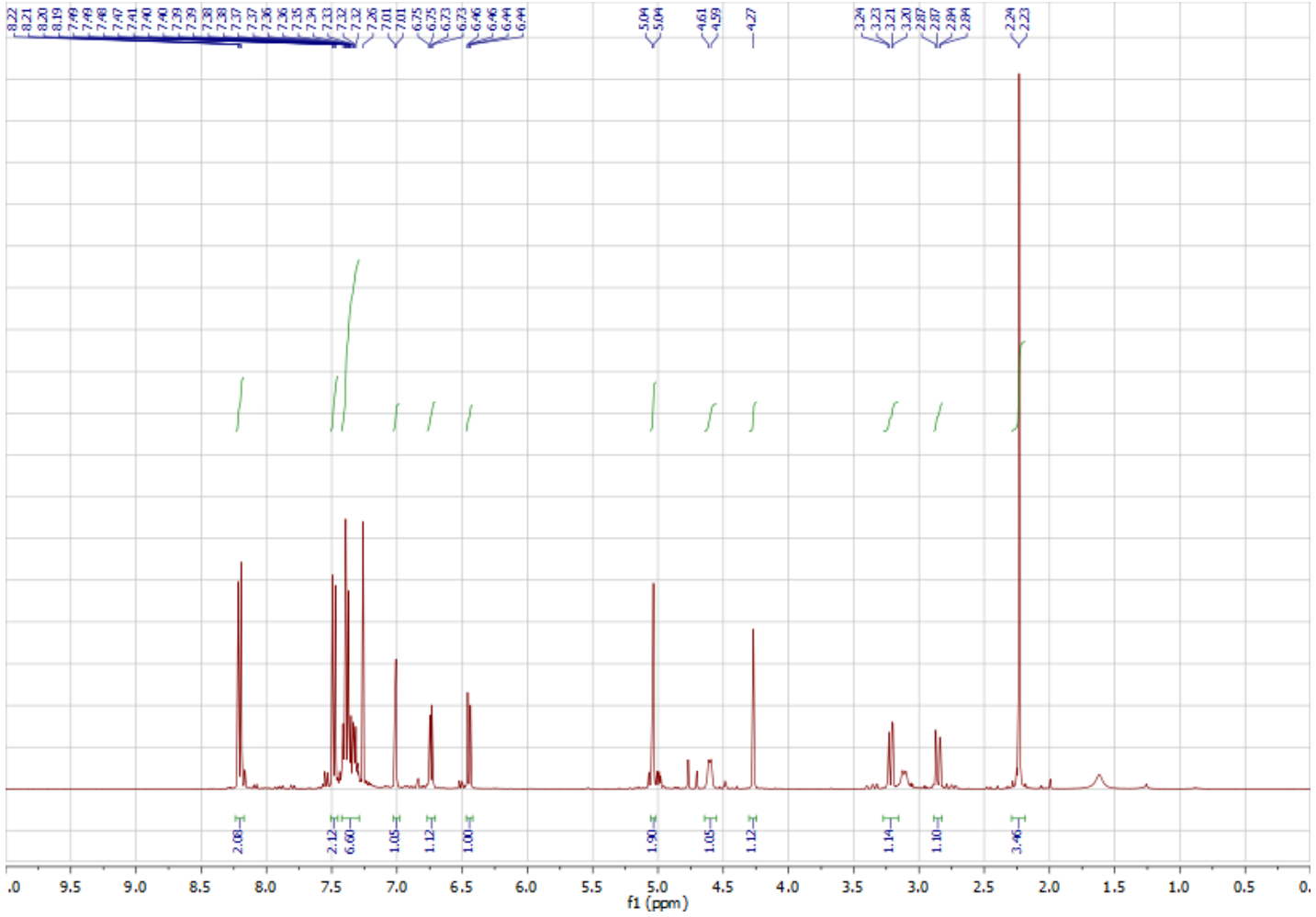


Figure A88 ^{1}H NMR spectra of **228** ($CDCl_3$).

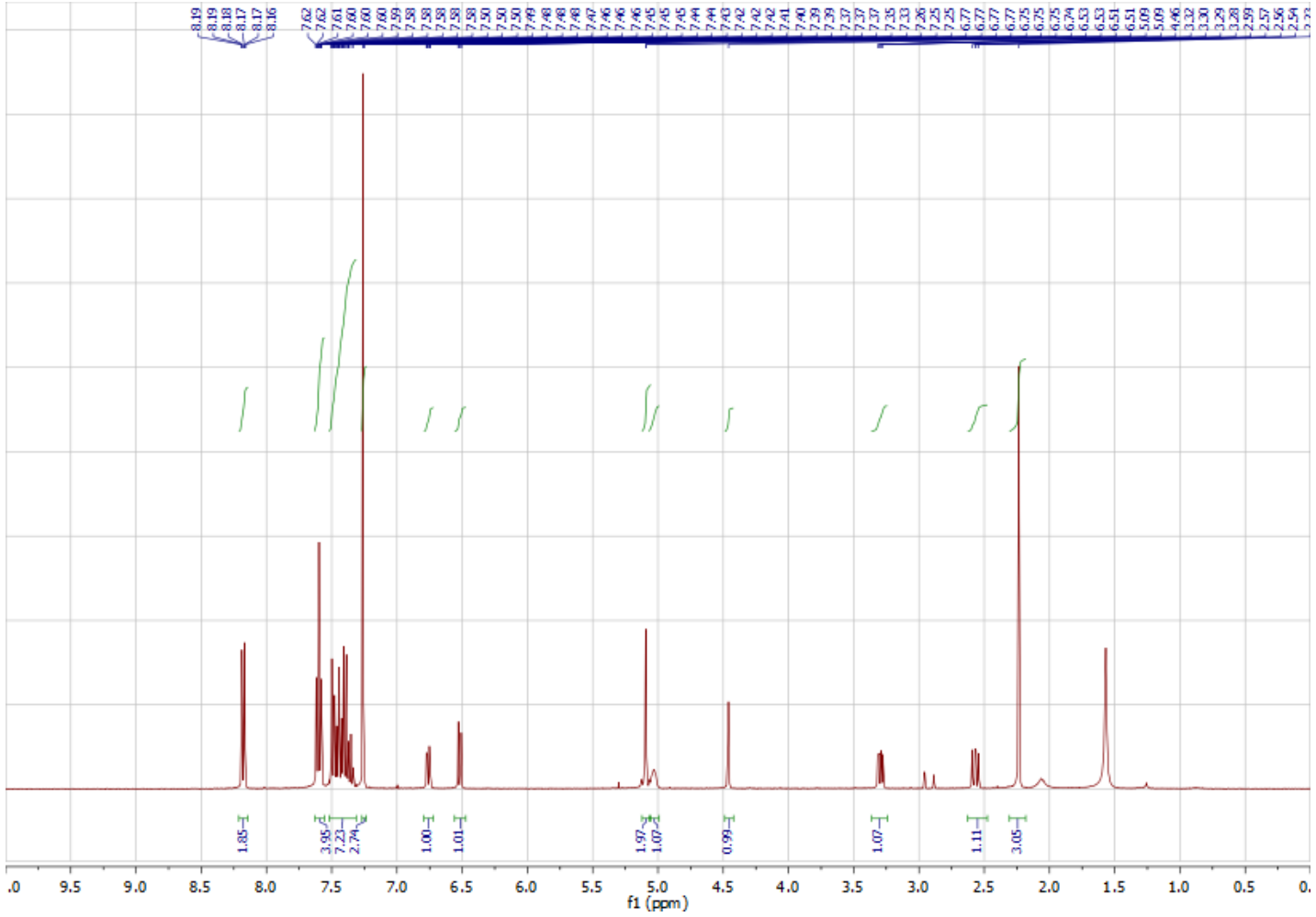


Figure A89 ^{1}H NMR spectra of **229** ($CDCl_3$).

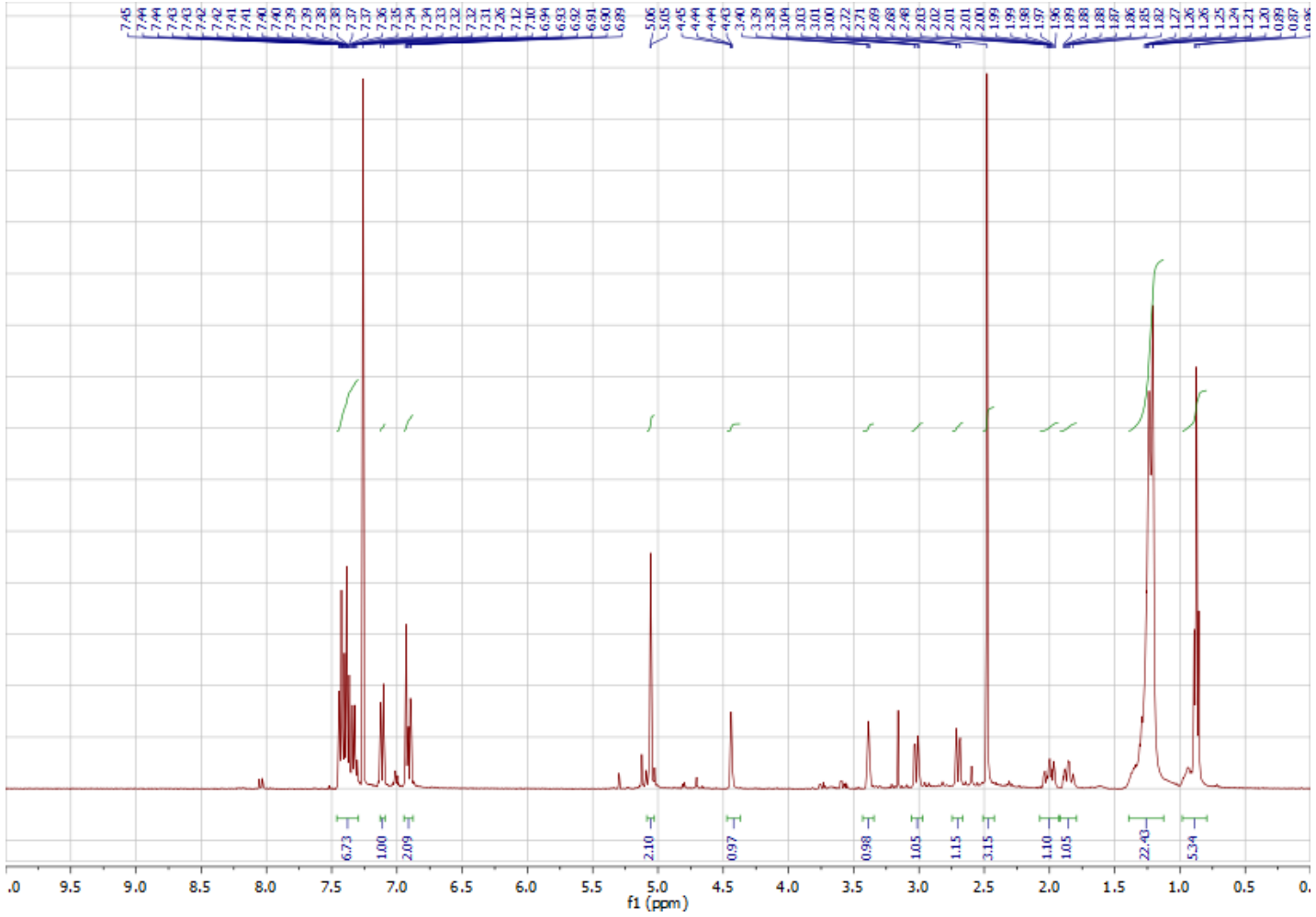


Figure A90 ^{1}H NMR spectra of **230** ($CDCl_3$).

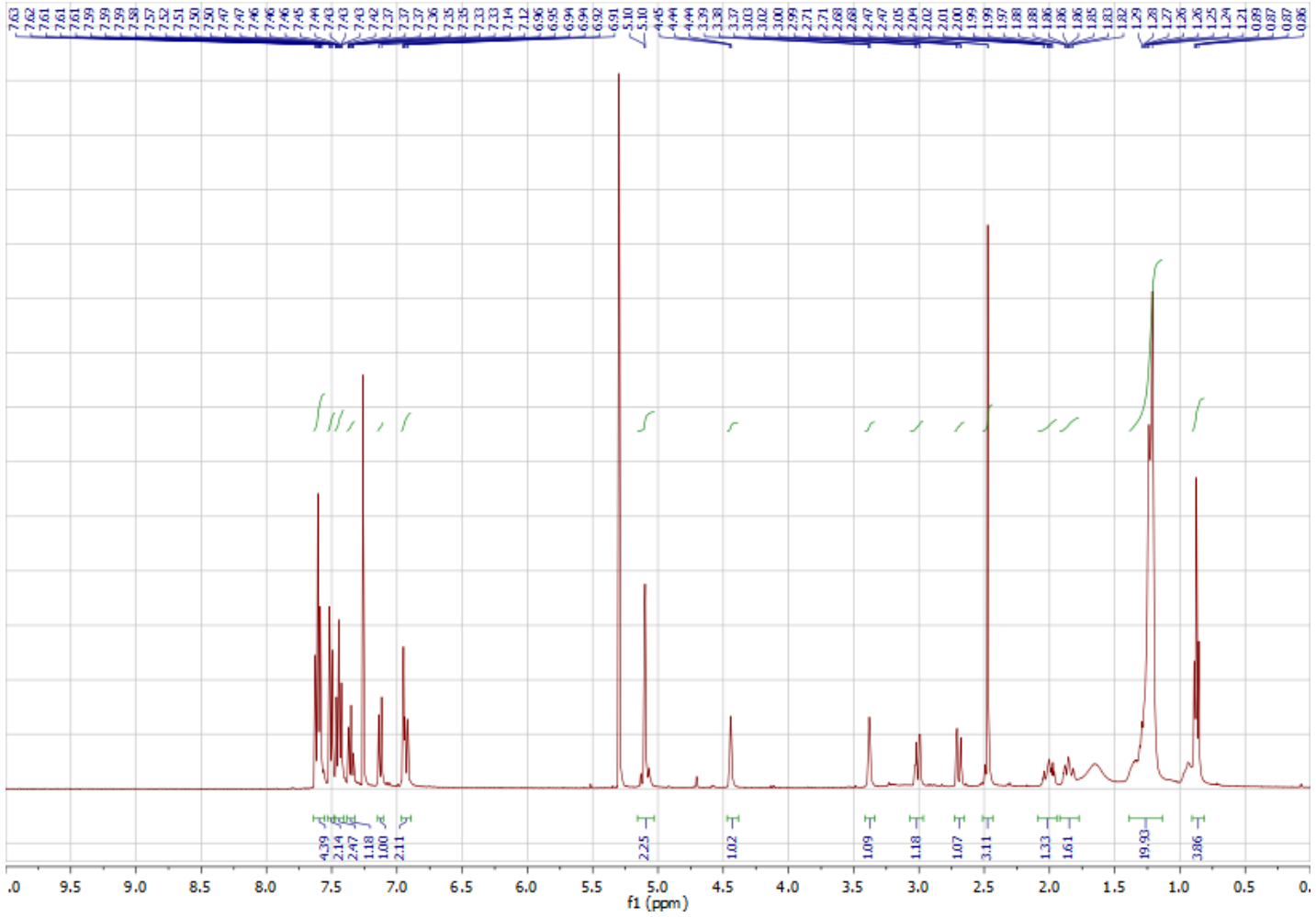


Figure A91 ^{1}H NMR spectra of **231** ($CDCl_3$).

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