Department of Applied Chemistry

Synthesis of Biphenyl-Biphenyl Derivatives as Insulin Mimetics

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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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Contents

Abstract

This thesis describes the synthesis of some biphenyl-biphenyl analogues for the treatment of diabetes. Researchers at Curtin University of Technology have reported the discovery of small molecule insulin mimetics. One of the reported compounds (**IM140**) is active in an animal model of diabetes. The structure of **IM140** comprises of a biphenyl left hand side, a linker and a xanthone right hand ring fragment (right hand side). The key features of **IM140** are believed to be the biphenyl moiety on the left hand side and the two carboxylic acids from the right hand side. The primary goal of this thesis is to synthesize different analogues to optimize orally-available small molecule insulin mimetics for the treatment of diabetes. In this work we focus on analogues in which the xanthone portion is replaced with synthetically more amenable frameworks.

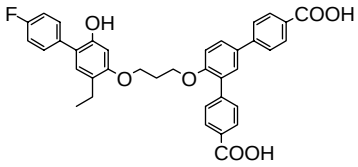
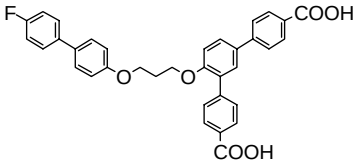
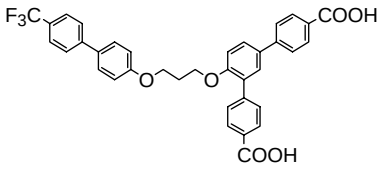
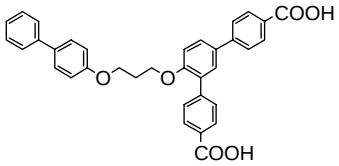
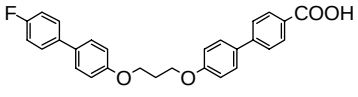
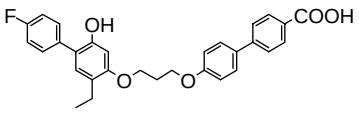
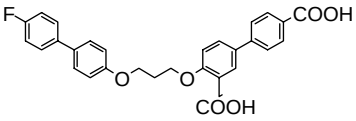
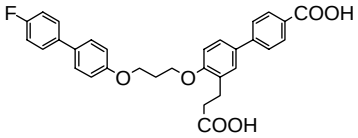
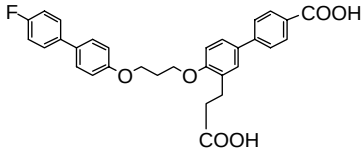
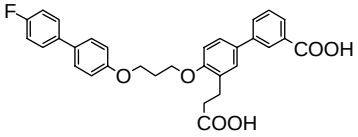
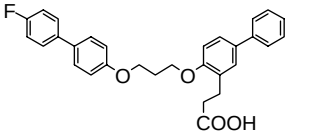
Chapter I provides an introduction on the biological aspects and background of this project and a literature review on the chemistry of one of the most popular cross-coupling reactions, the Suzuki coupling reaction.

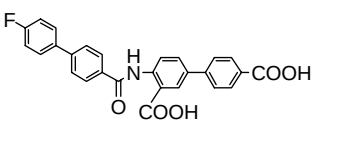
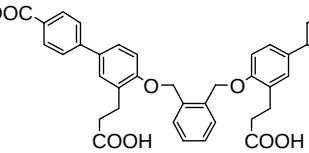
Chapter II describes the synthesis of four analogues with a triphenyl moiety as the right hand side. In this chapter the synthesis of four different left hand side components and two different right hand side components are described. The synthesis of four drug analogues is also described.

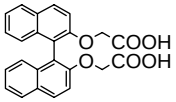
Chapter III focuses on the investigation of the impact of the two carboxylic acid groups on the right hand side. The synthesis of seven biphenyl-biphenyl analogues is described.

Chapter IV describes the synthesis of three analogues with different linkers. The structures of the synthesized drug analogues are presented on the next page.

The following analogues were synthesized and characterized and have been submitted for biological testing



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Abbreviations

NBS	N-bromosuccinimide
ether	diethyl ether
DMSO	dimethyl sulfoxide
Triflate, TfO-	trifluoromethanesulfonate
DME	dimethoxyethane
Cy	cyclohexyl
DMF	dimethylformamide
THF	tetrahydrofuran
dppf	1,1′-bisdiphenylphosphinoferrocene

Chapter I Introduction

Part A: Biology background

1.1 Overview of diabetes

1.1.1 Introduction of diabetes

Approximately 3500 years ago, the Egyptians noted a fatal disease whereby patients suffered from frequent and voluminous urination and they lost their ability to utilize the sugar in their blood.[1] In the first century A.D., the word "diabetes", from the Greek word meaning "siphon" or "pipe-like", was used to describe this disease. The urine of sufferers was sweet to taste as it contained high levels of sugar. The Latin word for honey, "mellitus", was added to the name in the seventeenth century. Nowadays, diabetes mellitus is known as a chronic disorder of glucose metabolism: glucose is overproduced by the liver and underutilized by other organs.

Diabetes is a metabolic disorder characterized by insufficient insulin secretion, resistance to the action of insulin or both. According to the World Health Organization (WHO) classification of diabetes (1980, revised 2002) there are two kinds of diabetes, which are determined by the clinical description of the patient: Type I diabetes, which is characterized by absolute deficiency of insulin, and Type II diabetes, which is characterized by the presence of insulin resistance.[2]

Type I diabetes, also known as insulin-dependent diabetes mellitus (IDDM), is a very serious disease. IDDM arises following the autoimmune destruction of the

pancreatic β-cell, which may be promoted by viral, genetic and other factors.[3,4] This leads to the pancreas not producing enough insulin even though the blood glucose level is very high. This form of diabetes occurs in 10-15% of all cases of diabetes[5] and it can occur at any age, but usually appears in children and adolescents. Eventually all type I diabetes patients require insulin therapy to maintain normoglycemia.* Frequent urination (polyuria), constant thirst (polydipsia), and excessive hunger (polyphagia) are the classic symptoms of type I diabetes. They are often accompanied by fatigue or weakness, and then rapid weight loss as the body begins to fail from lack of nourishment.

Type II diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM), is less severe but more common and it may go undetected for many years causing irreversible microvascular damage. It occurs when there is sufficient insulin made by the pancreas but the cells of the body are resistant to its action which results in the blood glucose level being too high. Type II diabetes usually occurs in people age 30 or older, but it is rising among children who are overweight and inactive. Most individuals with type II diabetes experience thirst, tiredness and frequent urination and some of them may have other symptoms such as blurred vision and dyslipidemia†. They are also more likely to be affected by "metabolic syndrome"‡.

* Normal concentration of glucose in the blood.
† A condition of abnormal concentration of lipids or lipoproteins in the blood.
‡ People with the "metabolic syndrome" are at increased risk of heart disease, stroke and vascular disease. The principal risk factor for this "metabolic syndrome is abnormal obesity and insulin resistance.

1.1.2 Discovery of insulin

Before the twentieth century there was no effective treatment for the sufferers of type I diabetes. Individuals with the insulin-dependent form of diabetes died a slow death characterized by progressive weight loss and were susceptible to infection, gangrene, blindness and non-healing wounds. This tragedy lasted for centuries until the discovery of insulin.

In 1889, two German scientists Oskar Minkowski and Joseph von Mering, observed a swarm of flies feeding on dog's urine after the dog's pancreas had been removed.[6] The dog developed similar symptoms to human diabetes and died eventually of ketosis.[*] On testing the urine, they found it rich in sugar, thus demonstrating the relationship between the pancreas and diabetes. In 1901, Eugene Opie identified the specific role of the islets of Langerhans[†], and he wrote in his publication: "Diabetes mellitus is caused by the destruction of the islets of Langerhans and occurs only when the bodies (the islets) are in part or wholly destroyed."[7] Over the next two decades, several attempts were made to isolate the secretion of the islets as a potential treatment, but none of them succeeded until Banting and Best isolated insulin in 1922. Banting tied a ligature around the pancreatic duct and several weeks later all the digestive cells had died and had been absorbed by the immune system, leaving thousands of islets. These islets were isolated and used to produce insulin. Collip, a biochemist, joined the team to purify the protein and after a month he successfully purified insulin. A fourteen-year-old

[*] A stage of metabolism when the body converts fat to ketone bodies; acetone is a byproduct of ketosis and can be detected on the breath of uncontrolled diabetics. Severe ketosis can damage the liver and kidneys.

[†] Irregular cluster of cells scattered throughout the tissue of the pancreas that secrets insulin, glucagon and somatostatin.

diabetic received the first injection of insulin on January 11, 1922. However, the extract was too impure and he suffered a severe allergic reaction and further injections were cancelled. After one and a half weeks, Collip further purified the original extract in order to perform another injection on the patient on January 23, 1922. This injection dramatically reduced hypoglycaemia* in the patient, without obvious side-effects. This discovery was a landmark treatment for diabetes, changing the lives of millions of diabetics today. In recognition of this achievement, the 1923 Nobel Prize was awarded to Banting and Macleod, who in turn shared their prize with Best and Collip, respectively.[8]

1.1.3 A worldwide disease

Currently diabetes affects more than 245 million people over the world and this number is expected to be 380 million by 2025 (**Figure 1.1a**).[9] The five countries with the largest number of diabetics, India, China, United States, Russia and Germany, have more than 120 million diabetics (**Figure 1.1b**).[9] In Australia, 3.6% of the population, 0.7 million people, are reported to have diabetes in 2007 and this number is expected to rise to 1.23 million in three years.[10,11] As people with diabetes are at increased risk of various complications such as kidney failure, cardiovascular disease, and nerve damage,[12] diabetes mellitus is considered a significant underlying cause of death. In 2007, diabetes is expected to cause 3.8 million deaths worldwide, similar to the devastation of HIV/AIDS.[13]

* Abnormally low level of sugar in the blood.

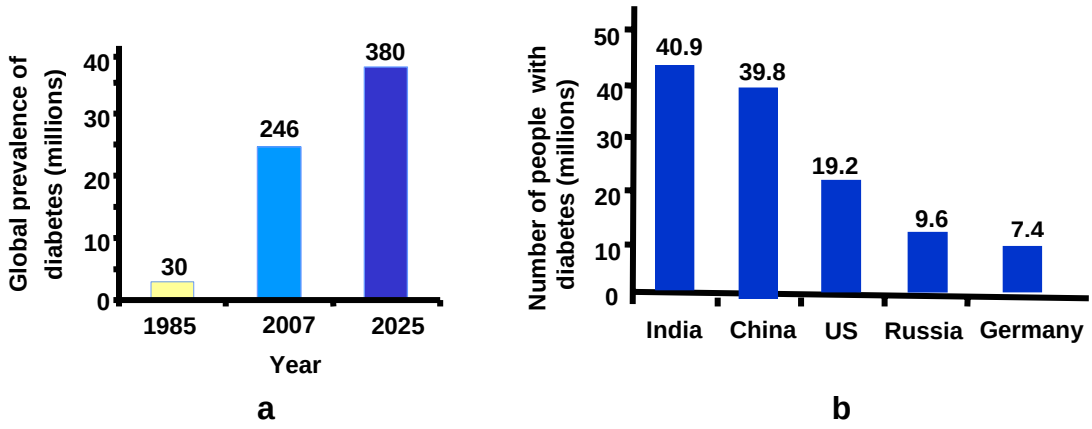


Figure 1.1 The global prevalence of diabetes a) the global trends and b) the incidence by country[14]

Diabetes mellitus is the fifteenth most costly disease worldwide.[10] According to the American Diabetes Association, the direct and indirect costs of diabetes in the United States was US$ 132 billion in 2002.[15] In Australia, over $204 million was spent in 2001 by the Australian Government and people with diabetes on antidiabetic drugs and diabetes testing agents.[16] By 2025, the worldwide burden is expected to be in excess of US$ 302 billion annually.[17] Consequently, there is an urgent need for new therapies for this disease.

1.2 Insulin

1.2.1 Insulin structure

Insulin is a 51 amino acid peptide-hormone with the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$, and a molecular weight of 5733 Da.[18] Insulin consists of two disulfide-bond linked peptide chains: the A and the B chains, named for their relatively acidic and basic nature. The A and B chains comprise twenty one and thirty amino acids, respectively. The amino acid sequence of insulin, the first protein to have its sequence determined, was determined by Fred Sanger and his colleagues (**Figure 1.2**).[19] Sanger was awarded the 1955 Nobel Prize for this discovery.[20,21] Insulin was also the first protein to be chemically synthesized and the crystal structure was one of the first determined by X-ray crystallography.[22,23] More recently, human insulin was the first protein to be produced by recombinant DNA technology for clinical use.[24]

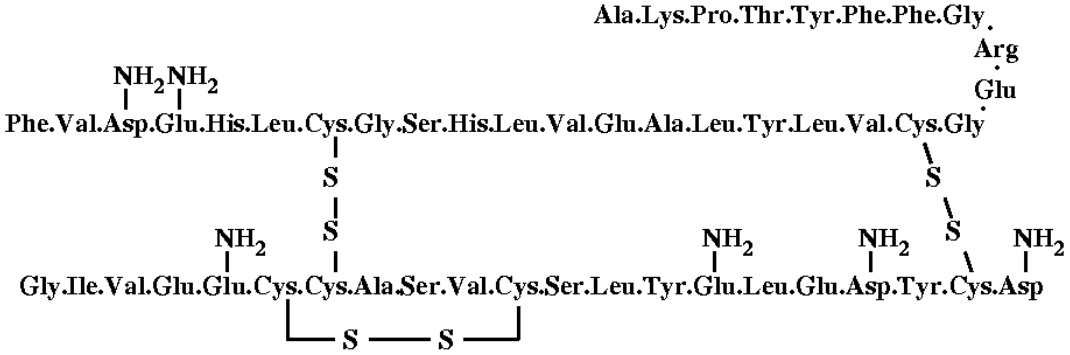


Figure 1.2 The sequence of human insulin by three amino acid codes[19]

Insulin is synthesized in the pancreas as inactive precursor forms. The immediate precursor of insulin is proinsulin which consists of a single polypeptide chain consisting of 86 amino acid residues.[25] Proinsulin is converted to active insulin

by the action of specific peptidases* that cleave two peptide bonds to yield insulin and a C-peptide.[26]

Insulin molecules have a tendency to form dimers in solution due to the inter-molecular hydrogen-bonding and hydrophobic interactions.[27] In the presence of zinc ions, insulin further aggregates into hexameric units (**Figure 1.3**). Upon extracellular release, the hexamers dissociate into dimers and eventually the dimers dissociate into monomers, which are the biologically active form. Monomers and dimers readily diffuse into the blood, whereas hexamers diffuse poorly. Hence, absorption of insulin preparations containing a high proportion of hexamers is delayed. The tendency of insulin to form aggregates is a significant problem because of the slow release of insulin from the injection site. On the other hand, the more stable hexamers have led to the development of slower acting insulin which allows for a more constant level of insulin in diabetics. This interesting phenomenon has stimulated development of a number of recombinant insulin analogues. For example insulin Lispro®, formerly called Lyspro®, was the first commercially available insulin analogue. Compared with regular human insulin, insulin Lispro® offers the advantages of faster subcutaneous absorption and a shorter duration of action.[28,29]

* A specific enzyme that catalyze the hydrolysis of peptides to amino acids

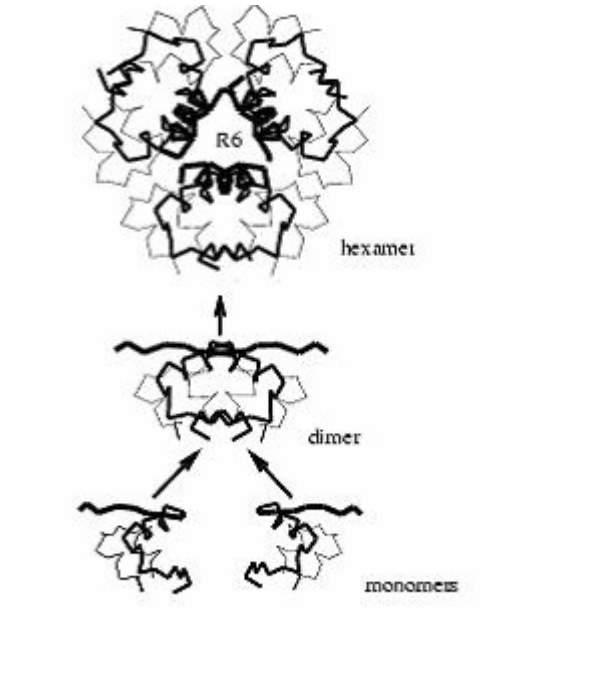


Figure 1.3 Dimers and hexamers of insulin in solution[30]

1.2.2 Function of insulin

The human pancreas is an organ which performs both endocrine* and exocrine† functions. The pancreas contains two kinds of cells, the acinar or glandular cells and groups of small, irregular polygonal cells: the former secretes digestive enzymes and the latter produces pancreatic endocrine hormones. The polygonal cells were named as islets of Langerhans since their discovery by Langerhans in 1867. Endocrine cells make up only 1-2% of the weight of the pancreas. The rest of the organ is exocrine tissue that produces bicarbonate ions and digestive enzymes. The islets of Langerhans are scattered among the exocrine tissues and secrete two hormones directly into the circulatory system. These islets are composed of at least two types of cells, α cells and β cells: α cells produce a hormone named glucagon which stimulates the enzyme phosphorylase to produce glucose from carbohydrates;

* Internal secretion of hormones
† external secretion of hormones

β cells synthesize insulin which allows body cells to absorb and use glucose thereby decreasing the blood sugar level.[31,32] Both insulin and glucagon play key roles in maintaining glucose homeostasis.

Normally, people experience an increase in blood glucose level following ingestion of food. When the level of glucose increases, a precise amount of insulin is released by the β cells of the islets of Langerhans and is transported throughout the body in the blood. Insulin then binds to receptors in its target tissues (liver muscle and fat tissues) and this triggers the appropriate intracellular signalling pathways that promote glucose uptake and utilization. For example, insulin stimulates liver cells and enzymes such as glycogen phosphorylase* and glycogen synthase† to store glucose in the form of glycogen.[33,34] When blood sugar levels decrease, glucagon is secreted. Glucagon signals the liver cells to increase glycogen hydrolysis, which promotes the release of glucose from glycogen and the process of glycogenesis (the generation of glucose from non-carbohydrates precursors such as acids). Thus glucose is released back into circulation to maintain glucose homeostasis.

The other important role that insulin plays is to modify the adipose tissue so that they are more effective in breaking down, taking up, and storing fats. In addition, insulin stimulates the synthesis of lipids, which is more efficient in engery storage than glycogen.[35] Finally, insulin stimulates the uptake of amino acids and the synthesis of protein by the liver, muscle and other cells. This action must proceed very quickly because insulin can still stimulate the conversion of excess amino acids to glucose and fat.

* An enzyme which breaks up glycogen to glucose subunits
† An enzyme which convert excess glucose into a polymer chain for storage as glycogen

Insufficient insulin will reduce the transport of glucose into muscle and adipose tissue. Since glucose is not rapidly taken up by these tissues, the inability to control blood sugar levels is the typical characteristic of diabetes. If the normal blood glucose level is exceeded, the excess glucose will spill into the urine. This is always accompanied by an increased excretion of urine, and therefore the diabetic has polyuria and an attendant dehydration and hemoconcentration.

1.3 Insulin receptor

The first event in insulin action is the binding of insulin to a glycoprotein receptor on the surface membrane of the cell. This large complex macromolecule is named the insulin receptor.

1.3.1 Structure of the insulin receptor

The insulin receptor is a tyrosine kinase* receptor found in organisms as primitive as cnidarians† and insects. It has a molecular weight of 450 kDa, minimally composed of two 130 kDa α-subunits and two 90 kDa β-subunits in a disulphide-linked complex.[36] The complete amino acid sequence of the α and β subunits have been deduced from a human placental cDNA clone, which provided valuable information about the structural features of the insulin receptor.[37,38] The α-subunit contains a cysteine rich region analogous to the epidermal growth factor (EGF) receptor and the insulin-like growth factor-I (IGF-1) receptor.[37,39] The β subunit of the receptor protein contains a cytoplasmic domain analogous to the *src* family of specific protein kinases indicating that the insulin receptor is a member of this family.[39] These days it is well known that insulin binds to the α-subunit of the insulin receptor and that the binding activates the β-subunit which is an insulin responsive tyrosine kinase.[40-42]

In 1991, electron microscopy showed the structure of the insulin receptor to be a "T" or "Y" shaped entity, with the two β-subunits forming the base of the T or Y, and the two α-subunits branching from the top of the β-subunits.[43,44] Several attempts

* Any of various enzymes that catalyse the transfer of a phosphate group from ATP to an acceptor
† Invertebrate animals characterized by a symmetrical body including jellyfishes, hydras and corals

have been made to determine the 3D structure but none of them clearly provided the whole three-dimension structure until 2006. In 2006, the structure of the insulin receptor was reported by the team led by Dr Colin Ward of CSIRO Australia (**Figure 1.4**).[45] This discovery will accelerate the understanding of the mechanism of insulin binding to the insulin receptor.

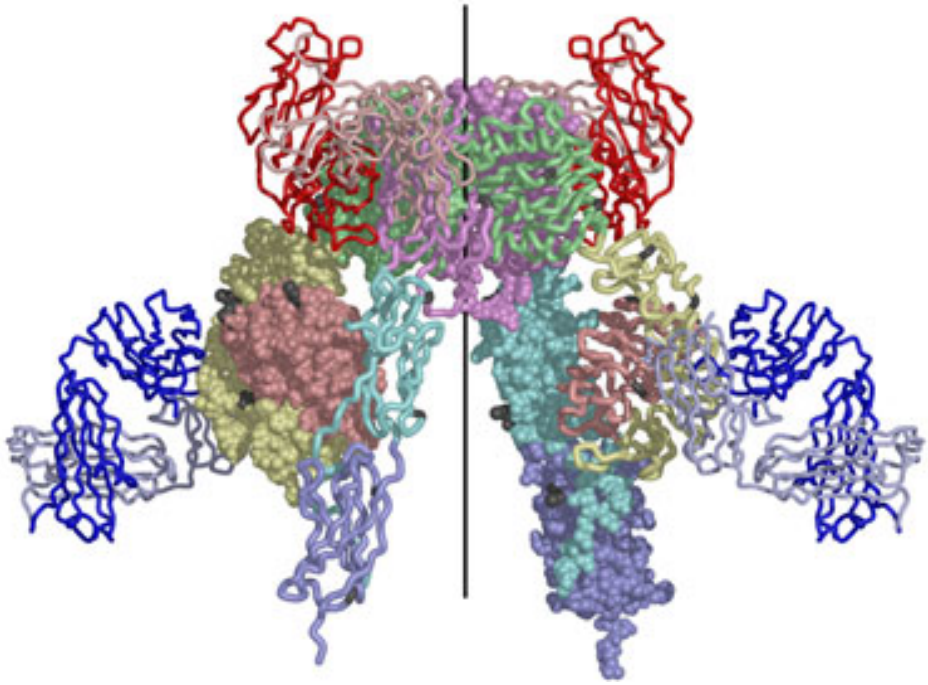


Figure 1.4 Structure of the insulin receptor as determined by X-ray crystallography[45]

1.3.2 Insulin binding to the insulin receptor

Although the structures of insulin and the insulin receptor have been determined, the interaction of insulin with its membrane receptor is still not completely understood. However, the team led by Dr Ward have now partially resolved the crystal structure of the insulin receptor[45] and this provides some insight into how insulin binds to the receptor. This model, for the first time, begins to

explain and tie together results gleaned from many previous studies of sequence variants.

A plethora of literature describes the key elements of insulin crucial for its interaction with the insulin receptor (A1, A2, A3, A17, A19, A21, B12, B16, B21, B24 and B25).[23,46-52] The possibility that the biologically active form of insulin may involve partial unfolding of the insulin B-chain through detachment of A-chain/B-chain contacts needs to be considered in any binding models.

A group led by Prof. Helmerhorst at Curtin University of Technology constructed a series of pharmocophores based on these 11 residues of insulin using both open and closed structures of insulin.[53] Searches were performed using these pharmacophores based on the selected residues. Relatively large tolerances (2-5Å) were used to account for the flexibility of insulin in solution, when compared to standard searching protocols. A total of approximately 2000 molecules matched the various queries. Most hits were found with a query that had the least number of elements (A21, B21, B24 and B25), in the closed form of insulin. It was recognised that some of the 11 amino acids may be more important than others in binding to the receptor, and the more open models did not identify many structural matches due to the difficulties in bridging the gap between distant pharmacophore points with small organic molecules.

Previous studies support the importance of the A21, B21, B24 and B25 residues for insulin binding to the insulin receptor.[46-52] The A21 (asparagine) is crucial to the activity of insulin and removal of this residue by carboxypeptidase

results in a 90% loss of activity;[48] replacement of B21 (glutamic acid) by another amino acid decreases binding by 75% relative to the native insulin;[49] the importance of B24 (phenylalanine) is inferred from low activity B24 analogues where the replacement of B24 with leucine or alanine leads to analogues with 70% less activity than native insulin;[54] replacement of B25 (phenylalanine) with several amino acids causes over 95% decrease in the binding activity.[50] Nakagawa and Tager postulate that insulin undergoes a concerted change upon interaction with its receptor and that this change requires the presence of a β-aromatic ring in the B25 position.[55] A separate observation by Markussen supports this premise.[56] They found covalent linkage of the A1-B29 residues in insulin leads to an analogue with similar tertiary structure to native insulin, but the mobility of the B-chain is severely restricted. In conclusion, Mirmira and Tager proposed a model for the interaction of insulin with its receptor in 1989.[57] The first step upon receptor binding is that the B24 side-chain is displaced into a position equivalent to that obtained by D-amino acids in the B24 position and requires the orientation provided by residues B26-B30. In the second step, it is proposed that the main chain B22-B30 undergoes a conformational change, mediated through B25, leaving insulin in an active conformation to bind fully with its receptor.

1.4 Insulin mimetics

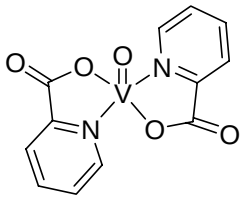
Normally peptide hormones, like insulin, are given by parenteral injection because they can be destroyed by proteolytic enzymes in the stomach. Most people inject insulin with a syringe that delivers insulin just under the skin. This is inconvenient, has significant lifestyle implications and can cause local pain, itching, lipodystrophy* and infection. Researchers are now developing several new methods for delivering insulin. These include the insulin patch[58] and inhaled insulin.[59] The insulin patch, when placed on the skin, will give a continuous, low dose of insulin. To adjust insulin doses before meals, users pull off the tab on the patch to release insulin. Inhaled insulin delivery systems deliver insulin as a dry powder, inhaled through the mouth directly into the lungs where it passes into the bloodstream. This aerosol delivery system is about the size of a flashlight and uses rapid-acting insulin. Unfortunately, neither method is as effective as insulin injections. Delivery using these new technologies is relatively inefficient and more expensive, efficiency of insulin uptake varies markably between individuals, and inhaled insulin is not suitable in patients who may be respiratory compromised. Consequently, there is a substantial demand for the alternative technologies to allow the delivery of insulin as "inhaled" or "oral".

The development of non-peptidyl, insulin mimetic drug molecules has been considered one of the "holy grails" in pharmaceutical medicine and has been pursued by a number of major pharmaceutical companies,[60] albeit with limited success to date. The competitive advantage for these insulin mimetics may include cost and ease of manufacture, chemical and formulation stability, reduced probability of immune

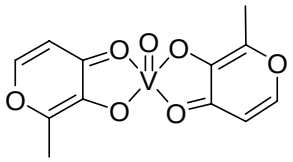
* Defective metabolism of fat.

response, and the rapid acceptance of an orally delivered drug. Such non-peptidyl insulin mimetics may also have unique advantages in controlling body weight and may provide a novel approach for the treatment of obesity and related metabolic disorders. Some vanadium-based insulin mimetics, and compounds developed from a non-peptidyl fungal metabolite have been reported but these compounds have not yet proved successful for the treatment of diabetes.[61,62]

It was discovered nearly 28 years ago that vanadium(V) as vanadate and vanadium(IV) as vanadyl can mimic the effects of insulin. Many organic ligands have been developed to form vanadium complexes to reduce the toxicity and to improve the aqueous solubility and lipohilicity.[63] In 1999, Guo and Sandler reported some less toxic vanadium complexes with various different ligands being tested (**Figure 1.5**).[64] However these compounds have a narrow therapeutic index before toxic effects (such as gastrointestinal stress) start to take effect.



bis(methylpicolinato)vanadium derivative



bis(maltolato)oxovanadium

Figure 1.5 Examples of organic vanadium complexes with insulin like activity[64]

Recently, several new approaches to deliver insulin orally have been reported. Drinkable oral insulin liquid and capsules from Helmy,[65] nanoparticles consisting of chitosan and poly-γ-glutamic acid from Lin[66] and absorption promoters and enhancers from Ghilzai[67] are a few developments in progress. However, these methods are also at an early stage of development and suffer many of the problems

discussed earlier that are associated with the inhaled and "patch" insulin. Therefore, an entirely organic insulin mimetic compound would be highly desirable.

Recently, researchers at the Western Australian Biomedical Research Institute (WABRI) at Curtin University of Technology found small molecule insulin mimetics: these compounds bind to the insulin receptor, promote the autophosphorylation and tyrosine kinase activity of the insulin receptor and lead to the downstream events associated with insulin action. One of the reported leading compounds, named **IM140** (**Figure 1.6**), is active in an animal model of diabetes.[53] However, it lacks potency and its properties for oral delivery are less than optimal.

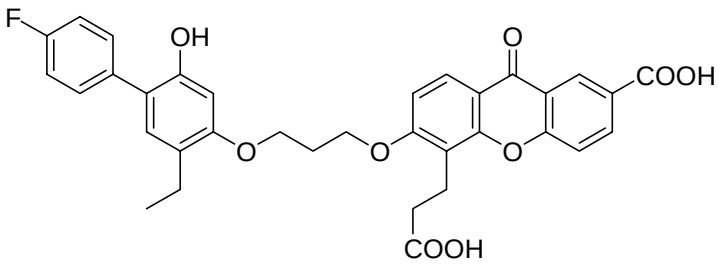
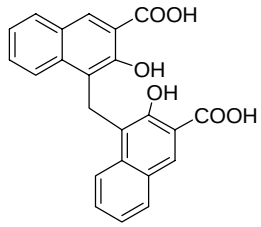


Figure 1.6 Structure of **IM140**[53]

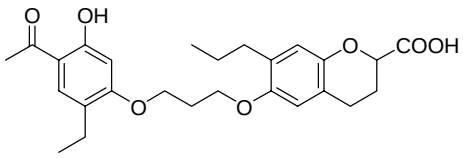
1.5 Early lead compound (IM140) summary[53]

1.5.1 Origin of the Insulin Mimetics project

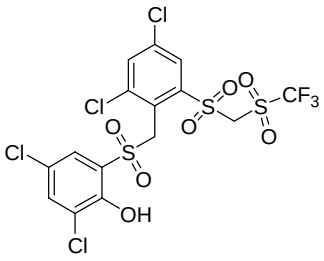
When the biochemists from WABRI were studying the mechanism of insulin binding to the insulin receptor at the molecular level,[18] four amino acid residues were found to be more important than the others. Therefore the eleven-point binding model was simplified into a four-point binding model and the research was directed to find small molecules fitting this model to be used as templates for the development of new drugs for treating diabetes. Of the series of compounds initially tested, four compounds, **IM25**, **IM71**, **IM103** and **IM175** (**Figure 1.7**) were identified to competitively bind to the insulin receptor. The activities of these compounds were 186, 137, 48 and 108 μM, respectively (**Figure 1.8**). The analogue activity was tested by endocrinologists from WABRI using a competition biding assay for the insulin receptor against radio-labelled insulin.



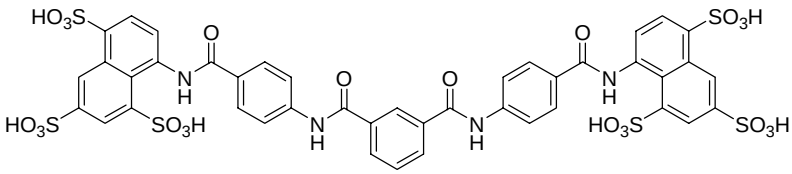
IM125



IM71



IM103



IM175

Figure 1.7 Structures of **IM25**, **IM71**, **IM103** and **IM175**[53]

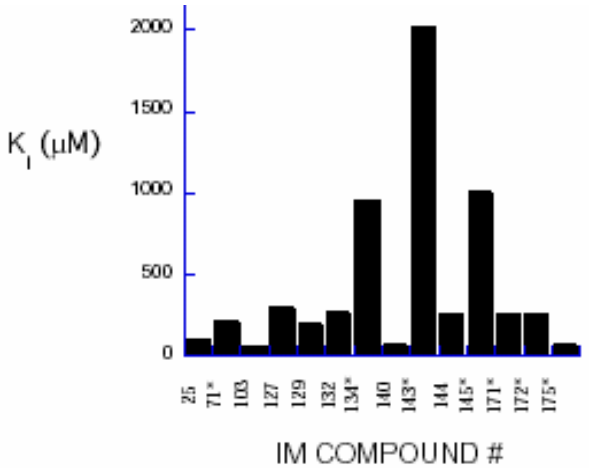


Figure 1.8 Biological activities of IM compound[53]

IM71 and **IM103** were then used as search queries, resulting in the identification of 58 compounds. Of these, 19 were available for screening. Ten of these compounds, **IM127**, **IM129**, **IM132, IM134, IM140, IM143, IM144, IM145, IM171 and IM172** (**Figure 1.9**), competed with ^{125}I labelled insulin for binding to the insulin receptor, with activities ranging from 1 μM for **IM140** to 2000 μM for **IM143** (**Figure 1.8**). All of these compounds except **IM145** were derived from **IM71**. Each compound was classified as either an agonist* or antagonist† of insulin action by testing the activity of each compound in a number of bioassays. The bioassays included an immunoassay that specifically measures the tyrosine kinase activity of insulin receptors and an assay that measures the ability of compounds to promote glucose uptake into 3T3-L1 adipocytes (fat cells). The specificity of the compounds was also evaluated by comparing their ability to displace radio-labelled insulin and insulin-like growth factor-1 (IGF-1) from their respective, cognate receptors. Two compounds, **IM140** and **IM175** were classified as agonists. The other 10 compounds were classified as antagonists of insulin action. The two agonists may be developed as insulin mimetics, while the antagonists may be useful for treatment

* A chemical that activates a specific receptor to induce a full or partial response
† A chemical capable of counteracting the effects of other drugs

of insulin overdose, insulinomas [*] and other causes of hyperinsulinaemia. [†]

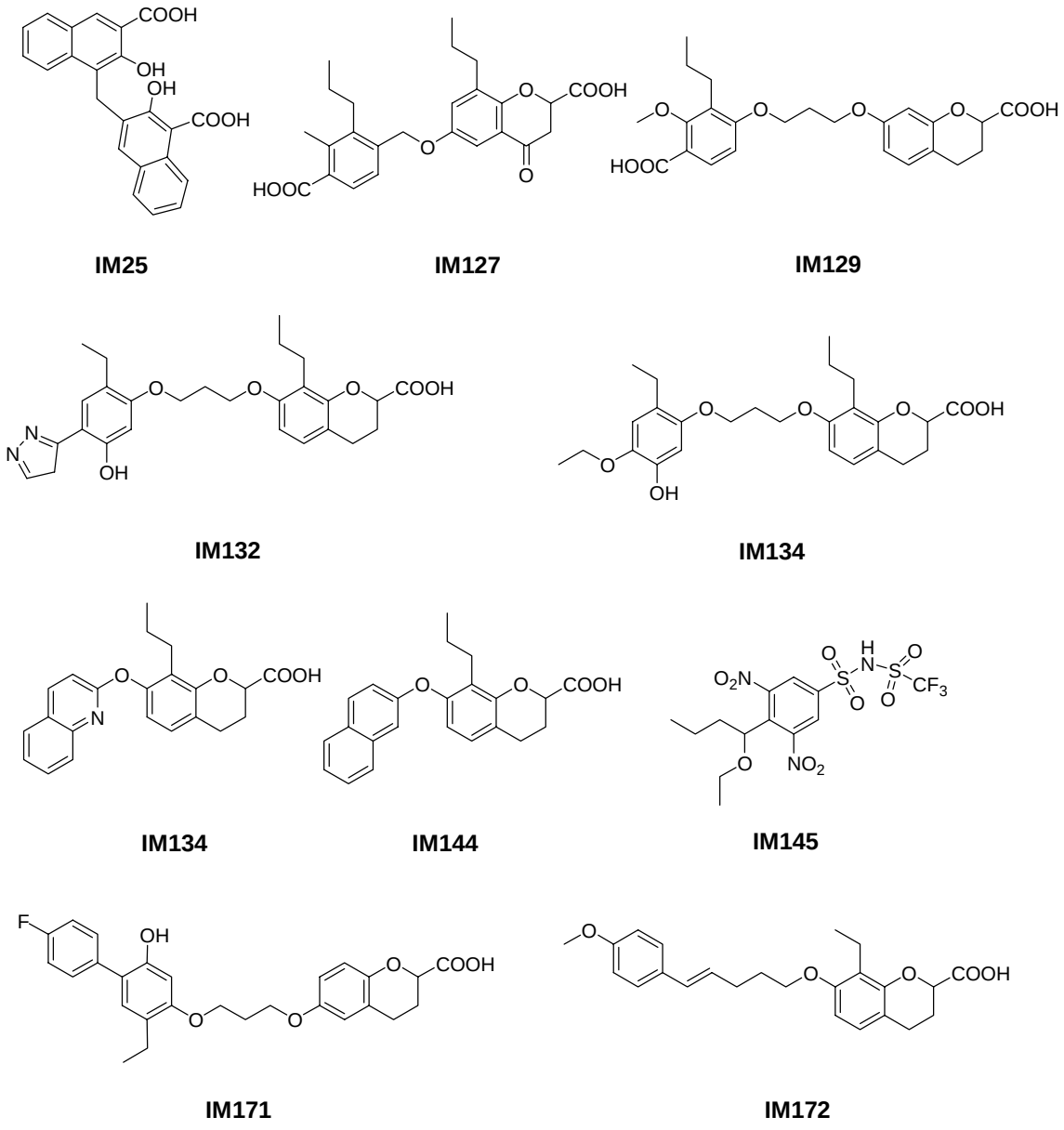


Figure 1.9 Structures of 10 antagonists[53]

Insulin-like growth factor-1 (IGF-1) is a growth factor which has a very similar sequence to insulin and it was evaluated as a stringent marker of specificity because IGF-1 and insulin are homologous proteins. **IM140** was much more specific as a competitor for insulin binding (1 μM) than IGF-1 binding (at concentrations up

[*] A benign tumor of β-cells of pancreas which may produce signs of hypoglycemia
[†] The presence excess insulin in blood

to 1000 μM, **IM140** was completely ineffective in displacing IGF-1 binding). In contrast, **IM175** was over 4-fold more specific for the IGF-1 receptor (30 μM) than for the insulin receptor (130 μM). **IM140** and **IM175** also promoted the tyrosine kinase activity of the insulin receptor and the uptake of glucose into 3T3-L1 adipocytes in accord with their relative binding potencies. At a submaximal dose of insulin, these effects were additive with insulin in each assay. In a preliminary animal trial, in streptozotocin* induced diabetic mice, **IM140** was delivered by injection and found to lower blood glucose levels in a statistically significant and dose dependent manner (**Figure 1.10**).

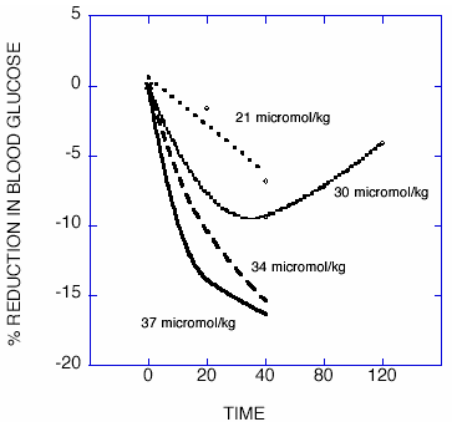


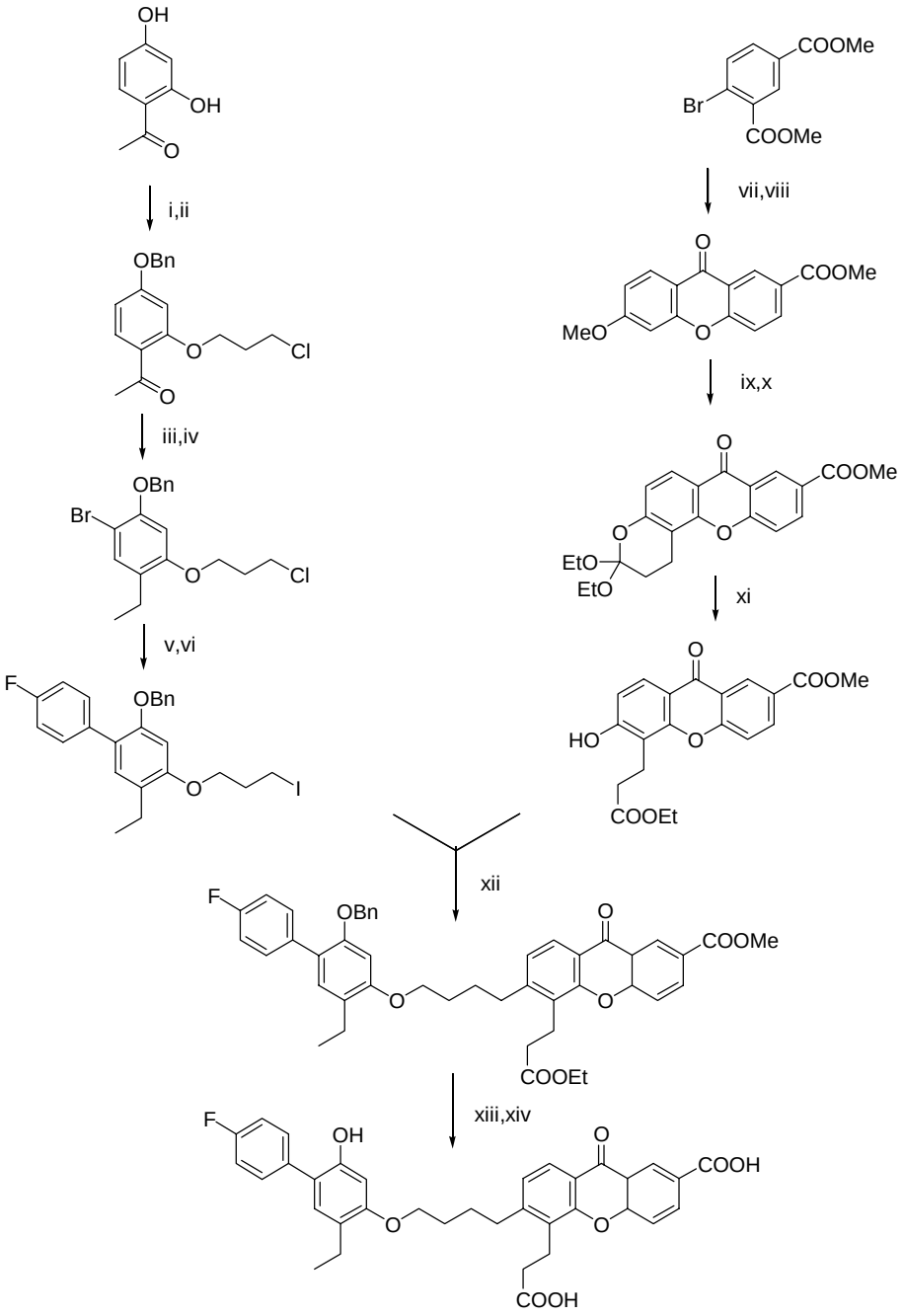
Figure 1.10 Biology activity of **IM140**†

1.5.2 Synthesis of IM140

The synthesis of **IM140** (**Scheme 1.1**) reported by Saweyer *et al*. is a lengthy, multi-step convergent procedure.[68] The strategy of **IM140** synthesis is to prepare the biphenyl and xanthone moieties separately and link the final product, which allows the preparation of a large number of analogues. For example, 7 different biphenyl

* An antibiotic which actives against tumors but damages insulin-producing cells
† Courtesy of E. Helmerhorst and B. Plewright, Curtin University of Technology

derivatives (LHS) can be coupled to 5 different xanthones (RHS) to deliver 35 analogues.



Reaction reagents: i) $PhCH_2Br$, K_2CO_3, butanone; ii) $BrCH_2CH_2CH_2Cl$, K_2CO_3, butanone; iii) Et_3SiH, trifluoroacetic acid, CCl_4; iv) NBS, CCl_4; v) 4-fluorophenylboronic aicd, EtOH, benzene, aqueous Na_2CO_3, $Pd(PPh_3)_4$; vi) NaI, butanone; vii) Cu, K_2CO_3, pyridine, 3-methoxyphenol; viii) aq. NaOH; methanesulfonic aicd, P_2O_5; ix) pyridine-HCl, MeOH/HCl; x) $(EtO)_3CCH=CH_2$, H^+, toluene; xi) EtOAc, aq. HCl; xii) K_2CO_3, KI, butanone; xiii) H_2, 10% Pd/C, EtOAC; xiv) aq. NaOH, MeOH, THF.

Scheme 1.1 Synthesis of **IM140**

The synthesis of the xanthone right hand side is the main source of difficulty in the **IM140** synthesis scheme. The first step of this synthesis is an Ullman coupling using a copper bronze catalyst with a low yield (~30%). Hence it would be desirable to develop a much simpler right hand side, with biaryl or triaryl systems being an ideal substitute.

1.5.3 Analogues of IM140

IM140 has many hallmarks that make it appropriate as a lead for the development of insulin mimetics. For example, two key chemical features of **IM140** are the presence of a biphenyl moiety and carboxylic acid functional groups, which are both "privileged" substructures appearing in many successful drug molecules and play a major role in molecular recognition. Therefore the main strategy is to maintain those essential substructures and to modify other groups to discover better analogues as insulin mimetics. These analogues should have acceptable physical properties for oral purposes and excellent biological activity to be a drug.

1.5.3.1 Physical properties

Physical properties have a profound influence on molecules' chemistry and biological activity. Typical bioavailability parameters for oral delivery of a "drugable" molecule include absorption and permeability, aqueous solubility, lipophilicity, dissociation constant and solution/solid-state stability. A number of computational programs are available for profiling compounds with pharmaceutical properties.

As an orally administered drug, it must be absorbed and reach the bloodstream or the site of action. Permeability and solubility are the two most important factors influencing oral absorption of drugs. With the rapid rise of the pharmaceutical industry, computational chemists have developed many programs to calculate molecular properties including permeability and solubility. Lipinski's "Rule of 5"[*] is one of the most widely used rules for predicting the absorption and permeability.[69] "Rules of 5" states that poor absorption or permeation is likely when:

1. There are more than 5 H-bond donors (expressed as the sum of –NH and –OH groups);
2. The molecular weight is more than 500;
3. log P (lipophilicity) > 5 (or Mlog P > 4.5); [†]
4. There are more than 10 H-bond acceptors (expressed as the sum of nitrogen and oxygen atoms).

If a compound violates more than two criteria, it is likely to encounter absorption and permeability issues. Substrates for biological transporters and peptidomimetics are exempt from these rules.

Aqueous solubility is the most important pharmaceutical property in controlling drug efficiency. The computational prediction for solubility has been established for many years since the initial work published by Yalkowsky *et al.*[72] The overall accuracy of the predicted values can be in the vicinity of 0.5 to 1.0 log unit. Although the selection of new drug candidates can not be made only on the basis of these predicted parameters, these predictions may help to direct improvements in targeting molecules to optimize their drug-like properties.

[*] "Rule of 5" is named because each of the four parameters are all close to 5 or a multiple of 5.
[†] MLog P means Log P calculated by the method of Moriguchi.[70,71]

Lipophilicity is defined as the ability of a chemical to dissolve in fat or non-polar solvents. The partition coefficient (*P*) is a measure of how a compound partitions between an organic phase and water phase. It is defined in **Eq. 1.1** whereby the log *P* is defined as lipophilicity. Lipophilicity has been shown in Lipinski's "Rule of 5" to be critical for oral absorption and permeability.

$$P = \frac{[\text{Species}]_{\text{Org}}}{[\text{Species}]_{\text{Water}}} \qquad \textbf{(Eq. 1.1)}$$

1.5.3.2 Biology activities

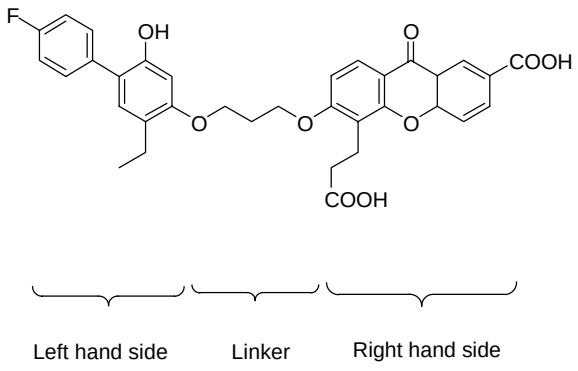
The active pharmacophore of insulin which yielded **IM140** was used to design novel and potent molecules as insulin mimetics. The molecules were designed by considering the distances and torsion angels between the various features of the pharmacophore. The conformational space of the designed molecules was searched and representative low-energy conformations were selected for further analysis. Each conformation was superimposed on the pharmacophore features and its Root Mean Square Deviation[*] (RMSD) was determined. Finally, an average RMSD value of all conformations was used as a measure of accuracy of fit, in order to give an indication of the molecule's ability to take up the conformation of the pharmacophore.

[*] Often used in 3D geometry of molecules to measure structure similarity.

The designed molecules were also docked onto the binding site of the insulin receptor using the program $F_{LEX}X^{*}$, which was developed by Rarey *et al.* in 1996.[73] The resulting binding models were energy minimised and analysed for consistency with the pharmacophore hypothesis. The prediction of binding models provides a fuller picture of the likely molecular interactions responsible for activation of the insulin receptor and suggests ways of enhancing such interactions. Docking computations also yield predictions of the free energy of binding which can be used to rank compounds on the basis of their potential binding affinity to the insulin receptor. This part of the molecular modeling was carried out by the WABRI molecular modeling team.

1.5.3.3 Modification of IM140 and first generation analogues

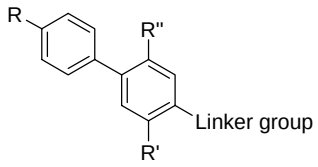
Since the synthesis of **IM140** starts from relatively simple starting materials, there is much potential for modification to produce analogues. Through the synthesis and testing of such analogues, a better understanding of how these compounds interact with the insulin receptor may be obtained. For the purpose of developing analogues, the structure of **IM140** can be divided into three regions: a left hand side (LHS), a linker group and a right hand side (RHS) (**Figure 1.11**).



[*] $F_{LEX}X$ is a program which is used for molecular docking based on an incremental construction strategy. It considers ligand molecular flexibility including multiple conformations for ring systems. The scoring of the placements is performed with a variant of Böhm's empirical scoring function

Figure 1.11

The left hand side is a relatively simple structure and has some potential for further simplification by the removal of the ethyl and hydroxyl groups; indeed developing analogues without these components could be used to gauge the role these groups play in binding to the insulin receptor. A similar strategy can be applied to the fluoro group, by replacing it with different substituents (**Figure 1.12**).



R=F,CF_3,H
R'=Et, H
R''=OH, H

Figure 1.12

There are also potential alternatives for the linker being used in **IM140**. The current propanediol linkage provides a flexible structure, but its flexibility might decrease the specificity of the binding to the insulin receptor. A less flexible structure would be ideal to restrict the functional groups to a precise configuration. Therefore some analogues with a fixed, planar linker were proposed. Less flexible linkers which are similar in length to the propanediol-based link were chosen, including amide-based linkers and bishydroxymethylbenzene-based linkers (**Figure 1.13**).

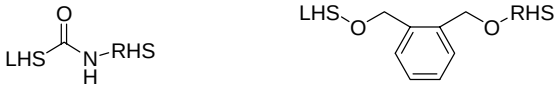
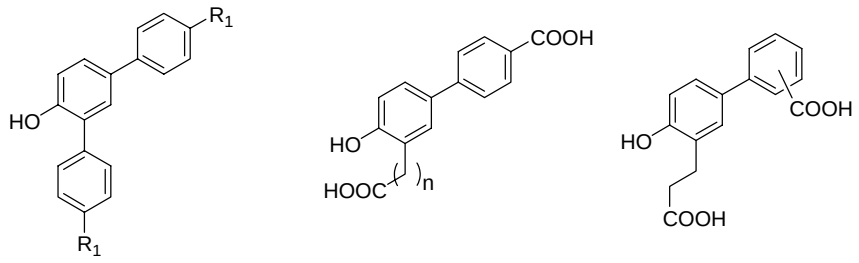


Figure 1.13

Alternatives to the right hand side xanthone group are being investigated in an effort to develop a synthetically more amenable group (without compromising the biological activity), as this is an important criterion for commercialization. Synthesis of the xanthone group is currently the rate limiting process. The key questions to be addressed with respect to the xanthone portion are i) the importance of the two carboxylic acid groups; ii) the impact of changing the length of the carbon chain bearing the carboxylic acid groups; iii) the need for the structurally rigid xanthone scaffold. Therefore, this thesis will focus on the synthesis of compounds replacing the xanthone group with a biphenyl or triphenyl group. Some modification to the right hand side that will be considered for the production of new analogues is shown below (**Figure 1.14**).

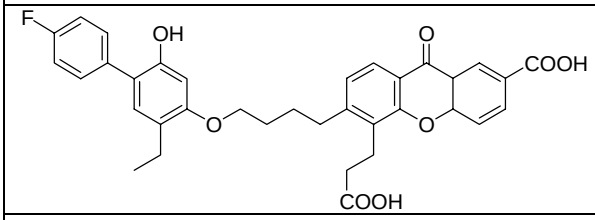
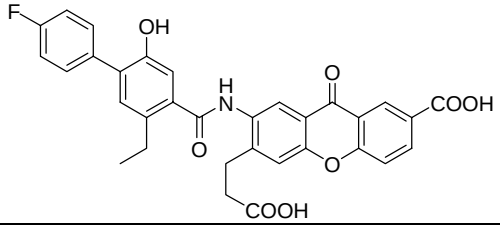
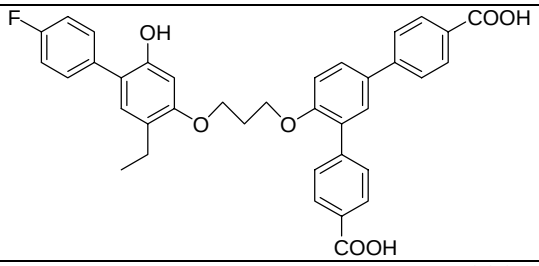
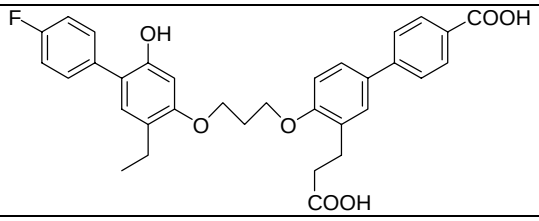


R_1 = carboxylic acid or tetrazole n = 0, 1, 2

Figure 1.14

Table 1.1 illustrates the key physiochemical data and molecular modeling predictions calculated for **IM140** and synthetic targets. **Appendix I** provides a more comprehensive list of compounds for which the calculations were made. However, it must be recognized that the insulin receptor model provides a guide only, and a crystal structure with ligand bound within its binding pocket is not yet available. Validation of activity of the selected compounds demands their careful analysis in a series of bioassays.

Table 1.1 Computational calculations for **IM140** and some analogues

Structure	ClogP[*******]	%HIA[††††††††]	Pharm. Fit[‡‡‡‡‡‡‡] (RMSD)	Mol. Wt.
	-0.45	40.0	2.87	598.6
	1.91	63.0	2.88	567.5
	1.74	63.0	2.74	604
	-0.23	64.0	2.89	556.6

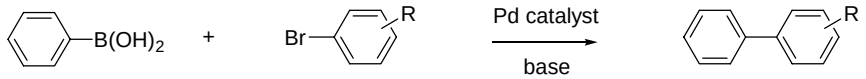
Since the left and right hand sides of designed targets are biaryls/triaryls, the most important chemistry involved in this thesis will be the formation of biaryls. Compared to the synthesis of xanthone moiety, the synthesis of biaryl/triaryl moieties is much easier and provides more scope for variety. This is especially true since the Suzuki cross coupling reaction was developed. In order to synthesize

[*******] Calculated Log*P*.
[††††††††] Human intestinal absorption. It is the dose of orally administered drug that reaches the hepatic portal vein. The molecules are classified as low absorption 0-20%, medium 21-69% and high 70-100%.
[‡‡‡‡‡‡‡] Fit of the molecule onto the pharmacophore. The lower the value, the better the fit.

unsymmetrical multifunctional biaryls for both the left and right hand sides, an understanding of the Suzuki cross coupling reaction is necessary.

Part B: The Suzuki cross coupling reaction§§§§§§§

Biaryls and their homologues are common important skeletons of functional molecules or materials such as liquid crystals, ligands, polymers and molecules of medicinal interest.[74] The increasing importance of biaryls has led to rapid progress in the development of synthetic methodologies for the construction of these moieties. The formation of a carbon-carbon bond between two aromatic rings is the key step in building the biaryl framework. In order to form these molecules from two monoaryl precursors, many catalytic methods have been developed. During the past forty years the most important cross-coupling reactions such as Kumuda coupling,[75] Negishi coupling,[76] Stille coupling,[77] Heck coupling,[78] Sonogashira coupling,[79] Buchwald coupling[80] and Suzuki coupling[81] have involved the use of transition metal catalysts to control chemoselectivity and hence productivity. Currently the most versatile method for the synthesis of substituted biaryls is the coupling reaction of an aryl halide and an organoboron in the presence of a palladium catalyst and a base (**Scheme 1.2**). This method was developed by Akira Suzuki and is commonly known as the Suzuki coupling reaction (also known as the Suzuki-Miyaura coupling reaction).



Scheme 1.2 The Suzuki coupling reaction

§§§§§§§ Due to the extensive application of the Suzuki coupling reaction, this introduction will focus on the formation of biaryls which is relevant to this thesis

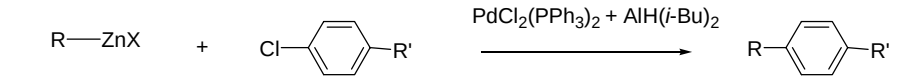
1.6 Development of cross coupling reactions

In 1972, the first cross-coupling reaction of a Grignard reagent and an alkenyl- or aryl- halide catalyzed by a Ni(II) complex [**Scheme 1.3(a)**] was reported by Kumada and Tamao.[75] Three years later, the palladium-catalyzed reaction involving a Grignard reagent was first reported by Murahashi.[82] This coupling reaction was widely extended by Negishi using organo-zinc and aluminum reagents [**Scheme 1.3(b)**].[83] Unlike the Kumada coupling, the Negishi coupling reaction tolerates functional groups such as esters, amines, nitriles and nitro groups.

R= Et, *n*-Bu

dppe= 1,2-bisdiphenylphosphinoethane

(a) Kumada coupling



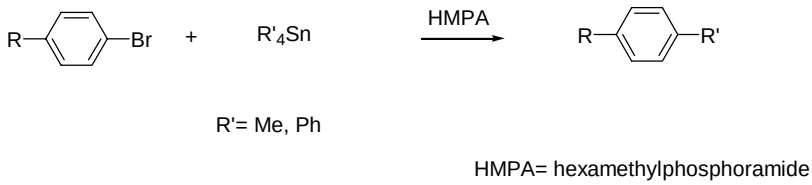
X= Br
R= Ar, $ArCH_2$

R'= OCH_3, NO_2, CN, $COOCH_3$

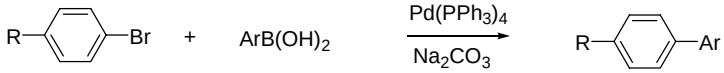
(b) Negishi coupling

Scheme 1.3

In 1979, the Stille reaction was developed for the synthesis of biaryls from arylstannanes ($ArSnR_3$) and aryl halides or triflates [**Scheme 1.4(a)**].[77] The Stille reaction is very versatile and can proceed under mild conditions, but the toxicity of the organotin reagents and byproducts are two major drawbacks of this reaction.[84] In the same year, when the Suzuki group was trying to synthesize conjugated dienes stereo- and regioselectively, it was found that the cross coupling of an aryl halide and an aryl boronic acid proceeded very well in the presence of a palladium complex and a base [**Scheme 1.4(b)**].[81] This reaction proved to be extremely versatile and had many advantages such as the ready availability of structurally diverse boronic acids,[85] low-toxicity and mild reaction conditions, including the use of aqueous solvents.



(a) Stille reaction



(b) Suzuki reaction

Scheme 1.4

1.7 Mechanism of Suzuki coupling reaction

From the mechanistic viewpoint, Suzuki proposed a catalytic cycle for the Suzuki cross-coupling reaction, as shown in **Figure 1.15**.[86] This catalytic cycle superficially explains the mechanism of the Suzuki coupling reaction, which involves three main steps: oxidative addition, transmetalation, and reductive elimination. Firstly, the cycle is initiated by the oxidative addition of the aryl halide to a Pd(0) species. Secondly, the transmetalation of a nucleophilic carbon atom from boron to Pd produces the intermediate R^2-Pd(II)-R^1. Finally, reductive elimination of the cross-coupling product creates the desired product R_1-R_2 and regenerates the Pd(0) catalyst for a new circulation. Although many of the processes, including ligand exchange, are not yet clear, the presence of the two intermediates R^2-Pd(II)-X and R^2-Pd(II)-R^1 have been characterized by electrospray mass spectrometry.[87]

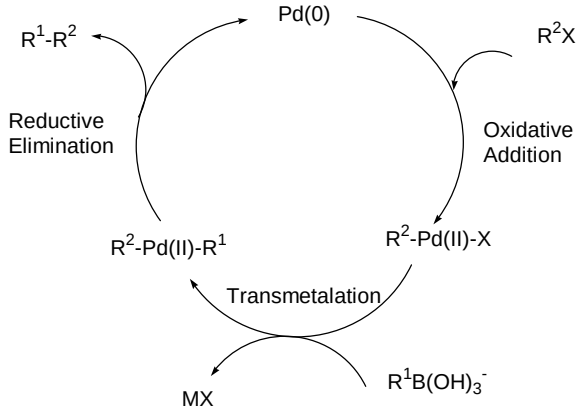


Figure 1.15 Suzuki catalytic cycle

It is now widely accepted that palladium(0) is stabilized by ligands and isomerization occurs after the oxidative addition and before the reductive elimination.[83-87] A modified mechanism for the Suzuki coupling reaction has been proposed (**Figure 1.16**).[88]

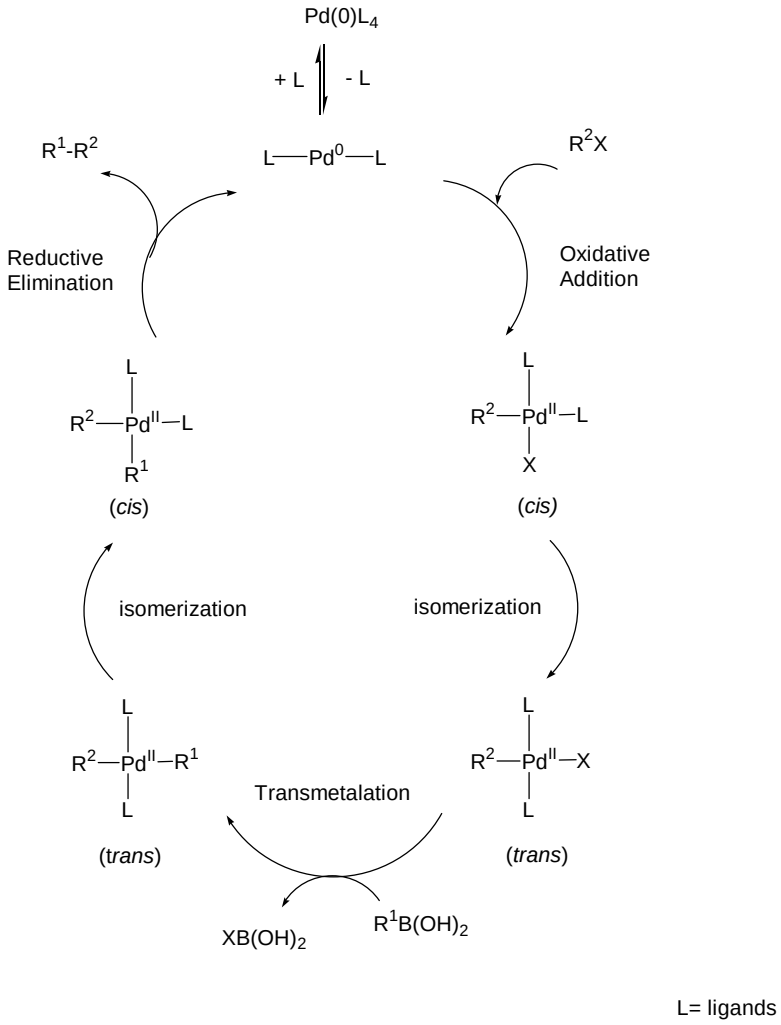


Figure 1.16 Expanded Suzuki catalytic cycle

First the active 14 electron palladium(0) catalyst is generated from the 18 electron palladium(0) reagent e.g. $(Ph_3P)_4Pd$. Oxidative addition to the zerovalent palladium complex is believed to proceed *via* a concerted insertion of the PdL_2 moiety into the R-X σ bond.[89] The initial products have a *cis* structure, but in most cases, the isolated products are in *trans* configuration.[90] It can be presumed that the addition is a two-step sequence: oxidative addition followed by isomerization (**Figure 1.17**).[91] This addition is slow and is often the rate-determining step in the catalytic cycle. Generally, the reactivity of halides and triflates for oxidative addition decreases in the order: I>OTf>Br>>Cl.

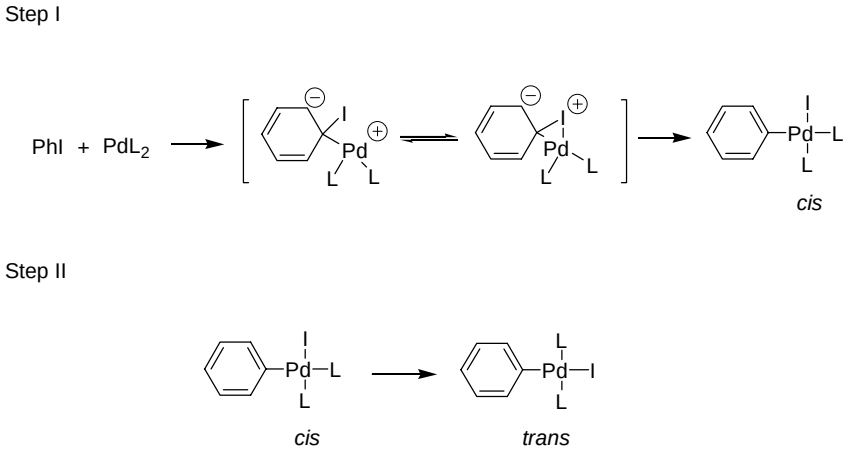


Figure 1.17

For the transmetalation process there are two main proposals: path A and path B (**Figure 1.18**).[92] In path A, the base attacks the organoboronic acid to form the borate, $RB(OH)_2(OR')^-$, which reacts with the organopalladium complex to produce the complex *trans*-$PdR^1R^2L_2$. In path B, the base substitutes the halide on the palladium species to form an (oxo)palladium(II) complex,[93] which undergoes transmetalation with the boronic acid to provide the complex *trans*-$PdR^1R^2L_2$.

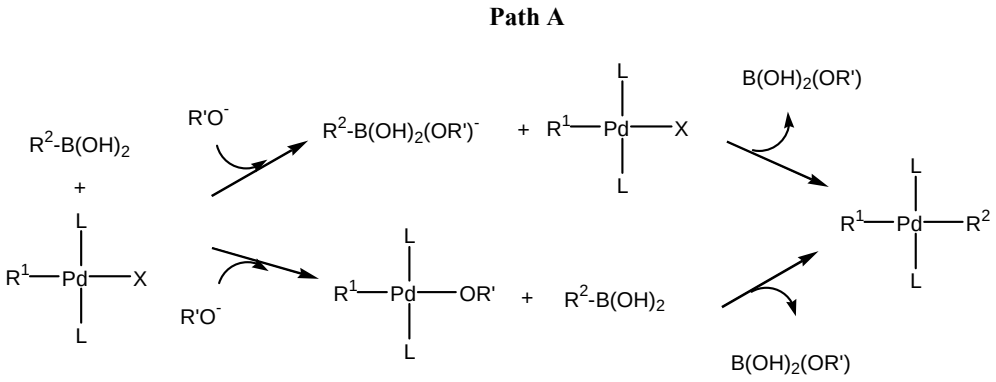


Figure 1.18

In the next step, isomerization of the *trans*-$PdR^1R^2L_2$ isomer affords the *cis*-isomer.[94] The interconversion is practically thermoneutral since the *trans* isomers are only slightly more thermostable than the *cis* isomers. In the case of the complex $Pd(PPh_3)_2(HC{=}CH_2)_2$, the energy level of the *trans* isomer is 15.5 kJ/mol more

favourable than the *cis* isomer.[88] Reductive elimination occurs following isomerisation to the *cis*-isomer, which affords the biaryl product. This step is characterized by the reduction of the formal oxidation state and the coordination number by two.[94] Most of the Suzuki coupling reactions undergo this process *via* a four-coordinate complex (**Figure 1.19**).[95]

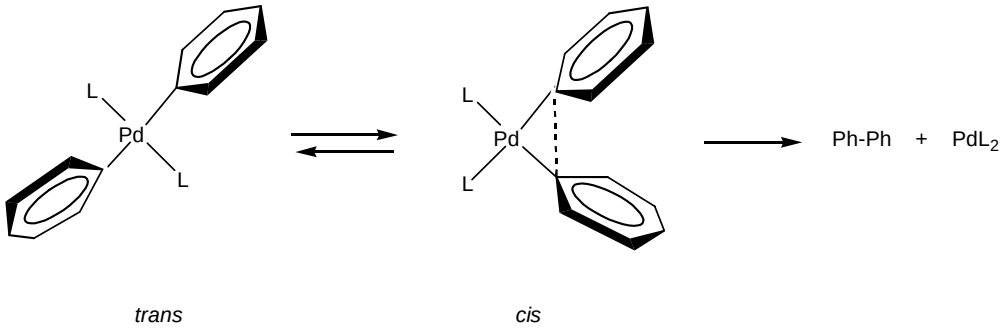


Figure 1.19

1.8 Suzuki coupling reaction developments

There are four important elements in the Suzuki coupling reaction: a palladium catalyst; an organohalide; an organoboron and a base. Since the discovery of the Suzuki coupling reaction, various modifications have been made on these four elements. Numerous palladium pre-catalysts or co-ligands have been developed. Reaction conditions, yields, efficiency and versatility have been extensively improved.[85] Many aryl bromides, iodides and trifluoromethanesulfonates (triflates) have been used in the Suzuki reaction in the past years, but recently new catalysts have allowed the use of aryl chlorides, which are cheaper and more diverse.[96,97] A number of bases have also been used such as Et_3N,[98] Cs_2CO_3,[99] and K_3PO_4,[100] as well as different temperatures and reaction solvents including water.[101]

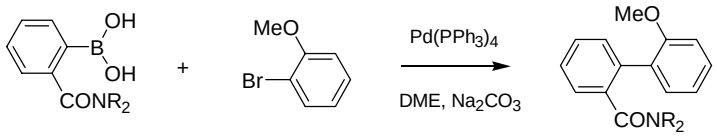
1.8.1 Catalyst development

Palladium catalysts can be divided into three main groups based on the type of the ligands: catalysts with phosphine ligands, catalysts with phosphine-free ligands and "ligand-free" catalysts.

1.8.1.1 Catalysts with phosphine ligands

Phosphine ligands are the most common ligands used for the palladium pre-catalyst used in the Suzuki coupling reaction. There are a series of factors which are responsible for the success of these complexes: i) the phosphine-based catalyst are generally stable under prolonged heating; ii) electron rich phosphine ligands accelerate the rate of oxidative addition; iii) the basic phosphine attaches to the palladium atom tightly to form the palladium complex and prevents Pd metal precipitating; iv) the sterically bulky structure of the ligands enhances the rate of reductive elimination.

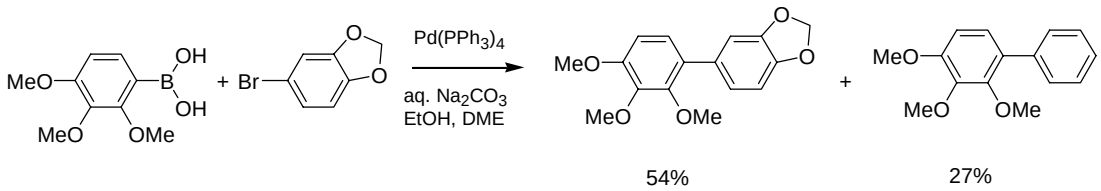
Among all the available phosphine ligands the most popular and frequently used is triphenylphosphine, commonly as tetrakistriphenylphosphinepalladium(0) [$Pd(PPh_3)_4$]. This catalyst is versatile, unaffected by the presence of water, tolerates a wide range of functionality and does not generate toxic byproducts. A combination of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in dimethoxyethane (DME) has proven to be successful in the Suzuki cross coupling reaction as reported in the literature (**Scheme 1.5**).[102]



R= *i*-Pr

Scheme 1.5

However, there are two main drawbacks with the use of $Pd(PPh_3)_4$ which limits its application: the formation of undesired coupled byproducts (either from homocoupling between aryl halides or aryl boronic acids or with phenyl group of the ligand) and high sensitivity towards oxygen.[103] In 1992, Marcuccio *et al.* reported the formation of a byproduct caused by coupling of an aryl boronic acid and a phenyl group from the triphenylphosphine ligand (**Scheme 1.6**).[104]



Scheme 1.6

In order to increase the activity of the catalyst and eliminate the formation of byproducts, numerous new ligands have been developed including 1,1-bis(diphenylphosphanyl)ferrocene (dppf) and tri-*o*-toluylphosphine [P(*o*-tol)$_3$].[105-107] Pre-catalysts made with these new ligands have a high turnover number and greatly reduce the problem of undesired coupling. A further significant improvement has been the development of palladacycle catalysts, where a bidentate metal ligand is bound to the ligand by P & C-donor groups (**Figure 1.20**).[108] These palladacycle catalysts are comparatively inexpensive and able to give high conversion at very low concentration. The following (**Figure 1.20**) are some examples of high-efficiency catalysts.[109,110]

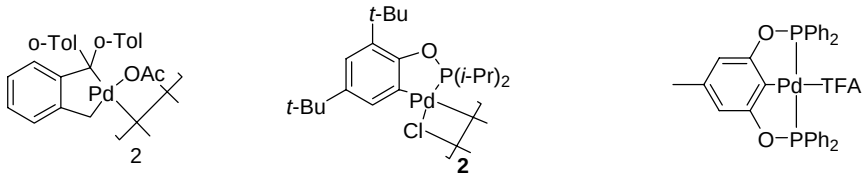
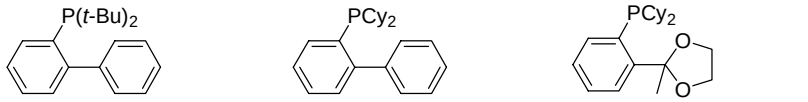


Figure 1.20 Palladacycle catalysts for Suzuki coupling

In recent years, many catalysts have been discovered that enable Suzuki cross-coupling with wide range of aryl chlorides. Generally, aryl chlorides are quite inert to oxidative addition because of the strength of the C-Cl bond [bond dissociation energy for phenyl halides (PhX) are 96, 81, 65 kcal/mol at 298K for X= Cl, Br, I respectively].[111] However, their low cost and the wide diversity of available compounds makes them attractive reagents. Remarkable progress was achieved in 1998 with the application of new ligands, such as P(*t*-Bu)$_3$, tricyclohexylphosphine (PCy_3) and 2-(di-*tert*-butyl-phosphanyl)biphenyl (**Figure 1.21**), together with $Pd(OAc)_2$ to achieve the coupling with aryl chlorides.[112] Since then, many metalphosphine systems have been discovered and many aryl chlorides have been used for the synthesis of biaryls (**Figure 1.21)**.[113,114] This includes palladium complex with electron rich phosphine ligands like $Pd_2(dba)_3{\cdot}CHCl_3$[********].[115]



cy= cyclohexylphosphine

Figure 1.21 New ligands for the coupling of aryl halides in Suzuki reactions

******** dba=dibenzylideneacetone

1.8.1.2 Catalysts with phosphine-free ligands

Traditionally phosphine-palladium complexes have been employed in the Suzuki coupling reactions, but their sensitivity to oxygen and high cost have become the major drawbacks, especially in large scale synthesis. Oxygen-free conditions are required to minimize the oxidation of phosphines and Pd(0) species. There has been a significant interest in the development of more effective phosphine-free catalysts and many advances have been made in this area. Many new palladium complexes have been developed bearing *N*-heterocyclic carbene (NHC) ligands (**Figure 1.22**).[116,117]

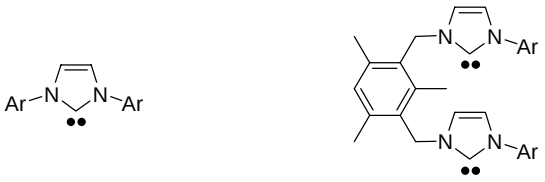
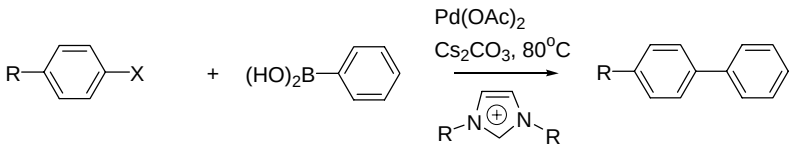


Figure 1.22 Examples of NHC ligands used in Suzuki coupling reactions

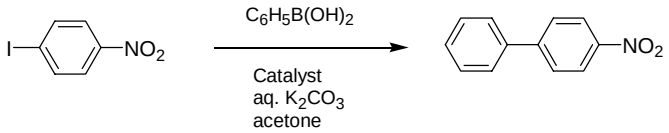
Nucleophilic *N*-heterocyclic carbenes, such as the imidazole-2-ylidenes, have been widely used as replacements for phosphine ligands in homogeneous catalysis (**Scheme 1.7**).[118,119] Interesting properties of the species include their extraordinary thermal stability and high dissociation energy of the Pd-NHC bond, which limits ligand dissociation and thus limits the requirement for an excess of ligand to prevent catalyst deactivation/decomposition.[119]



Scheme 1.7

1.8.1.3 "Ligand-free" catalyst

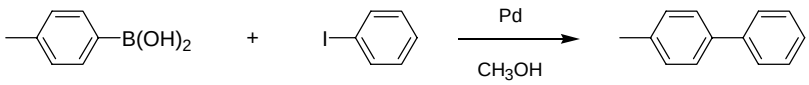
Catalysts with ligands are generally used since they are quite thermo-stable. However, very fast coupling reactions can be achieved by using palladium pre-catalyst such as $Pd(OAc)_2$ without additional complex ligands. Wallow *et al.* demonstrated this coupling reaction catalysed by a so called "ligand-free" catalyst system (**Scheme 1.8**).[120]



Catalyst
$Pd(OAc)_2$ 0.75 h 98%; cf. $Pd(PPh_3)_4$ 8 h, 23%

Scheme 1.8

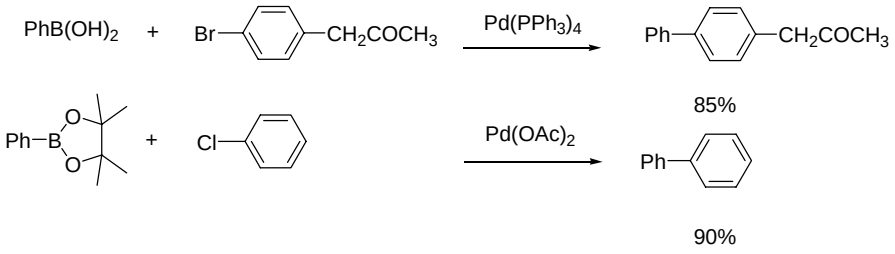
In 2001, Kabalka *et al.* reported that palladium powder and potassium fluoride were effective in coupling arylboronic acids and iodobenzene in methanol (**Scheme 1.9**).[121] The palladium metal can be recovered by simple decantation and the catalyst was used eight times without significant loss in the yield. In the same year, Leblond *et al.* reported that palladium on carbon with a judicious solvent system (dimethylacetamide:water, 20:1) was efficient in the coupling of *para*-substituted aryl chlorides and arylboronic acids.[122] More importantly, no homocoupled byproduct was formed using this heterogeneous system and the product was obtained selectively.



Scheme 1.9

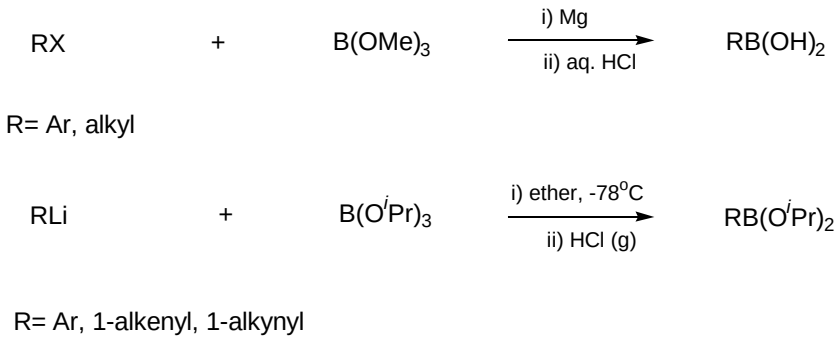
1.8.2 Preparation of organoboron reagents

Organoborons, including boronic acids and boronic esters, ††††††††† are important reagents in the Suzuki coupling reaction (**Scheme 1.10**)[123] and several methods for the synthesis of organoborons have been reported.[95,124,125] The popular methods are the synthesis from organomagnesium or organolithium reagents and aryl borates, or the hydroboration of alkenes and terminal alkynes.



Scheme 1.10

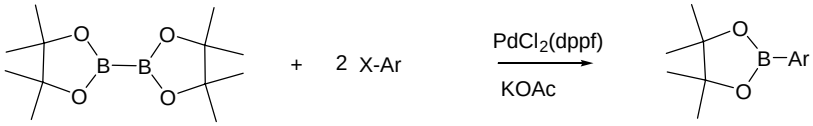
The classical synthesis of aryl- and 1-alkenylboronic acids, or their esters, involves the reaction of Grignard reagents or lithium reagents with an alkyl borates to provide relatively simple boron compounds in large quantities (**Scheme 1.11**).[125,126] The application of these procedures suffers from the formation of byproducts including di- and tri-alkylated boranes. A later development includes the use of organolithium reagents and triisopropyl borate to produce boronic esters in high yields, often in more than 90% yield (**Scheme 1.11**).[127]



Scheme 1.11

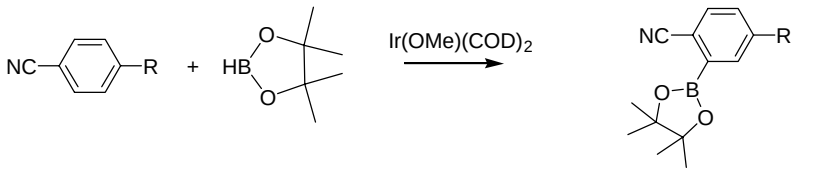
††††††††† Dialkylboranes were also used in the Suzuki reactions, but as they are not related to this thesis they will not be discussed here.

Arylboranes can also be prepared by a palladium-catalyzed cross-coupling reaction of the pinacol ester of diboronic acid and an aryl halide.[128] This reaction is catalyzed by $PdCl_2$(dppf) in the presence of KOAc and suitable for different functional groups such as cyano, ester and carbonyl groups (**Scheme 1.12**).



Scheme 1.12

Recently Ir-catalyzed borylation of 4-substituted benzonitrile was reported to synthesize a multifunctional arylorganoboron (**Scheme 1.13**).[129] Various functional groups are tolerated in this reaction.



R= NMe_2, COOMe, NHAc, CF_3

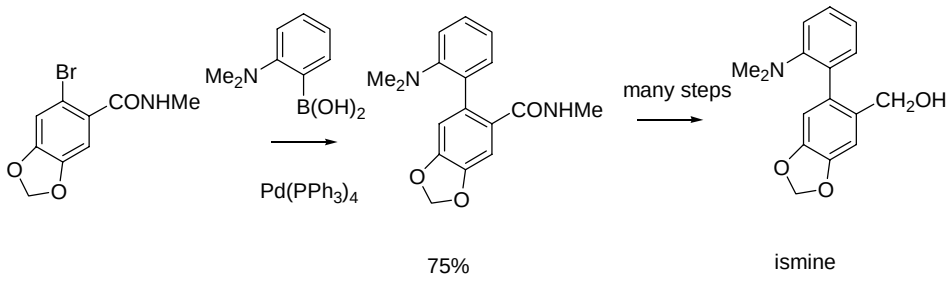
Scheme 1.13

1.9 Synthesis of biaryls and related applications

There are many advantages of the Suzuki coupling reaction, and it has been applied into a great number of areas, especially in synthesizing biologically active molecules. As an illustrative example, Eli Lilly built a pharmacophore for the nicotinic receptor from 18 known efficacious biaryls. Out of twenty-four potential agonist models, nine compounds were synthesized *via* Suzuki-coupling reactions and four of them had micromolar activity.[130]

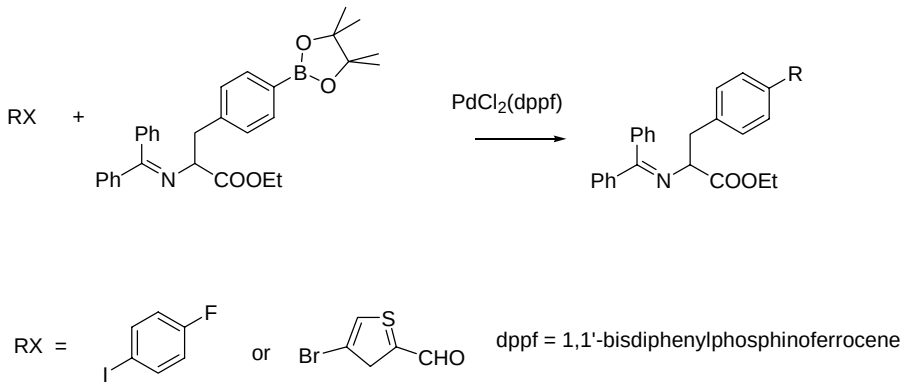
One of the key advantages of the Suzuki coupling reactions is its versatility. Many functional groups such as aldehydes, esters, amides and nitriles can be tolerated in this reaction, which makes this coupling reaction a common choice to synthesize biaryls, especially unsymmetrical, multifunctional biaryl analogues of **IM140**. A few examples are now detailed to demonstrate the versatility of this reaction.

Ismine, an aromatized relative of many of the more common *Amaryllidaceae* alkaloids, was isolated by Highet in 1961.[131] The initial synthesis using Diels-Alder reactions encountered an unexpectedly low yield,[132] but the new synthetic route *via* Suzuki coupling delivered the unsymmetrical product smoothly (**Scheme 1.14**).



Scheme 1.14

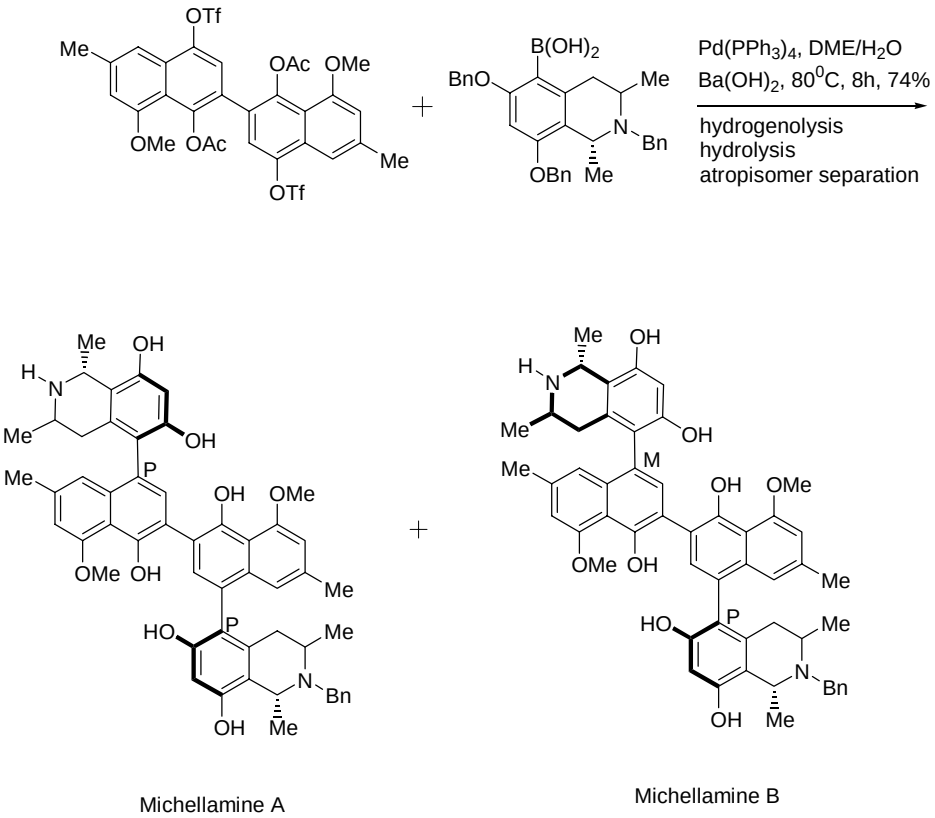
Recently, when Firooznia *et al.* synthesized a class of unnatural amino acids, including an imine, it was found that the Suzuki coupling reaction afforded the product in good yield, even in the presence of aldehyde and ester groups (**Scheme 1.15**).[133]



Scheme 1.15

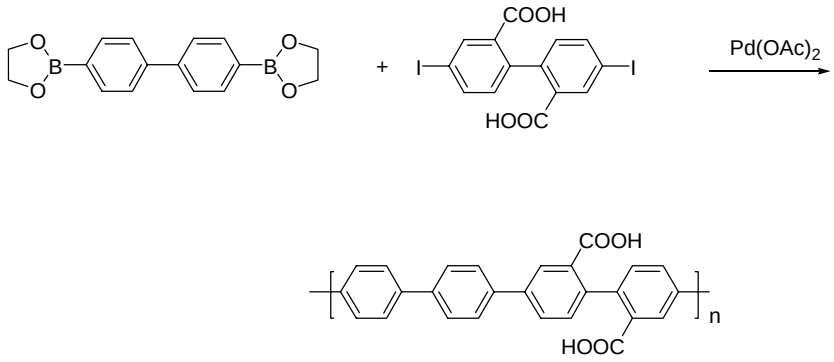
Triflates can be used in Suzuki coupling reactions as alternatives to the halides and this allows a wide range of readily available phenols to be used as precursors in coupling reactions. One of the examples is the synthesis of the anti-HIV alkaloids, michellamines A and B. These compounds have received considerable attention, especially after the United States National Cancer Institute published an announcement encouraging the research community to pursue synthetic and other studies aimed at the production of michellamine B.[134] The tetraaryl skeleton of the michellamines is constructed firstly through the formation of the inner (nonstereogenic) biaryl axis‡‡‡‡‡‡‡‡ followed by the formation of two other (stereogenic) axes *via* a double Suzuki-type cross-coupling reaction between a binaphthalene ditriflate and an isoquinolineboronic acid (**Scheme 1.16**).[135]

‡‡‡‡‡‡‡‡ Atropisomerism in biphenyls or binaphthalenes have been studied extensively. The existence of atropisomers in molecules is when the rotation is restricted by the structure. Oki has suggested when the free energy barrier is 61.5KJ mol^{-1} at 200K, 99.3 KJ mol^{-1} at 300K and 109.6 $KJmol^{-1}$ at 350K, the astropisomer can be isolated. It is difficult to isolate di-ortho substituted biphenyls unless substituents are large. However, an example of resolvable biphenyl astropismer is 1,1'-binapthyl.



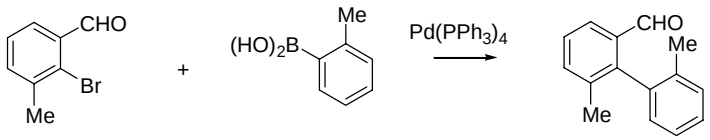
Scheme 1.16

Double or multiple Suzuki coupling reactions *in situ* can be performed conveniently, thus providing a new method to synthesize polymers. Aromatic, rigid rod-like polymers have been important targets in synthetic chemistry. These macromolecules play an important role in high-performance engineering materials, conducting polymers and nonlinear optical materials. The synthesis of the semiconductive, luminescent conjugated polymer was reported by Anderson *et al.* (**Scheme 1.17**).[136]



Scheme 1.17

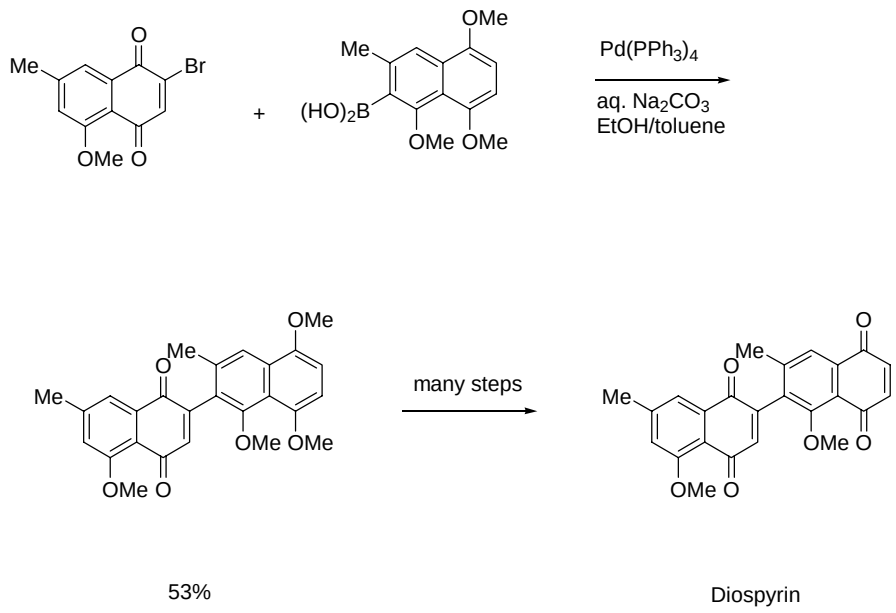
Steric hindrance has been a big problem in the cross-coupling step for the formation of substituted biaryls. Fortunately, this problem has not become a major concern for Suzuki coupling reactions. Konning *et al*. reported the Suzuki coupling of a sterically hindered bromide with boronic acids to give precursors for the synthesis of substituted phenanthrene derivatives in excellent yields (**Scheme 1.18**).[137]



Scheme 1.18

Additionally, steric hindrance of the organoboron units is also not a major factor for the Suzuki reaction. Diospyrin was first isolated in 1961 by Kapil and Dhar as an orange-red constituent of *Diospyros montana* Roxb. (*Ebenaceae*) §§§§§§§§.[138] In 2000, Mori and Yoshida reported the total synthesis by employing the Suzuki coupling reaction as a key step to connect the two 7-methyljuglone units (**Scheme 1.22**).[139] During this process, the hindered boronic acid does not significantly affect the formation of the biaryl species and the reaction yield is moderate (53%).

§§§§§§§§ A small or medium size tree found throughout India.



53%

Diospyrin

Scheme 1.19

Part C: Research aims and methodology

This project has two broad aims:

i) Synthesize and test first generation analogues of **IM140** including biaryl-, triaryl- and different linker analogues;

ii) Pursue a cross-disciplinary approach to the design, synthesis, testing and optimization of small oral insulin mimetics for the treatment of diabetes;

1.10 Strategy for synthesis of analogues

As discussed earlier, the modification will occur in the left hand side, the right hand side and the linker group (**Figure 1.23**). Therefore, the strategy of synthesis will be the convergent method, which means synthesizing both the left and right hand sides and then linking them with suitable linker group.

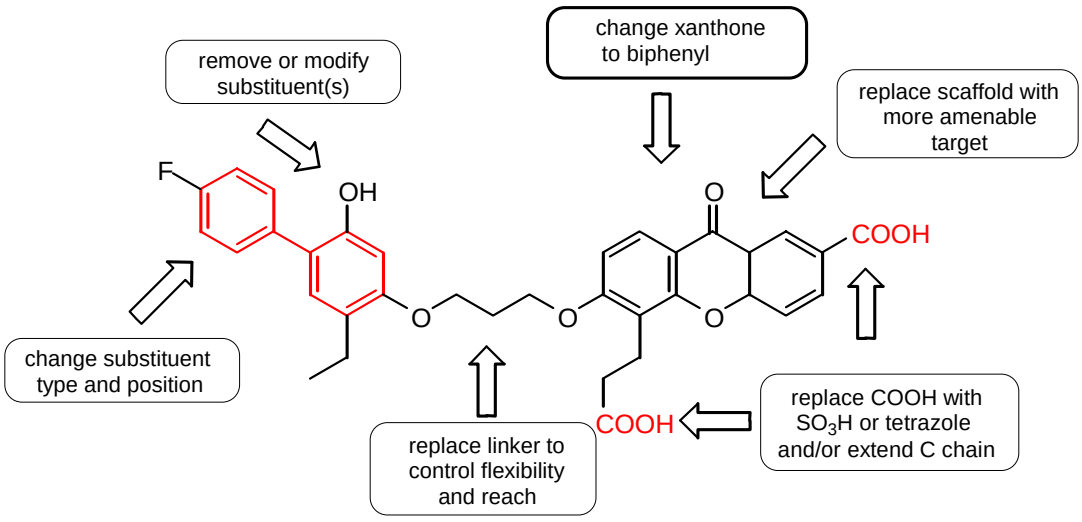


Figure 1.23 possible modifications to **IM140**

1.11 Bioassays

WABRI has a number of validated *in vitro* biological assays for measuring the insulin mimetic activity of analogues. It is not necessary for all the analogues to be tested in every assay. All the analogues will be funnelled down through a series of preliminary tests. Only those that have appropriate activity will be tested in cell culture and *in vivo* models, which will ensure that novel chemical entities are processed in a timely and cost-effective manner. The assays performed in sequence will be:

1) Competitive ligand binding assay

Every new chemical entity is catalogued, characterized, concentrations standardized and solubility assessed. Affinity for insulin receptor and the insulin-like growth factor-1 (IGF-1) receptor are determined and compared by evaluating the ability of compounds to compete with radio-labelled insulin and IGF-1 in binding to either the insulin receptors or to IGF-1 receptors.

2) Insulin receptor tyrosine kinase assay

Each novel chemical entity is tested to differentiate whether they are agonists or antagonists. Competitive binding and insulin receptor tyrosine kinase assays are used routinely to screen for compounds to be selected for further testing in the cell or *in vivo* assays.

3) *In vivo* bioassays

Only compounds with reasonable insulin receptor affinity (<500 nM), IRTK activity (<5 μM), affinity ratio for insulin receptor over insulin growth factor-1R and

that promote glucose uptake into cells (<5 μM), will be considered for animal testing. Target compounds need have appropriate solubility, permeability and absorption. Blood glucose monitoring of the *in vivo* effects of the insulin mimetics will be performed following the procedure of Schaffer *et al*.[140]

Once the biological activity has been tested, the data will be brought to the computer modelling to reshape the model to increase the accuracy of the prediction to generate the second generation leading candidate.

The three main types of analogues that will be discussed in this thesis are: biphenyl-triphenyl analogues (Chapter II), biphenyl-biphenyl analogues (Chapter III) and analogues with different linkers/structures (Chapter IV). Once the new analogues have been synthesized, they will be tested by the WABRI insulin mimetics team. The biological testing of the compounds is beyond the scope of this study.

Chapter II Synthesis of biphenyl-triphenyl analogues

2.1 Introduction

Since **IM140** was found to be a lead candidate for an insulin mimetic drug,[141] much interest has been focused on modifying **IM140** in order to provide enhanced potency and efficacy. The key strategy employed in this work was to keep the most important groups, the two aromatic rings of the biphenyl on the left hand side and the two carboxylic acids on the right hand side, and make modifications on the rest of the structure. There are two main aims in this strategy: 1) to adjust the position and the distance of these groups to increase the drug efficiency; 2) to simplify the synthetic route to provide a shorter and easier pathway to the drug, which is of paramount importance for industrial production. One of the initial ideas was to replace the right hand side xanthone group with a more easily accessible triphenyl moiety to give **1** (**Figure 2.1**). In this modification, the side chain is replaced by a more rigid structure; therefore the carboxylic acid is locked into a fixed position. Computer modelling indicates the pharmacophore fit of **1** is similar to that of **IM140**.

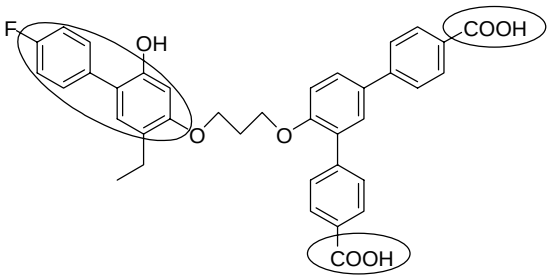


Figure 2.1 Structure of **1** with the principal binding groups circled

Changing the left hand side of the molecule was also viewed as a valuable route to generate **IM140** analogues, which would, in turn, provide a greater understanding of the mechanism of insulin binding to the insulin receptor. Computer modeling suggests that neither the ethyl nor the hydroxyl group of **IM140** is involved to any significant extent in the binding to the insulin receptor. The synthesis of the original left hand side of **IM140** requires six steps with an overall yield of 28%,[68] and it was envisaged that the synthesis of analogues without these two groups could be greatly simplified. Therefore, a series of different left hand sides were targeted for coupling with the triphenyl right hand side in order to obtain the new analogues.

A molecule in which the carboxylic acid groups of **1** are replaced with tetrazole moieties were also targeted for synthesis. Tetrazole is a five member ring with four nitrogen atoms and one carbon atom (**Figure 2.2**). Most tetrazoles do not have outstanding biological activities, but they are highly resistant to biological degradation which makes them ideal as isosteric replacements for various functional groups.[142] Ionized tetrazoles are ten times more lipophilic than the corresponding carboxylic acid, which allows these compounds to penetrate biological membranes with greater ease.[143] Since tetrazole derivatives possess unique energetic and chemical properties, they have been widely used in medicine, biochemistry and other fields of human activity.[142]

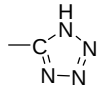


Figure 2.2 Structure of tetrazole

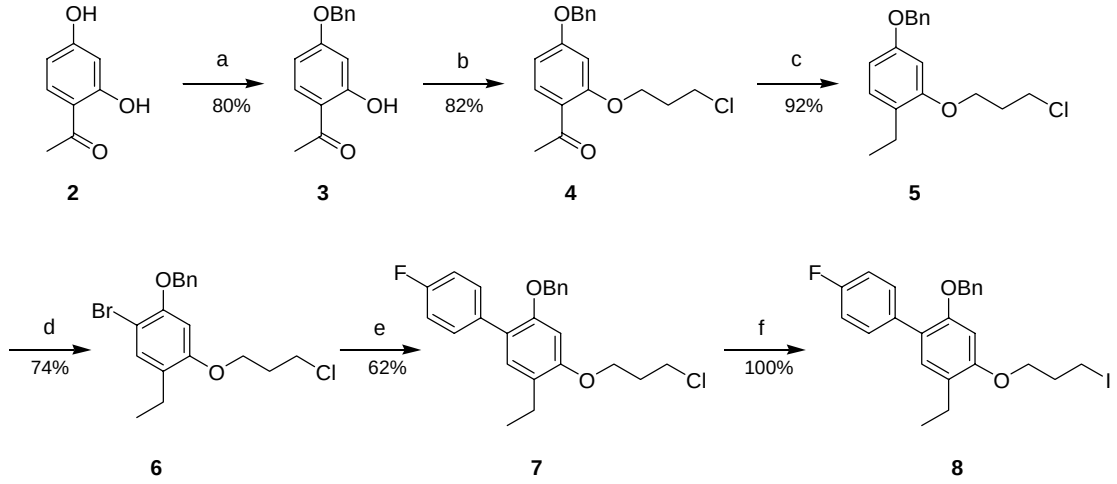
Thus, three main syntheses will be discussed in this chapter: 1) replacement of the xanthone group with a triphenyl moiety; 2) synthesis of derivatives with different left hand sides and 3) synthesis of the tetrazole derivative.

2.2 Results and discussion

2.2.1 Synthesis of the triphenyl analogue

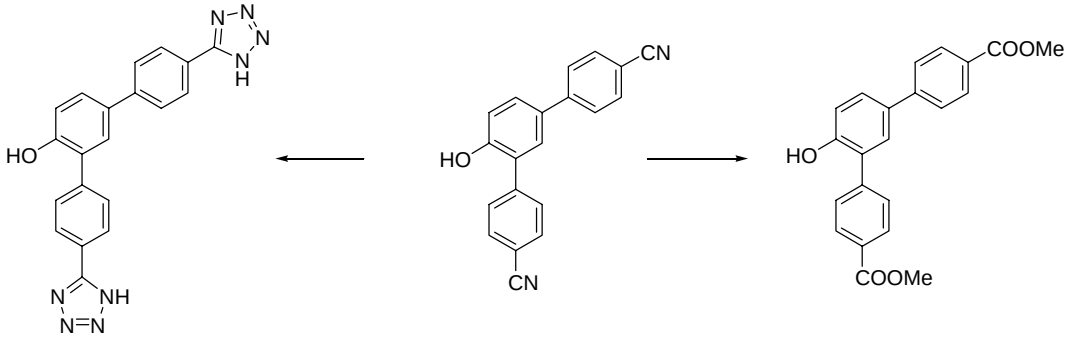
The triphenyl analogue **1** was prepared by a convergent synthesis, whereby both sides were prepared separately and then coupled together to give the final product.

The synthesis of the normal left hand side was conducted according to a literature procedure (**Scheme 2.1**).[68] It started with the benzylation of 2,4-dihydroxyacetophenone to selectively protect the *para*-hydroxyl group followed by introduction of the 3-chloropropoxyl linker group. Reduction of the carbonyl group in compound **4** with triethylsilane provided the ethyl group (within compound **5**), and subsequent bromination with *N*-bromosuccimide introduced a bromine atom to the aromatic ring (Compound **6**). The biphenyl framework was then constructed from the bromide *via* a Suzuki coupling reaction. Treatment of this biphenyl (**7**) with sodium iodide converted the chloride into the more reactive iodide (**8**) for subsequent coupling with the right hand side.



Scheme 2.1 Reagents: a) BnBr, K_2CO_3, butanone; b) $BrCH_2CH_2CH_2Cl$, K_2CO_3, butanone; c) Et_3SiH, trifluoroacetic acid, CCl_4; d) NBS, CCl4; e) 4-fluorophenyl-boronic acid, EtOH, aqueous Na_2CO_3, $Pd(PPh_3)_4$, benzene; f) NaI, butanone;

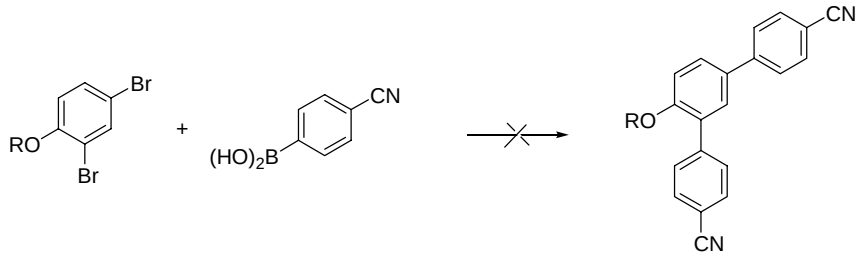
During the synthesis of the right hand side, the compound **9** was chosen as the preliminary target for the synthesis of the triphenyl moiety because it was expected that the nitrile groups of **9** could be readily converted into esters to give **10** or tetrazole to give **11** (**Scheme 2.2**).[144,145]



11 9 10

Scheme 2.2

The initial plan for synthesizing **9** was to construct the triphenyl skeleton *via* a one step double Suzuki coupling reaction starting from 2,4-dibromophenol. Unfortunately the products obtained from the reactions contained a complex mixture (*para*-, *ortho*- and other impurities) which were inseparable (**Scheme 2.3**). After many attempts at preparing a variety of similar analogues to **9** using the Suzuki coupling reactions, the hydroxyl group on the aromatic ring was found to be unsuitable for this type of reaction (**Table 2.1**).[*********] Therefore the hydroxyl group of **12** was protected as a benzyl ether and the Suzuki coupling reaction was carried out again. Unfortunately, a complex mixture was obtained and isolation of the desired product was unsuccessful. Shortly after the triphenyl derivative **9** and **10** had been synthesized, Sinclair and Sherburn reported one step double Suzuki coupling reaction could be carried out with diiodobenzene.[146]



12 R= H
13 R= Bn

14 R= H
15 R= Bn

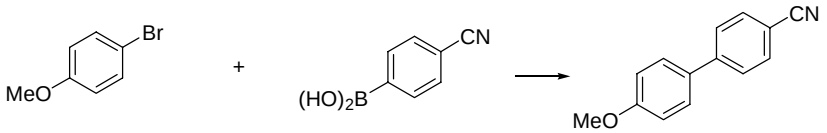
Scheme 2.3 *Reagents*: $Pd(PPh_3)_4$, Na_2CO_3, C_6H_6, EtOH, H_2O

[*********] Selected aromatic halides were reacted with boronic acid in the presence of 10% $Pd(PPh_3)_4$, aq. Na_2CO_3 and benzene and the resulting products were monitored by GC-MS

Table 2.1 Outcome of reactions of selected aryl bromide in Suzuki reactions as monitored by GC-MS

Aryl halide	Desired product achieved
4-Bromopheonol	No
1-Benzyloxy-4-bromobenzene	Yes
5-Bromosalicylialdehyde	No
4-Bromo-2-[1,3]dioxolan-2-ylphenol	No
2-Benzyloxy-5-bromobenzaldehyde	Yes

Given the difficulty experienced in carrying out the double Suzuki coupling, the synthetic route was changed to build the triphenyl skeleton *via* two independent Suzuki coupling reactions. Firstly 4-bromoanisole was treated with 4-cyanophenylboronic acid in the presence of a palladium catalyst to produce 4-(4'-cyanophenyl)anisole (**16**) (**Scheme 2.4**). When tetrakistriphenylphosphine palladium was used as catalyst, a significant amount of the cross coupled byproduct 4-cyanobiphenyl (10 to 30%) was obtained. This phenomenon has been reported previously by Marcuccio.[104] This byproduct, with very similar structure (and polarity) to the desired product was a significant concern as its removal from the reaction mixture by chromatography was very difficult. After several attempts with different catalysts and solvents **(Table 2.2**), 5% palladium acetate with triphenylphosphine under oxygen-free conditions was found to be the preferred catalyst and conditions for coupling without generating the homo-coupled byproduct.



CM1 CM2 **16**

CM: Commercial availble start material

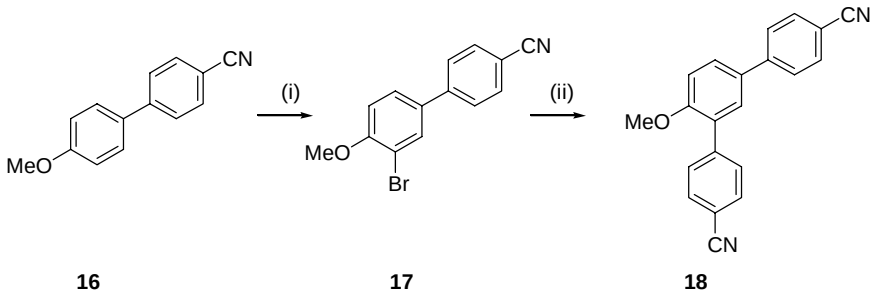
Scheme 2.4 *Reagents*: $Pd(OAc)_2$, PPh_3, K_2CO_3, THF, DME/H_2O

Table 2.2 Different systems investigated in the synthesis of biaryls, as monitored by GC-MS

Palladium catalyst	Palladium%	Degassed	Solvent	Homo-coupled byproduct	Unreacted halide
$Pd(PPh_3)_4$	10%	No	Benzene	Yes	None
$Pd(PPh_3)_4$	5%	No	Benzene	Yes	None
Pd/C	5%	Yes	Benzene	No	Yes
$Pd(OAc)_2$	5%	No	Water	No	Yes
$Pd(PPh_3)_4$	5%	Yes	DMF	Yes	None
$Pd(PPh_3)_4$	5%	Yes	DME/THF	Yes	None
$Pd(OAc)_2/PPh_3$	5%	Yes	DME/THF	No	None
$Pd(OAc)_2/PPh_3$	3%	Yes	DME/THF	No	Yes

Analysis of the ^1H and ^{13}C NMR spectra confirmed the formation of **16**. In the ^1H NMR spectrum the aromatic region integrated for eight protons, relative to integration of the methoxy peak (δ_H 3.87), which was consistent with the desired compound. The ^{13}C NMR spectrum showed nine signals with δ_C between 165 and 110 ppm which was consistent with eight different aromatic carbon atoms and one cyano carbon atom. The IR spectrum showed a strong peak at 2222 cm^{-1} which was typical for a cyano group. GC-MS showed a peak for the molecular ion at *m*/*z* 209, which was consistent with the formula $C_{14}H_{11}NO$.

Having synthesized **16**, the next step was to introduce a bromine atom into the *ortho*-position of the activated aromatic ring in preparation for the next Suzuki coupling reaction. Bromination with an equivalent of bromine in acetic acid provided **17** in good yield (83%), while NBS in acetonitrile at room temperature did not (13%) (**Scheme 2.5**). The Suzuki coupling reaction was then carried out to introduce the third aromatic ring to the parent skeleton.



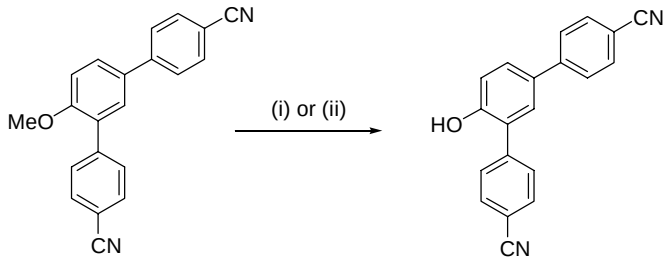
16 **17** **18**

Scheme 2.5 *Reagents*: (i) Br_2, CH_3COOH, 50 ºC; (ii) $Pd(OAc)_2$, PPh_3, K_2CO_3, *p*-$NCC_6H_4B(OH)_3$, THF, DME/H_2O

The ^1H NMR spectrum of **18** supported the formation of the triphenyl structure. Integration of the aromatic protons (δ_H 7.46-8.12 ppm) indicated the presence of 11 protons relative to the 3 protons of the methoxy group (δ_H 4.08). The ^{13}C NMR spectrum exhibited 16 peaks with δ_C between 100 and 165, which was consistent with the 14 different aromatic carbon atoms and 2 carbon atoms from the cyano groups. The GC-MS showed a peak for the molecular ion at *m*/*z* 310 which was consistent with the molecular formula $C_{21}H_{14}N_2O$.

Methyl aryl ethers are generally difficult to demethylate under mild reaction conditions. The demethylation of **18** was first attempted using the traditional deprotecting reagent boron tribromide.[147] This method afforded the desired product very smoothly (75%). An alternative method using pyridine hydrochloride was also

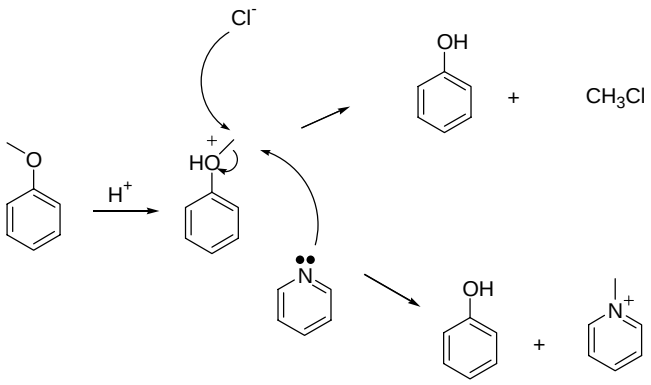
investigated.[148] After heating at 170 ºC for 3 hours the desired product **9** was readily obtained in good yield (80%) (**Scheme 2.6**). Although both methods provided the desired product, the later was more convenient overall.



18 **9**

Scheme 2.6 *Reagents*: (i) BBr_3, CH_2Cl_2, -78 ºC;
(ii) pyridine hydrochloride, 170 ºC, 3 h

Although, the mechanism of demethylation by pyridine hydrochloride has not been determined, to the best of our knowledge a possible mechanism is suggested in **Scheme 2.7**. The first route was favoured because the product methyl chloride is a gas, which is readily removed from the reaction mixture. This will drive the reaction in the right direction.



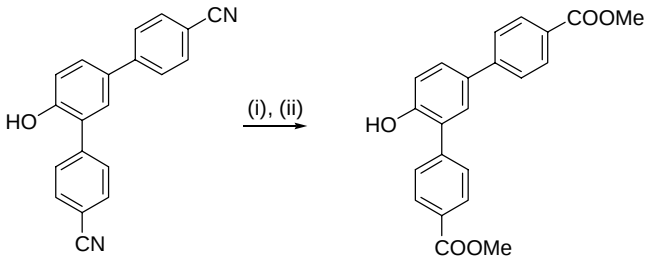
Scheme 2.7 possible mechanism

The absence of the signal for the methoxy group in the ^1H and ^{13}C NMR spectra of **9** confirmed successful completion of the deprotection and the GC-MS

analysis showed a peak for the molecular ion at *m*/*z* 296 which was consistent with the molecular formula $C_{20}H_{12}N_2O$.

Having successfully synthesized **9**, there are two synthetic routes to the desired drug analogues: i) convert nitrile group into either the carboxylic acid or tetrazole followed by coupling of the left hand side; ii) couple the left and right hand side together, and then convert the nitrile into the required functional groups.

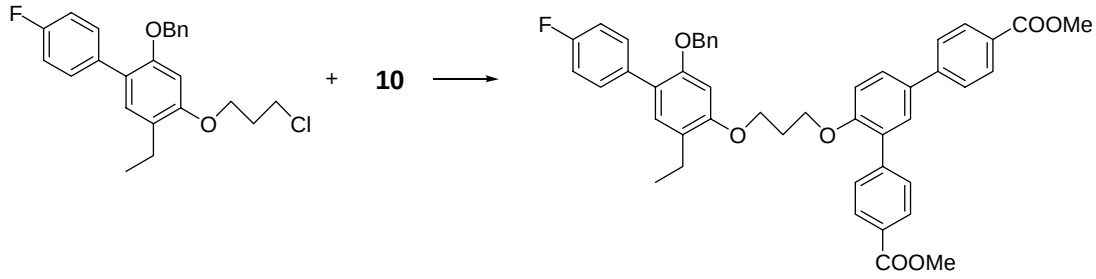
The conversion of the nitrile group into the methyl esters was carried out using 15% methanolic potassium hydroxide for three days followed by esterification of the resulting carboxylic acid with methanol/sulfuric acid to provide the right hand side ester **10** (**Scheme 2.8**).[144] The absence of signals for the nitrile groups in the IR spectrum and the presence of signals at 1718 cm^{-1} for the carbonyl groups clearly indicated the success of hydrolysis. The NMR and GC-MS spectra were consistent with that conclusion.



9 **10**

Scheme 2.8 *Reagents*: (i) 15% KOH, MeOH; (ii) H_2SO_4, MeOH

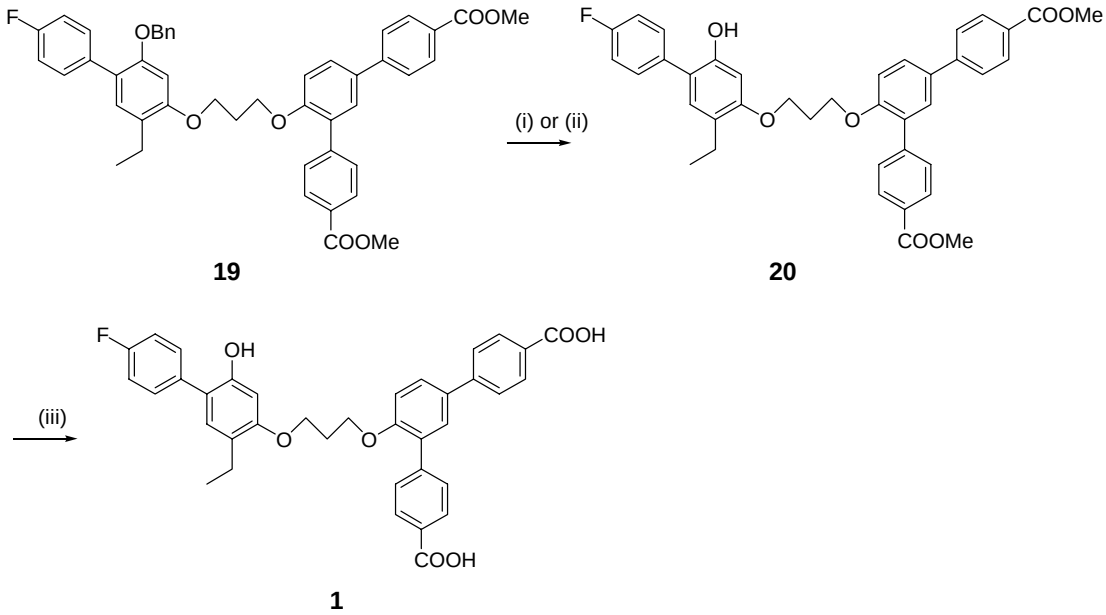
After both of the sides had been prepared, the next step is to couple them together to produce the protected analogue **19** (**Scheme 2.9**).



8 **19**

Scheme 2.9 *Reagents*: K_2CO_3, butanone

After having successfully synthesized **19**, the rest of the synthesis simply involved deprotection (debenzylation and hydrolysis). Two methods were investiagted for the debenzylation step (**Scheme 2.10**). The first method was hydrogenolysis catalyzed by palladium on carbon to remove the benzyl group. The second method was to use trimethylsilyl chloride with sodium iodide to react *in situ*. Both of the reactions worked well but the latter method was less hazardous and more convenient to carry out. The ester groups were then hydrolyzed using sodium hydroxide in methanolic THF to provide the desired analogue **1** in good yield (84%).



19 **20**

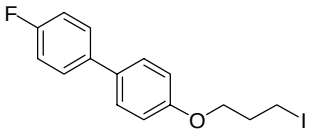
1

Scheme 2.10 *Reagents*: (i) Pd/C, H_2, EtOAc; (ii) Me_3SiCl, NaI, acetonitrile; (iii) THF, MeOH, NaOH; HCl

Analysis of the ^{1}H and ^{13}C NMR spectra of **1** confirmed the formation of the desired product. The two triplets at δ_H 4.39 and 4.14 exhibited the presence of the linker group. The triplet at δ_H 1.17 showed the methyl group from the left hand side, although the $ArCH_2$ was coincidental with the DMSO peak. The absence of resonances in the ^{1}H NMR spectrum attributed to the benzyl group showed the success of debenzylation and the disappearance of a signal due to the methyl ester illustrated the success of hydrolysis. The ^{13}C NMR spectrum was also consistent with that expected for **1**. The elemental analysis (**C** 71.0; **H** 5.1%) was consistent with the formula $C_{37}H_{31}FO_7 \cdot H_2O$ (**C** 71.1; **H** 5.3%).

2.2.2 Synthesis of simplified triphenyl analogues

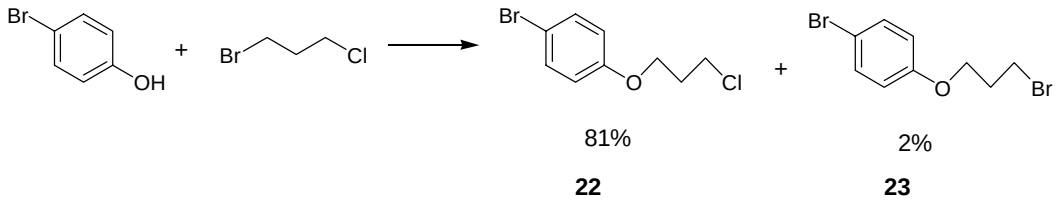
While the introduction of a triphenyl carboxylic acid moiety was successfully achieved, the next analogue of interest was that resulting from the simplified right hand side iodide **21** (**Figure 2.3**).



21

Figure 2.3

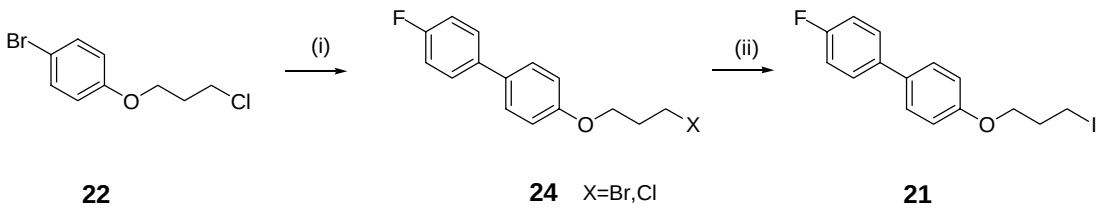
The treatment of 4-bromophenol with excess 1-bromo-3-chloropropane and potassium carbonate provided a mixture of **22** and **23** in the ratio of 97:3 as determined by GC-MS (**Scheme 2.11**). As both the chloride and the bromide will be converted into the more reactive iodide later, there is no need to separate these and the mixture was used in the subsequent reaction.



Scheme 2.11 *Reagents*: K_2CO_3, butanone/DMSO

This coupling reaction is a variation of the Finkelstein reaction. Sodium iodide is soluble in butanone (and acetone), while sodium chloride is insoluble in butanone. When an alkyl chloride is mixed with sodium iodide in butanone, sodium chloride will precipitate from solution, thus driving the reaction towards production of the reactive alkyl iodide. That's why we use sodium iodide and butanone in situ to acceletrate the coupling reaction. Acetone could be used in this reaction as well, but the reaction temperature would be a little lower (56 ^{o} C) than butanone (80 ^{o} C).

Suzuki coupling reaction on the mixture of compounds **22** and **23** formed the biphenyl derivative **24**. While purifying the reaction mixture by chromatography, it was found that the chloride and bromide were easily separable. Both of the halides were iodinated to afford the simplified left hand side **21** (**Scheme 2.12**).



Scheme 2.12 *Reagents*: (i) $Pd(OAc)_2$, PPh_3, K_2CO_3, *p*-$FC_6H_4B(OH)_2$, THF, DME,H_2O; (ii) NaI, acetonitrile

The ^{1}H NMR spectrum confirmed the formation of the simplified left hand side **21**. The two triplets at δ_H 4.14 and 3.45 were assigned to the methylene protons

adjacent to the oxygen and the iodine atoms respectively. The integration indicated 8 aromatic protons relative to the methylenes of the linker. The multiplet at δ_H 2.29 was assigned to the methylene group in the middle of linker. GC-MS showed one peak for the molecular ion at *m*/*z* 356, which was consistent with the formula $C_{15}H_{14}FIO$.

An interesting observation in the ^{13}C NMR spectrum of **21** was the fluorine long range coupling. There were twelve peaks ranging from δ_C 115 to 165 which were consistent with the four different aromatic carbon atoms of the phenoxy ring and four doublets due to the carbon atoms of the fluorophenyl ring. This phenomenon was concordant with spin-spin interaction in fluorinated aromatic compounds.[149] **Figure 2.4** illustrates the long range fluorine coupling of the four different aromatic carbon atoms. The coupling constants from C4' to C1' were -245.3, ††††††††† 21.4, 8.0, 3.5 Hz respectively. In contrast to the carbon-proton couplings of benzene ($J_3 > J_2$),[151] the two-bond carbon fluorine coupling constant (J_{FCC}) was larger than the three-bond coupling constant (J_{FCCC}). The reason was due to the strong positive polarization of the fluorine within the coupling path.[152]

††††††††† This coupling constant was defined as a negative coupling constant because those two coupled nuclei had parallel orientation of nuclear spins.[150]

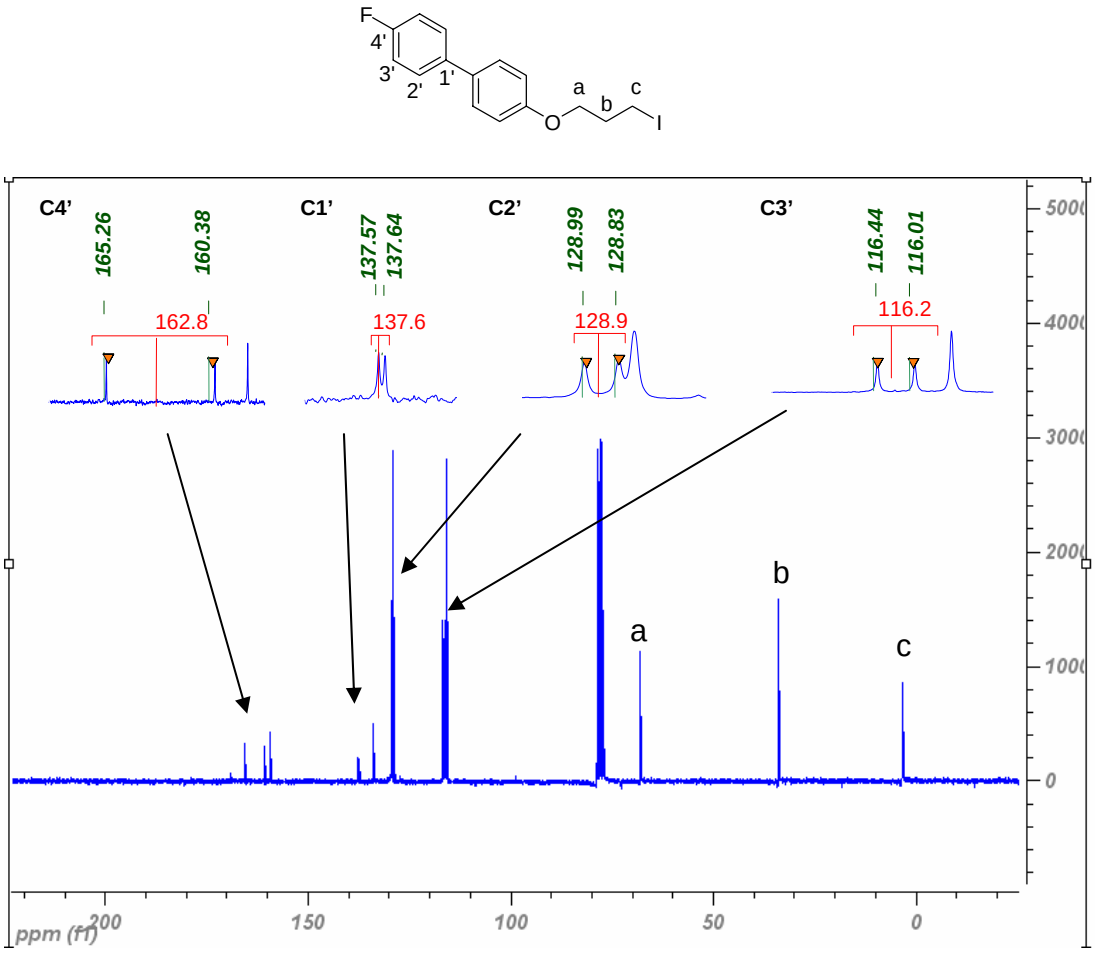
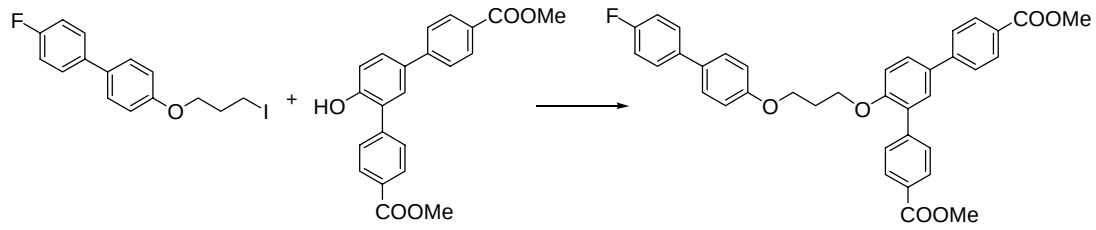


Figure 2.4 Proton-decoupled ^{13}C NMR spectrum of **21** (50 MHz)

The synthesis of the simplified left hand side took three steps with an overall yield of 61% compared to the original left hand side which required six steps with a yield of 28%.

Coupling the simplified left hand side, with the right hand side compound **10** provided the intermediate **25** in moderate yield (61%) (**Scheme 2.13**).

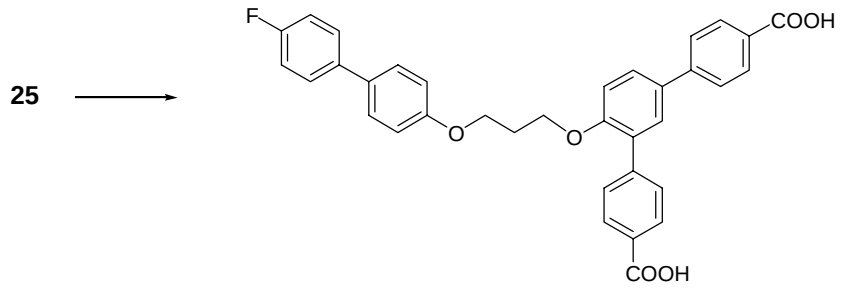


21 **10** **25**

Scheme 2.13 *Reagents*: K_2CO_3, acetonitrile

The ^1H and ^{13}C NMR spectra of **25** indicated the successful linkage between the two sides. In the ^1H NMR spectrum two triplets at δ_H 4.25 and 4.06 confirmed the presence of the linker groups. Two singlets at δ_H 3.93 and 3.91 were assigned to the two methyl ester group. Relative to those methyl ester groups, the large group of signals in the aromatic region, with an integration of 19 protons, was consistent with the number of aromatic protons in **25**. In the ^{13}C NMR spectrum the two carbonyl groups were not distinguishable, this may be due to the low field of the NMR spectrometer. The four doublets due to carbon-fluorine coupling could be observed as usual. In the upfield region the signals due to the two oxymethylene carbon atoms could be observed, but the two signals due to the methoxy groups were coincident.

Hydrolysis of the two ester groups produced the final target **26** (**Scheme 2.14**). The absence of signals for the methoxyl group in both the ^1H and ^{13}C NMR spectra indicated that the hydrolysis had gone to completion and the elemental analysis (**C** 74.2, **H** 4.8%) was consistent with its formula $C_{35}H_{27}FO_6$ (**C** 74.7, **H** 4.8%).

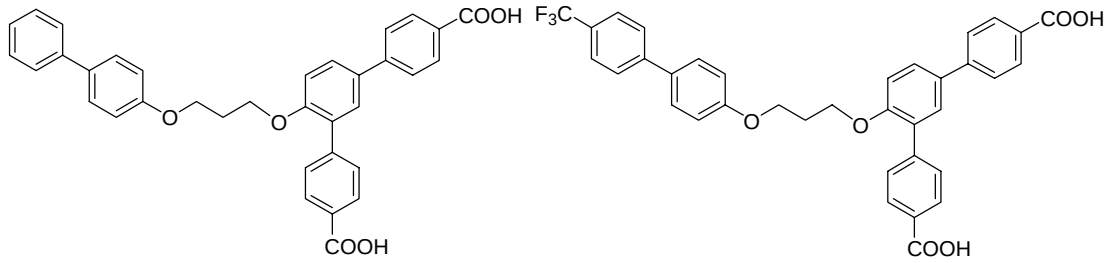


26

Scheme 2.14 *Reagents*: THF, MeOH, NaOH,

2.2.3 Synthesis of analogues with different left hand sides

In order to investigate the functional role of the fluorine group at the 4′-position of the biphenyl, another two analogues (**27** and **28)** with different left hand sides were synthesized (**Figure 2.5**).

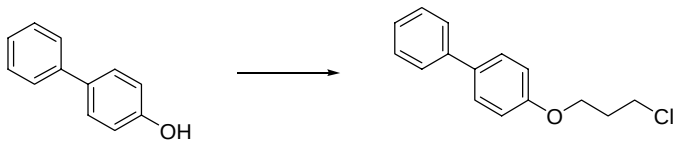


27 **28**

Figure 2.5 Two drug analogues

Treatment of 4-hydroxybiphenyl (**30**) with 1-bromo-3-chloropropane and potassium carbonate produced the intermediate **29** in good yield (75%) (**Scheme 2.15**). The successful synthesis of **29** was confirmed by analysis of the ^{1}H and ^{13}C NMR spectra. The triplet at δ_H 4.16 was attributed to the oxymethelene protons and the triplet at 3.77 to the methylene next to the chlorine atom. The ^{13}C NMR spectrum showed 8 signals between δ_C 110 and 165 which was consistent with the

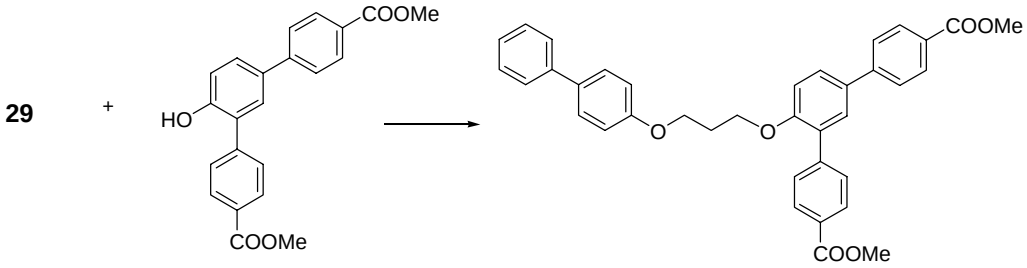
number of the different aromatic carbon atoms in **29**. GC-MS showed the purity was >99% and the MS exhibited the molecular ion *m*/*z* at 246 and 248 which were consistent with the formulas $C_{15}H_{15}{}^{35}ClO$ and $C_{15}H_{15}{}^{37}ClO$.



30 **29**

Scheme 2.15 *Reagents*: $BrCH_2CH_2CH_2Cl$, K_2CO_3, butanone

The left hand side chloride **29** was used directly in coupling to the triphenyl moiety, **10**, in the presence of sodium iodide (**Scheme 2.16**). The iodide intermediate was presumably formed *in situ* during the reaction and subsequently reacted readily with the triphenyl moiety. This reaction proceeded in a reasonable yield (61%).



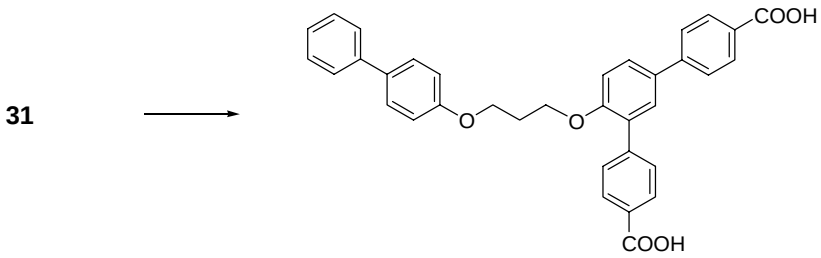
10 **31**

Scheme 2.16 *Reagents*: K_2CO_3, NaI, butanone

Analysis of the the ^1H and ^{13}C NMR spectra confirmed the formation of **31**. In the ^1H NMR spectrum, the triplets at δ_H 4.25 and 4.07 were consistent with the two oxymethylenes and indicated the successful linkage of both sides. Furthermore, relative to those four protons integration indicated that there were twenty aromatic protons consistent with the structure. In the ^{13}C NMR spectrum there were only eighteen signals for the aromatic carbon atoms and only one signal for the carbonyl carbon atom, which indicated the two carbonyl carbons are indistinguishable and some of the aromatic carbon signals were coincident with each other. In the upfield

region the peak at δ_C 52.8 was assigned to two OCH_3 groups which was consistent with the coincidence of carbonyl signals.

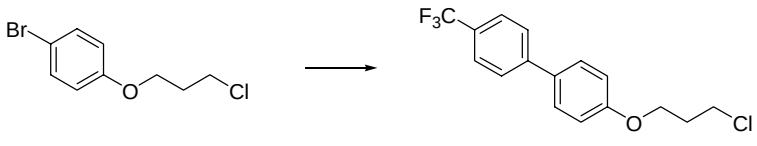
Hydrolysis of the ester in **31** afforded the final target **27** in excellent yield (95%) (**Scheme 2.17**). The absence of the signals due to the methoxy groups in both the ^1H and ^{13}C NMR spectra confirmed the success of the hydrolysis reaction. The elemental analysis (**C** 74.6; **H** 5.0%) was consistent with the formula $C_{35}H_{28}O_6 \cdot H_2O$ (**C** 74.7; **H** 5.4%).



27

Scheme 2.17 *Reagents*: THF, MeOH, NaOH; HCl

Another left hand side analogue synthesized was the one with a *para*-trifluoromethyl group (**28**). This involved a Suzuki coupling reaction between **22** and 4-trifluromethylphenylboronic acid using palladium acetate and triphenylphosphine as the catalyst. This reaction provided the new left hand side component with a trifluoromethyl group in the *para*-position in good yield (85%) (**Scheme 2.18**).



22 **32**

Scheme 2.18 *Reagents*: $Pd(OAc)_2$, PPh_3, K_2CO_3, *p*-$CF_3C_6H_4B(OH)_2$, THF, DME/H_2O

The ^{1}H and^{13}C NMR spectra of **32** showed signals consistant with the attachment of aromatic ring and trifluoromethyl group. The triplet at δ_H 4.18 was assigned to the oxymethylenes and the triplet at δ_H 3.76 was assigned to the methylene next to the chlorine. Relative to those four protons, integration indicated eight aromatic protons, which was consistent with its structure. In the ^{13}C NMR spectrum the typical quartet at δ_C 126.4 confirmed the presence of the trifluoromethyl group (**Figure 2.6**). GC-MS showed a peak for the molecular ion at *m*/*z* 314/316, consistent with the molecular formula $C_{14}H_{14}{}^{35}ClF_3O$ and $C_{14}H_{14}{}^{37}ClF_3O$, and thus confirm the successful coupling of two mono-aryl precursors.

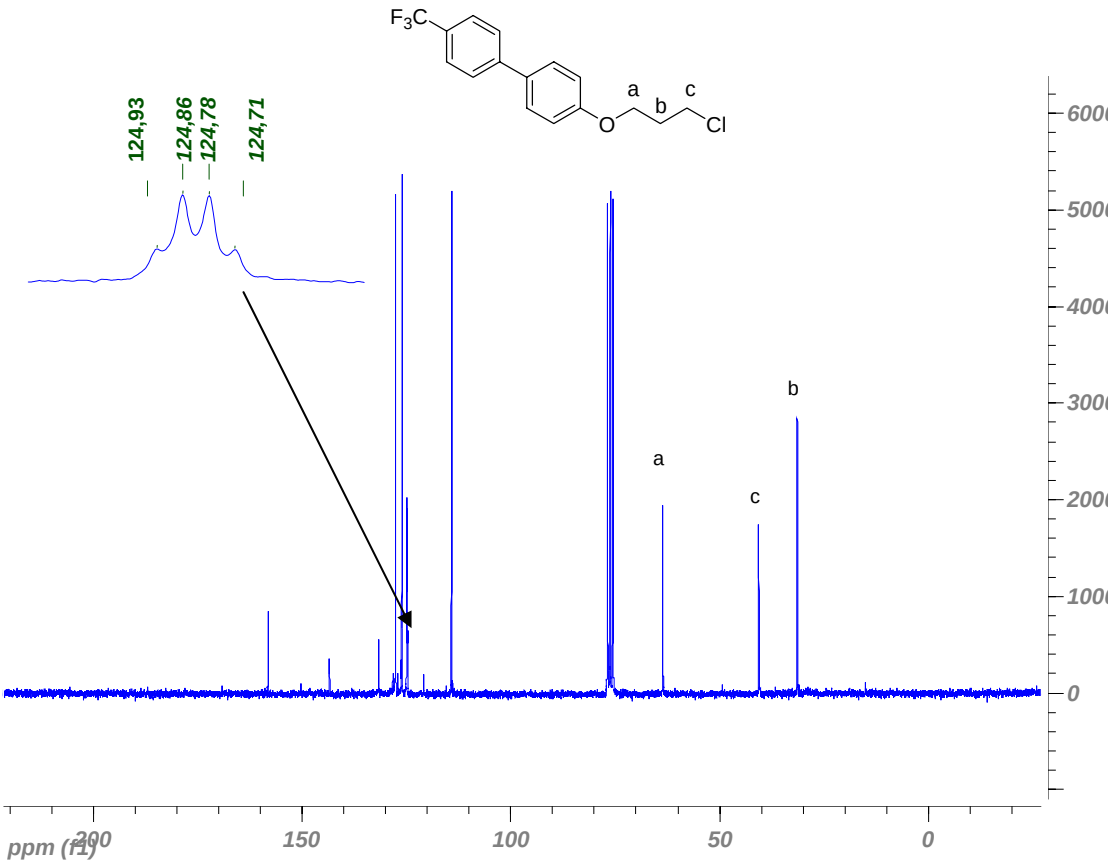
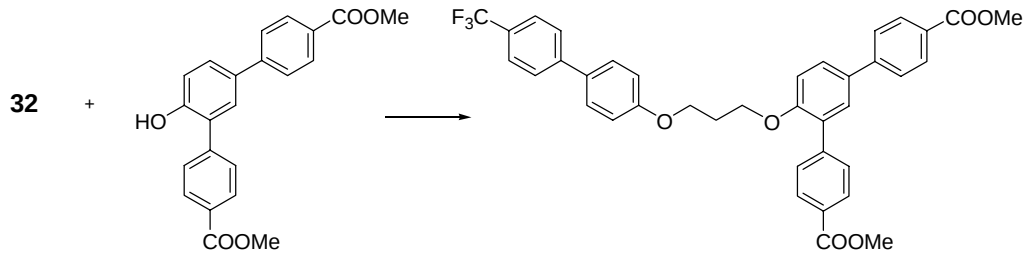


Figure 2.6 Proton-decoupled ^{13}C NMR spectrum of **32** (50.3 MHz)

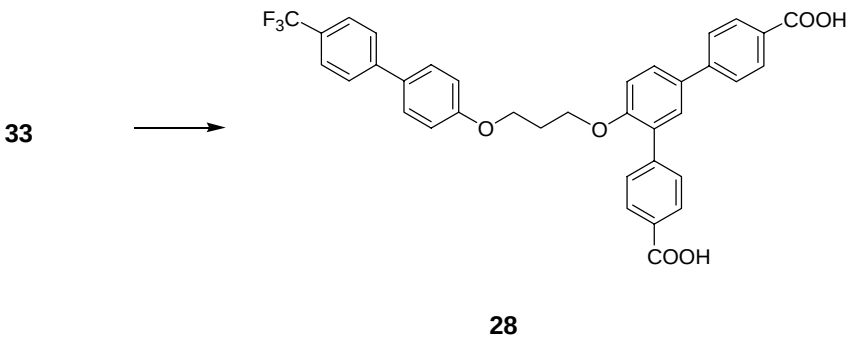
The coupling of the biphenyl derivative **32** with the triphenyl moiety **10** in the presence of sodium iodide afforded **33** (**Scheme 2.19**).



Scheme 2.19 *Reagents*: K_2CO_3, acetonitrile

The ^1H and ^{13}C NMR spectra confirmed the formation of the desired product. The two triplets at δ_H 4.23 and 4.08 showed the presence of the linker group while singlets at 3.92 and 3.94 indicated the presence of the methoxy groups. Relative to those protons, integration of the aromatic region indicated nineteen aromatic protons, consistent with the number of aromatic protons in **33**. In the ^{13}C NMR spectrum the typical quartet indicated the presence of the trifluoromethyl group, but the two carbonyl groups and two methoxy groups were unresolved at 50.3 MHz.

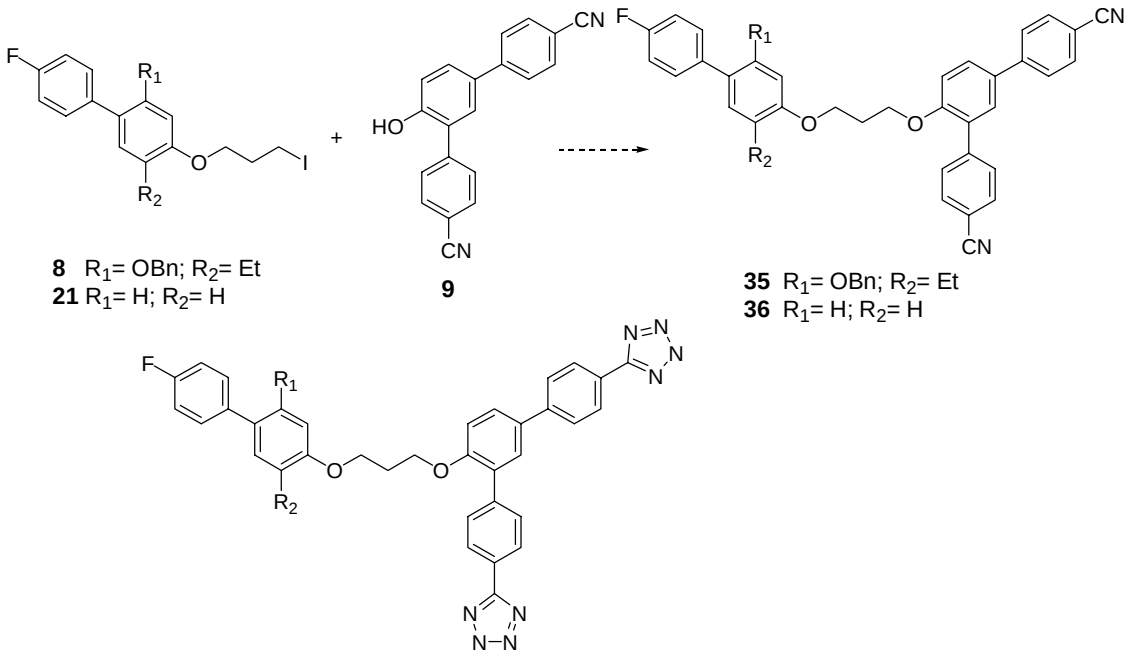
Hydrolysis of **33** afforded the final product **28** in good yield (83%) (**Scheme 2.20**). The absence of the signals due to methoxy groups indicated the success of this reaction.



Scheme 2.20 *Reagents*: NaOH, MeOH, THF; HCl

2.2.4 Synthesis of tetrazole analogue

The tetrazole analogue was scheduled to be synthesized by coupling either of the left hand side derivatives **8** or **21** with triphenyl moiety **9** (**Scheme 2.21**). The nitrile groups could then be converted into tetrazoles using sodium azide.[153] However, due to a shift in the synthetic focus, the synthesis of tetrazole analogues was postponed until the carboxylic acid analogues were tested for biological activity. Synthesis would only proceed if the acid showed moderate to good activity.



Scheme 2.21

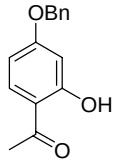
Experimental

Melting points were measured on a Barnstead Electrothemal IA9100 digital melting point apparatus without calibration. Infrared spectra were obtained on a Perkin Elmer FT-IR spectrometer 1760X using potassium bromide disc. Mass spectral data were obtained using an HP 6890 GC with Agilent 5973 network mass selective detector. Elemental analyses were obtained from the University of Tasmania. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured on a Varian Gemini-200 spectrometer (^{1}H: 200.0 MHz; ^{13}C: 50.3 MHz) using $CDCl_3$ as the solvent unless otherwise stated. All chemical shifts are reported in parts per million (δ) relative to $CHCl_3/CDCl_3$ solvent signals (^{1}H: 7.26 ppm; ^{13}C: 77.7 ppm). ^{1}H assignment abbreviations are the following: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet.

Analytical thin layer chromatography (TLC) was performed on silica gel (40-63 μm) precoated aluminum plates (Merck kieselgel 60 F_{254}). Silica gel chromatography was performed using silica gel (40-63 μm, Merck kieselgel).

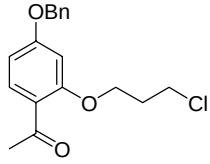
Materials were obtained from commercial sources and used without further purification unless noted otherwise. All the anhydrous solvents were purified according to the standard procedure described in Perrin and Amarego.[154] Tetrahydrofuran was distilled from sodium. All reactions were carried out under a nitrogen atmosphere unless noted otherwise.

4-Benzyloxy-2-hydroxyacetophenone (3)



4-Benzyloxy-2-hydroxyacetophenone was prepared by a variation of the method of Sawyer *et al*.[68] A mixture of 2,4-dihydroxyacetophenone (0.76 g, 0.005 mol), benzyl bromide (0.86 g, 0.005 mol), anhydrous potassium carbonate (1.38 g, 0.01 mol) and anhydrous acetone (10 mL) were heated at reflux (8 h). The reaction mixture was concentrated, acidified with hydrochloric acid (2 M, 10 mL) and extracted with ether. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalized from methanol to afford the desired product as a cream crystalline solid (0.96 g, 80%). m.p. 101.3-102.6 ºC, (Lit.[68] m.p. 101.5-101.6 ºC); ^{1}H NMR δ 7.63 (m, 1H, ArH), 7.26-7.42 (m, 5H, ArH), 6.52 (m, 2H, ArH), 5.09 (s, 2H, $ArCH_2O$), 2.55 (s, 3H, CH_3). The NMR data was consistent with the literature.

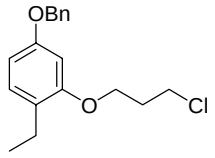
4-Benzyloxy-2-(3-chloropropoxy)acetophenone (4)



4-Benzyloxy-2-(3-chloropropoxy)acetophenone was prepared by a variation of the method of Sawyer *et al*.[68] A mixture of **3** (150 g, 0.618 mol), 1-bromo-3-chloropropane (245 mL, 2.46 mol), potassium carbonate (166 g, 1.20 mol), in butanone (1 L) was heated at reflux (24 h). The reaction mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (162 g, 82%). m.p. 68.0-70.5 ºC (Lit.[68] m.p. 69-70 ºC); ^{1}H NMR δ 7.82 (apparent d, *J*= 4 Hz, 1H, H6), 7.36-7.43 (m, 5H, ArH), 6.55-6.63 (m, 2H, ArH), 5.10 (s, 2H, $ArCH_2$), 4.18

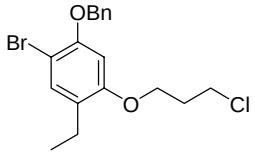
(t, *J*= 5.8 Hz, 2H, OCH_2), 3.76 (t, *J*= 6.2 Hz, 2H, CH_2Cl), 2.57 (s, 3H, CH_3CO), 2.27-2.41 (m, 2H, OCH_2CH_2). The NMR spectrum was consistent with the literature.

4-Benzyloxy-2-(3-chloropropoxy)ethylbenzene (5)



4-Benzyloxy-2-(3-chloropropoxy)ethylbenzene was prepared by the method of Sawyer *et al*.[68] Trifluoroacetic acid (44.4 g, 390 mmol) and triethyl silane (21.8 g, 188 mmol) were added to a solution of acetonphenone **4** (12.1 g, 31.6 mmol) in carbon tetrachloride (30 mL). The mixture was stirred at room temperature for 1.5 h, diluted with ethyl acetate, and washed with aqueous sodium carbonate solution (2 M). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (petroleum spirit) to afford the desired product as clear oil (10.6 g, 92%). ^{1}H NMR δ 7.38-7.52 (m, 5H, ArH), 7.06 (apparent d, *J*= 6.5, 1H, ArH), 6.54-6.59 (m, 2H, ArH), 5.06 (s, 2H, $ArCH_2O$), 4.12 (t, *J*= 5.2 Hz, 2H, OCH_2), 3.96 (t, *J*= 5.3 Hz, 2H, CH_2Cl), 2.60 (q, *J*= 6.5 Hz, 2H, CH_2CH_3), 2.32-2.39 (m, 2H, OCH_2CH_2), 1.20 (t, *J*= 6.5 Hz, 3H, CH_2CH_3). The NMR spectrum was consistent with the literature.[68]

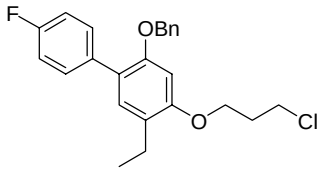
4-Benzyloxy-5-bromo-2-(3-chloropropoxy)ethylbenzene (6)



4-Benzyloxy-5-bromo-2-(3-chloropropoxy)ethylbenzene was prepared by the method of Sawyer *et al*.[68] *N*-bromosuccinimide (3.29 g, 18.5 mmol) was added to a stirred solution of the bromide **5** (5.63 g, 18.5 mmol) in carbon tetrachloride (60 mL). The reaction mixture was stirred at room temperature overnight, diluted with

dichloromethane and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford a colourless oil (5.23 g, 74%). ^{1}H NMR δ 7.22-7.58 (m, 6H, ArH), 6.54-6.59 (m, 1H, ArH), 5.18 (s, 2H, $ArCH_2O$), 4.02 (t, *J*= 5.2 Hz, 2H, OCH_2), 3.78 (t, *J*= 5.6 Hz, CH_2Cl), 2.70 (q, *J*= 6.1 Hz, 2H, CH_2CH_3), 2.42-2.47 (m, 2H, OCH_2CH_2), 1.25 (t, *J*= 6.1 Hz, 3H, CH_2CH_3), The NMR spectrum was consistent with the literature.

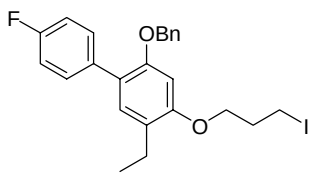
4-Benzyloxy-2-(3-chloropropoxy)-5-(4-fluorophenyl)-etheylbenzene (7)



4-Benzyloxy-2-(3-chloropropoxy)-5-(4-fluorophen- yl)-etheylbenzene was prepared by a variation of the method of Sawyer *et al*.[68] $Pd(PPh_3)_4$ (0.42 mg, 0.42 mmol) and aqueous sodium carbonate solution (2 M, 12.8 mL) were added to a mixture of aryl bromide **6** (3.28 g, 8.5 mmol) in benzene (5 mL/mmol aryl bromide). Another solution of 4-fluorophenylboronic acid (2.35 g, 17 mmol) in ethanol (10 mL) was added to the aryl bromide solution and the resulting mixture was heated at reflux (16 h). The reaction mixture was diluted with ethyl acetate and washed once with saturated aqueous ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product (2.1 g, 62%). ^{1}H NMR δ 7.61 (apparent d, *J*= 9.0 Hz, 2H, ArH), 7.24-7.55 (m, 7H, ArH), 7.21 (s, 1H, ArH), 6.63 (s, 1H, ArH), 5.09 (s, 2H, $ArCH_2O$), 4.13 (t, *J*= 5.8 Hz, 2H, OCH_2), 3.80 (t, *J*= 5.8 Hz, CH_2Cl), 2.65 (q, *J*= 7.0 Hz, 2H, $ArCH_2CH_3$), 2.25-

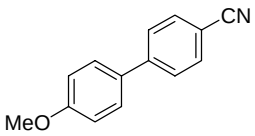
2.28 (m, 2H, OCH_2CH_2), 1.24 (t, *J*= 7.0 Hz, 3H, $ArCH_2CH_3$). The NMR spectrum was consistent with the literature.[68]

4-Benzyloxy-5-(4-fluorophenyl)-2-(3-iodopropoxy)ethylbenzene (8)



4-Benzyloxy-5-(4-fluorophenyl)-2-(3-iodopropoxy) ethylbenzene was prepared by the method of Sawyer *et al*.[68] A mixture of compound **7** (20.0 g, 50.2 mmol) and sodium iodide (75.3 g, 500 mmol) in butanone (200 mL) was heated at reflux (6 h). The reaction mixture was cooled, diluted with ether and washed twice with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product as a purple oil (24.6 g, 100%). ^{1}H NMR δ 7.47-7.54 (m, 2H, ArH), 7.02-7.32 (m, 8H, ArH), 6.58 (s, 1H, ArH), 5.03 (s, 2H, OCH_2Ar), 4.03 (t, *J*= 5.9 Hz, 2H, OCH_2), 3.40 (t, *J*= 6.2 Hz, 2H, CH_2I), 2.60 (q, *J*= 7.3 Hz, 2H, CH_2CH_3), 2.25-2.31 (m, OCH_2CH_2), 1.19 (t, *J*= 7.3 Hz, 3H, CH_2CH_3). The NMR spectrum was consistent with the literature.[68]

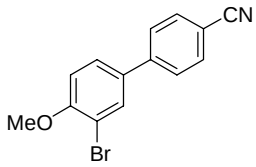
4'-Methoxy-biphenyl-4-carbonitrile (16)



A mixture of 4-bromoanisole (1.48 g, 8 mmol), 4-cyanophenylboronic acid (1.40 g, 9.6 mmol), palladium acetate (0.10 g, 0.4 mmol), potassium carbonate (2.6 g, 16 mmol), triphenylphosphine (0.11 g, 0.4 mmol), THF (10 mL), DME (10 mL) and water (5 mL) was degassed three times and then heated at reflux (16 h). The resulting solution was concentrated *in vacuo* and then the residue was diluted with ethyl acetate. The

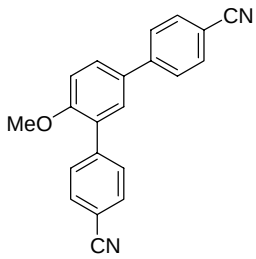
organic layer was washed once with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a white solid which was recrystalized from dichloromethane/petroleum spirit (1.25 g, 75%). m.p. 107-108 ºC (Lit.[155] m.p. 103-104 ºC), GC-MS showed the purity was >99%, *m*/*z* 209 (M^+, 100%, $C_{14}H_{11}NO$); IR ν_{max}/cm^{-1} (KBr): 2222 (C≡ N); ^{1}H NMR δ 7.50-7.67 (m, 6H, ArH), 7.00 (apparent d, *J*= 8.8 Hz, 2H, H3', 5'), 3.87 (s, 3H, OCH_3); ^{13}C NMR 160.9 (C4'), 145.9, 133.2, 132.2, 129.0, 127.8, 119.7, 115.3, 110.8 (Ar C, CN), 56.1 (OCH_3).

3'-Bromo-4'-methoxy-biphenyl-4-carbonitrile (17)



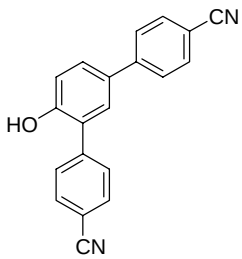
Bromine (1.92 g, 0.012 mol) was slowly added into a warm (50-60 ºC) solution of **16** (2.51 g, 0.012 mol) in acetic acid (20 mL). The reaction mixture was stirred for another half an hour and poured into a mixture of icy water (100 mL) and sodium metabisulfite (5 g). The resulting precipitate was collected and dried in vacuum desiccator. The residue was recrystallized from dichloromethane/petroleum spirit to afford a white solid (2.96 g, 86%). m.p. 125-127 ºC; GC-MS showed the purity >99%, *m*/*z* 287 (M^+, 100%, $C_{14}H_{10}{}^{79}BrNO$), 289 [$(M+2)^+$, 100%, $C_{14}H_{10}{}^{81}BrNO$]; IR ν_{max}/cm^{-1} (KBr): 2226 (C≡ N); ^{1}H NMR (d_6-acetone) δ 8.11 (d, *J*= 2.2 Hz, 1H, H2'), 7.95-8.01 (m, 4H), 7.91 (dd, *J*= 8.5, 2.2 Hz, 1H, H6'), 7.38 (d, *J*= 8.5 Hz, 1H, H5'), 4.12 (s, 3H, OCH_3); ^{13}C NMR 157.8, 144.8, 133.9, 132.9, 128.9, 128.6, 119.7, 114.0, 113.1, 111.9 (Ar C, CN), 57.2 (OCH_3), some signals were coincident with each other.

4'-Methoxy-[1, 1'; 3', 1''] terphenyl-4, 4''-dicarbonitrile (18)



A mixture of **17** (3.1 g, 12 mmol), 4-cyanophenyl boronic acid (3.0 g, 14 mmol), palladium acetate (0.14 g, 0.67 mmol), potassium carbonate (3.9 g, 24 mmol), triphenylphosphine (0.15 g, 0.67 mmol), THF (30 mL), DME (30 mL) and water (15 mL) was degassed three times and then heated at reflux (16 h). The resulting mixture was concentrated and the residue was diluted with ethyl acetate. The organic layer was washed once with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the product as a white solid (3.1 g, 84%) m.p. 116-118 ºC; GC-MS showed the purity was 97%, *m*/*z* 310 (M^+, 100%, $C_{21}H_{14}N_2O$); IR ν_{max}/cm^{-1} (KBr): 2222 (C≡ N); ^{1}H NMR (d_6-acetone) δ 7.92-8.12 (m, 8H, ArH), 7.76 (apparent d, *J*= 8.2 Hz, 1H, H6'), 7.46 (m, 1H, ArH), 7.15 (apparent d, *J*= 8.8 Hz, 1H, H5'), 4.08 (s, 3H, OCH_3); ^{13}C NMR (d_6-acetone) 157.0 (C4'), 144.4, 142.9, 134.0, 132.5, 131.6, 131.5, 130.4, 129.2, 129.0, 128.6, 127.2, 118.4, 116.2, 112.2, 110.2 (Ar C, CN), 55.3 (OCH_3).

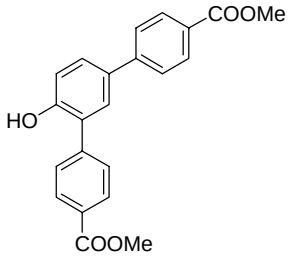
4'-Hydroxy-[1, 1'; 3', 1''] terphenyl-4, 4''-dicarbonitrile (9)



A mixture of **18** (0.78 g, 2.5 mmol) and pyridine hydrochloride (2.6 g, 25 mmol) was heated at 170-180 ºC (3 h). The residue was diluted with water (50 mL) and the resulting precipitate was collected and dried in desiccator. The crude product was purified by chromatography (30% ethyl acetate in petroleum spirit) to afford a pale yellow product (0.51 g, 80%) m.p. 231-234 ºC; GC-MS showed the purity was >99%, *m*/*z* 296 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 2231 (C≡ N); ^{1}H NMR (d_6-acetone) δ 7.84-

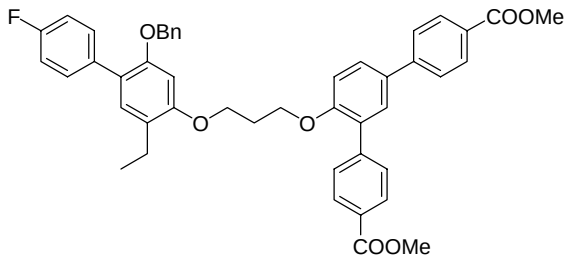
7.96 (m, 4H, ArH), 7.66-7.83 (m, 5H, ArH), 7.69 (dd, *J*= 2.2, 8.4 Hz, 1H, H6'), 7.18 (d, *J*= 8.4 Hz, 1H, H5'); ^{13}C NMR (d_6-acetone) 155.9, 145.7, 144.0, 133.5, 132.6, 132.0, 131.2, 130.3, 129.4, 128.0, 119.5, 118.0, 111.4, 111.2, 111.0 (Ar C and CN), some signals were coincidental with each other.

4'-Hydroxy-[1, 1'; 3', 1''] terphenyl-4, 4''-dicarboxylic acid dimethyl ester (10)



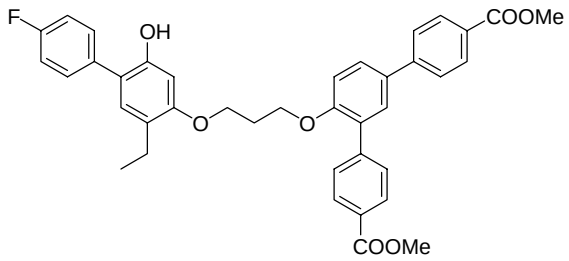
A solution of the dicyano derivative **9** (0.6 g, 2.0 mmol) and potassium hydroxide (3 g, 54 mmol) in methanol (20 mL) was heated at reflux (3 d). The residue was diluted with water and concentrated *in vacuo*. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was collected, dried and concentrated. The crude solid was dissolved in methanol (20 mL) and concentrated sulfuric acid (4 mL) and heated at reflux (16 hrs). The reaction mixture was then poured into ice water (100 mL) and the precipitate was collected and dried in desiccator. The crude product was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford a white solid (0.44 g, 61%). m.p. 166-167 ºC, GC-MS showed the purity was >99%, *m*/*z* 362 (M^+, 100%); IR ν_{max}/cm^{-1} (KBr): 1718 (C=O); ^{1}H NMR δ 8.10-8.18 (m, 4H, ArH), 7.50-7.66 (m, 6H, ArH), 7.07 (apparent d, *J*= 7.3 Hz, 1H), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR 167.7 (C=O), 167.4 (C=O), 153.5, 145.5, 142.4, 133.7, 131.1, 130.9, 130.3, 129.9, 129.2, 128.5, 127.2, 117.5 (Ar C), 52.9 (OCH_3), 52.8 (OCH_3), some signals are coincidental with each other.

3-(4-Methylcarboxyphenyl)-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy] propoxy] phenyl benzoic acid methyl ester (19)



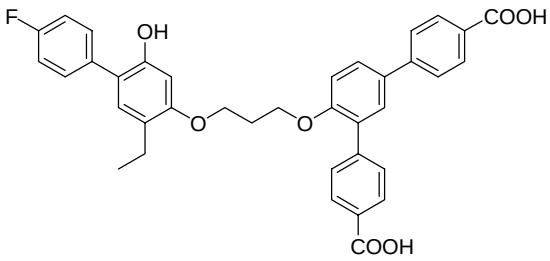
A mixture of left hand side **8** (1.5 g, 6.12 mmol), the diester **10** (1.23 g, 6.12 mmol), potassium carbonate (2.14 g, 15.3 mmol) and butanone (20 mL) were stirred for 24 hours and then concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (1.9 g, 43%). m.p. 101-103ºC; Found **C** 75.9, **H** 5.7%; $C_{46}H_{41}FO_7$ requires **C** 76.2, **H** 5.7%; ^{1}H NMR δ 8.00-8.08 (m, 5H, ArH), 7.45-7.62 (m, 10H, ArH), 6.98-7.23 (m, 6H, ArH), 6.47 (s, 1H, ArH), 4.94 (s, 2H, OCH_2Ar), 4.22 (t, *J*= 5.9 Hz, 2H, OCH_2), 4.00 (t, *J*= 5.5 Hz, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.55 (q, *J*= 7.5 Hz, 2H, CH_2CH_3), 2.11-2.20 (m, 2H, OCH_2CH_2), 1.13 (t, *J*= 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR 167.6 (2 x C=O), 162.3 (d, J_{FC}= -244.9 Hz), 157.2, 156.6, 155.0, 145.4, 143.6, 137.8, 135.1 (d, J_{FCCCC}= 3.1 Hz), 133.5, 131.7, 131.6, 131.1, 130.8, 130.3, 130.2, 129.9, 129.4, 129.3 (d, J_{FCCC}= 9.5 Hz), 129.1, 128.8, 128.3, 127.9, 127.6, 127.2, 126.2, 123.1, 115.3 (d, J_{FCC}= 21.0 Hz), 113.7 (Ar C), 71.8 (OCH_2Ar), 65.8 (OCH_2), 64.9 (OCH_2), 52.7 (2 x OCH_3), 29.8 (OCH_2CH_2), 23.3 (CH_2CH_3), 15.1 (CH_2CH_3).

3-(4-Methylcarboxyphenyl)-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy] propoxy]phenylbenzoic acid methyl ester (20)



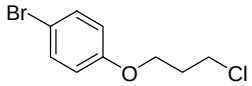
Trimethylsilyl chloride (0.58 g, 5.54 mmol) in dry acetonitrile (20 mL) was added to a mixture of **19** (1.9 g, 2.6 mmol) and sodium iodide (0.83 g, 5.54 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed with water, 10% sodium metabisulfate solution and brine. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetone/hydrochloric acid (20 mL) solution, stirred for half an hour and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The mixture was purified by flash chromatography (15% ethyl acetate in petroleum spirit) to afford a solid (1.2 g, 72%). ^{1}H NMR δ 8.01-8.08 (m, 4H, ArH), 7.06-7.80 (m, 12H, ArH), 6.61 (s, 1H, ArH), 4.32 (t, *J*= 6.0 Hz, 2H, OCH_2), 4.09 (t, *J*= 5.7 Hz, 2H, OCH_2), 3.89 (s, 6H, 2 x OCH_3), 2.58 (q, *J*= 7.4 Hz, 2H, $ArCH_2$), 2.21-2.27 (m, 2H, OCH_2CH_2), 1.14 (t, *J*= 7.4 Hz, 3H, $ArCH_2CH_3$). On large scale, the crude product was used in the next step without purification.

3-(4-Methylcarboxyphenyl)-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy] propoxy]phenyl benzoic acid (1)



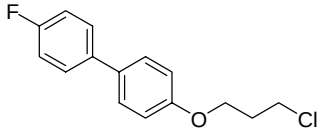
A solution of the diester **20** (200 mg, 0.32 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalized from acetone/petroleum spirit to afford a white solid (160 mg, 84%). m.p. 251-253 ºC; Found **C** 71.0, **H** 5.1%; $C_{37}H_{31}FO_7 \cdot H_2O$ requires **C** 71.1, **H** 5.3%; ^{1}H NMR (d_6-DMSO) δ 8.04-8.11 (m, 4H, ArH), 7.60-7.96 (m, 6H, ArH), 7.60-7.78 (m, 2H, ArH), 7.41 (apparent d, *J*= 8.8 Hz, 1H, ArH), 7.09-7.30 (m, 2H, ArH), 7.09 (apparent s, 1H, ArH), 6.65 (apparent s, 1H, ArH), 4.39 (t, *J*= 7.5 Hz, 2H, OCH_2), 4.14 (t, *J*= 7.2 Hz, 2H, OCH_2), 2.18-2.29 (m, 2H, OCH_2CH_2), 1.17 (t, *J*= 7.5 Hz, 3H, $ArCH_2CH_3$), the peak due to $ArCH_2CH_3$ (δ_H ~2.5) was coincidental to the peak of DMSO (δ_H 2.50); ^{13}C NMR 167.1, 156.1, 153.0, 143.6, 142.2, 135.0, 131.7, 130.7, 130.1, 129.9, 129.5, 129.4, 129.0, 128.1, 126.3, 122.7, 118.4, 114.7, 114.3, 113.3, 100.1 (Ar C), 64.9 (OCH_2), 64.0 (OCH_2), 28.5 (OCH_2CH_2), 22.1 ($ArCH_2$), 14.6 (CH_2CH_3), some signals are coincidental with each other.

4-Bromo-1'-(3-chloro-propoxy)benzene (22)



A mixture of 4-bromophenol (14.2 g, 0.082 mol), 1-bromo-3-chloropropane (33 g, 0.21 mol), anhydrous potassium carbonate (22.4 g, 0.16 mol) and dimethyl sulfoxide (50 mL) and butanone (130 mL) was heated at reflux for 24 hours. The resulting mixture was concentrated and the residue was diluted with ether. The organic layer was washed once with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product (17.1 g, 83%) as clear oil. The product was detected by GC-MS to be composed of 4-bromo-1'-(3-chloro-propoxy)benzene (**22**) [97.2%, *m*/*z* 248 (M^+, 29%, $C_9H_{10}{}^{35}Cl^{79}BrO$), 250 ($(M+2)^+$, 36%, $C_9H_{10}{}^{37}Cl^{79}BrO$, $C_9H_{10}{}^{35}Cl^{81}BrO$), 252 ($(M+4)^+$, 8.6%, $C_9H_{10}{}^{37}Cl^{81}BrO$), 174 (100%)] and 4-bromo-1'-(3-bromo-propoxy)benzene (**23**) [2.8%, *m*/*z* 292 (M^+, 22%, $C_9H_{10}{}^{79}Br^{79}BrO$), 294 ($(M+2)^+$, 45%, $C_9H_{10}Br^{79}Br^{81}O$), 292 ($(M+4)^+$, 22%, $C_9H_{10}{}^{81}Br^{81}BrO$), 174 (100%)]; ^{1}H NMR δ 7.43 (apparent d, *J*= 4.5 Hz, 2H, H3,5), 6.4 (apparent d, *J*= 4.5 Hz, 2H, H2,6), 4.14 (t, *J*=6.0 Hz, 2H, OCH_2), 3.68 (t, *J*=5.5 Hz, 2H, CH_2Cl), 2.22-2.40 (m, 2H, $OCH_2C\mathit{H}_2$); ^{13}C NMR 158.5 (C4), 133.0, 117.0, 113.8 (Ar C), 65.2 (OCH2), 42.0 (CH_2Cl), 32.8 ($OCH_2\mathit{C}H_2$). All the data was consistent with the literature.[156]

4'-(3-Chloro-propoxy)-4-fluorobiphenyl (24)

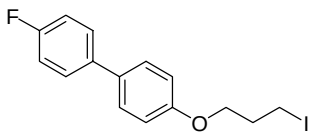


Method I A solution of **22** (4.67 g, 0.019 mol) in dimethoxyethane (60 mL) was added to a mixture of 4-fluorophenylboronic acid (3.31 g, 0.024 mol), tetrakistriphenylphosphine palladium (1.00 g, 0.1 mmol) and 2 M sodium carbonate solution (20 mL). The reaction

mixture was heated at reflux for 16 hours and the resulting mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford a cream solid (1.5 g, 30%). m.p. 41-43 ºC; GC-MS showed the purity was 95%, *m*/*z* 264 (M^+, 55%, C_{15} $H_{14}{}^{35}ClFO$), 266 ($(M+2)^+$, 17%, C_{15} $H_{14}{}^{37}ClFO$), 188 (100%); ^1H NMR δ 7.38-7.60 (m, 4 H, ArH), 6.80-7.15 (m, 4H, ArH), 4.16 (t, *J*= 6.3 Hz, 2H, OCH_2), 3.76 (t, *J*= 6.5 Hz, 2H, CH_2I), 2.27-2.29 (m, OCH_2CH_2), ^{13}C NMR 162.8 (d, J_{FC}= -235.3 Hz), 158.9, 138.6, 133.8 (d, J_{FCCCC}= 3.4 Hz), 128.9 (d, J_{FCCC}= 8.0 Hz), 128.7, 116.3 (d, J_{FCC}= 21.4 Hz), 115.5 (Ar C), 65.1 (OCH_2), 42.2 (CH_2Cl), 33.0 (OCH_2CH_2).

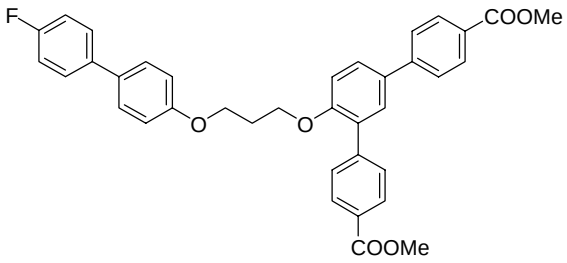
Method II A mixture of **22** (5 g, 0.02 mol) in dimethoxyethane (20 mL) was added to 4-fluorophenylboronic acid (3.4 g, 0.024 mol), palladium acetate (260 mg, 1.1 mmol), triphenylphosphine (302 mg, 1.1 mmol), potassium carbonate (6.9 g, 0.05 mol), tetrahydrofuran (40 mL) and water (15 mL). The reaction mixture was heated at reflux for 16 hours and the resulting solution was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed once with saturated aqueous ammonium chloride solution. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product (4.3 g, 82%). The spectra indicated the same as above.

4'-(3-Iodo-propoxy)-4-fluorobiphenyl (21)



Sodium iodide (8.0 g, 0.061 mol) was added to a solution of **24** (1.3 g, 4.9 mmol) in acetonitrile (20 mL). The reaction mixture was heated at reflux overnight and the resulting mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (1.49 g, 90%). m.p. 61-62 ºC; Found: **C** 50.5, **H** 3.9%, $C_{15}H_{14}FIO$ requires **C** 50.6, **H** 4.0%; GC-MS showed the purity was 98.5%, m/z 356 (M+, 100%); ^{1}H NMR δ 7.45-7.53 (m, 4H, ArH), 7.00- 7.22 (m, 4H, ArH) 4.14 (t, *J*= 5.8 Hz, 2H, OCH_2), 3.45 (t, *J*= 6.8 Hz, 2H, CH_2I), 2.29 (m, 2H, OCH_2CH_2); ^{13}C NMR 162.7 (d, J_{FC}= -245.3 Hz), 158.9, 137.6 (d, J_{FCCCC}= 3.4 Hz), 133.8, 129.0 (d, J_{FCCC}= 8.0 Hz), 128.7, 116.3 (d, J_{FCC}= 21.3 Hz), 115.6 (Ar C), 68.1 (OCH_2), 33.6 (OCH_2CH_2), 3.2 (CH_2I).

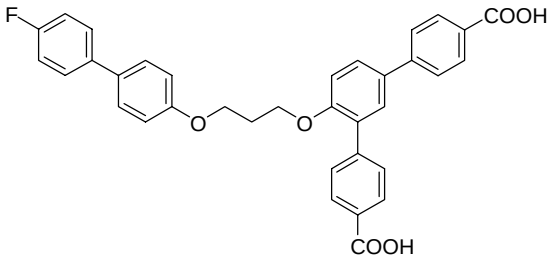
4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-[1,1';3',1'']terphenyl-4,4''-dicarboxylic acid dimethyl ester (25)



A mixture of the simplified left hand side **21** (2.2 g, 6.12 mmol), the diester **10** (1.23 g, 6.12 mmol), potassium carbonate (2.14 g, 15.3 mmol) and acetonitrile (20 mL) were stirred for 24 hours and the resulting solution was concentrated *in vacuo*. The

residue was diluted with ethyl acetate and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (2.2 g, 61%). m. p. 125-126 ºC; Found **C** 74.8, **H** 5.3%, $C_{37}H_{31}FO_6$ requires **C** 75.2, **H** 5.3%; ^{1}H NMR δ 8.04-8.11 (m, 4H, ArH), 7.42- 7.67 (m, 10H, ArH), 7.05- 7.14 (m, 3H, ArH), 6.88 (apparent d, *J*= 8.8 Hz, 2H, ArH), 4.25 (t, *J*= 6.0 Hz, 2H, OCH_2), 4.06 (t, *J*= 6.0 Hz, 2H, OCH_2), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.10- 2.25 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.7 (C=O), 162.7 (d, J_{FC}= -245.7 Hz), 159.0, 156.6, 145.5, 143.7, 137.7 (d, J_{FCCCC}= 3.4 Hz), 133.6, 131.2, 130.9, 130.3, 130.0, 129.3(d, J_{FCCC}= 9.1 Hz), 129.0, 128.8, 128.7, 127.3, 116.2 (d, J_{FCC}= 21.3 Hz), 115.5, 113.8 (Ar C), 65.8 (OCH_2), 64.9 (OCH_2), 52.7 (OCH_3), 29.8 (OCH_2CH_2), some signals are coincident with each other.

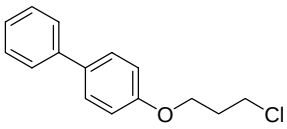
4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-[1,1';3',1'']terphenyl-4,4''-dicarboxylic acid (26)



A solution of the diester **25** (200 mg, 0.34 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated

in vacuo. The residue was recrystalized from acetone/petroleum spirit to afford the desired product as a white solid (154 mg, 81%). m.p. 279-281 ºC; Found **C** 74.2, **H** 4.8%; $C_{35}H_{27}FO_6$ requires **C** 74.7, **H** 4.8%; ^{1}H NMR (d_6-DMSO) δ 7.51-8.02 (m, 14H, ArH), 7.20-7.33 (m, 3H, ArH), 6.93-6.97 (m, 2H, ArH), 4.25 (t, *J*= 5.9 Hz, 2H, OCH_2), 4.08 (t, *J*= 5.9 Hz, 2H, OCH_2), 2.48-2.52 (m, 2H, OCH_2CH_2); ^{13}C NMR (d_6-DMSO) 167.2 (C=O), 167.1 (C=O), 161.4 (d, J_{FC}= -243.4 Hz), 158.0, 155.6, 143.6, 142.2, 136.2 (d, J_{FCCCC}= 3.1 Hz), 131.8, 131.7 (d, J_{FCCC}= 8.0 Hz), 129.9, 129.6, 129.3, 129.0, 128.1, 128.0, 127.7, 126.3, 115.4 (d, J_{FCC}= 21.0 Hz), 114.8, 113.6 (Ar C), 65.0 (OCH_2), 64.3 (OCH_2), 28.4 (OCH_2CH_2), some signals are coincident to each other.

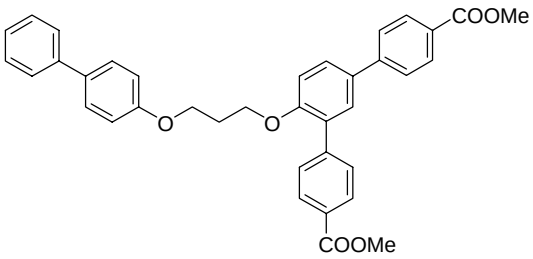
4-(3-Chloro-propoxy)biphenyl (29)



A mixture of 4-hydroxybiphenyl (1.7 g, 0.01 mol), 1-bromo-3-chloropropane (15.7 g, 0.1 mol), potassium carbonate (2.74 g, 0.02 mol) and butanone (20 mL) was heated at reflux for 24 hours. The reaction mixture was concentrated and the residue was diluted with ethyl acetate and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalized from dichloromethane/petroleum spirit to afford the desired product as a white solid (1.84 g, 75%). m.p. 66- 67 ºC, GC-MS showed the purity was > 99%, *m*/*z* 246 (M^+, 47%, $C_{15}H_{15}{}^{35}ClO$), 248 ($(M+2)^+$, 16%, $C_{15}H_{15}{}^{37}ClO$), 170 (100%); ^{1}H NMR δ 7.28- 7.58 (m, 7H, ArH), 6.95-7.02 (m, 2H, ArH), 4.16 (t, *J*= 5.9 Hz, 2H, OCH_2), 3.77 (t, *J*= 6.2 Hz, 2H, CH_2Cl), 2.20-2.32 (m, 2H, OCH_2CH_2); ^{13}C NMR 160.0 (C4), 141.5, 134.8,

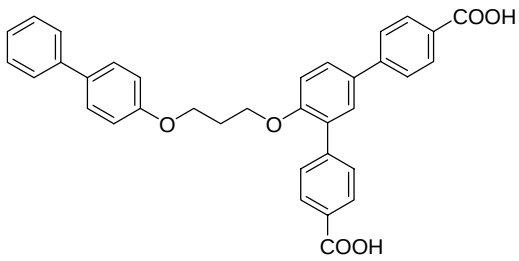
129.4, 128.9, 127.5, 127.4, 115.5 (Ar C), 65.1 (OCH_2), 42.2 (CH_2Cl), 33.0 (OCH_2CH_2).

4'-[3-(Biphenyl-4-yloxy)-propoxy]-[1,1';3',1'']terphenyl-4,4''-dicarboxylic acid dimethyl ester (31)



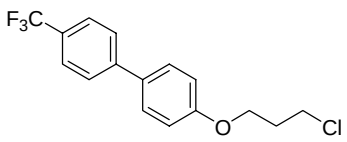
A mixture of **29** (0.49 g, 2 mmol), sodium iodide (1.5 g, 10 mmol) and butanone (30 mL) was heated at reflux overnight. Then diester **10** (0.72 g, 2 mmol) and potassium carbonate (0.55 g, 4 mmol) were added to the reaction mixture. The reaction mixture was heated at reflux for 12 hours and concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (15% ethyl acetate in petroleum spirit) to afford the desired product as a white solid which was recrystalized from dichloromethane/ petroleum spirit (0.70 g, 61%). m.p. 119-120 ºC; ^{1}H NMR δ 8.04-8.11 (m, 4H, ArH), 7.27-7.67 (m, 12H, ArH), 7.12 (apparent d, *J*= 8.8 Hz, 1H, ArH), 6.89-6.94 (m, 3H, ArH), 4.25 (t, *J*= 6.0 Hz, 2H, OCH_2), 4.07 (t, *J*= 5.9 Hz, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 2.19-2.26 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.7 (C=O), 159.0, 156.6, 145.5, 143.7, 133.6, 131.2, 130.8, 130.3, 130.0, 129.4, 129.2, 129.0, 128.8, 127.5, 127.4, 127.2, 115.4, 113.8 (ArC), 65.8 (OCH_2), 64.9 (OCH_2), 52.8 (2 x OCH_3), 29.8 (OCH_2CH_2), some signals are coincidental with each other.

4'-[3-(Biphenyl-4-yloxy)propoxy]-[1,1';3',1'']terphenyl-4,4''-dicarboxylic acid (27)



The solution of **31** (200 mg, 0.35 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 M, 5 mL) with stirring at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalized from acetone/petroleum spirit to afford a white solid (181 mg, 95%). m.p. 249-251 ºC; Found **C** 74.6, **H** 5.0%; $C_{35}H_{28}O_6 \cdot H_2O$ requires **C** 74.7, **H** 5.4%; ^{1}H NMR (d_6-DMSO) δ 8.06-8.12 (m, 4H, ArH), 7.40-7.96 (m, 14H, ArH), 7.06 (apparent d, *J*= 8.8 Hz, 2H, ArH), 4.36 (t, *J*=5.7 Hz, 2H, OCH_2), 4.33 (t, *J*=5.7 Hz, 2H, OCH_2), 2.20-2.25 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.2 (C=O), 167.1 (C=O), 158.0, 155.6, 143.6, 142.2, 139.8, 132.6, 131.8, 129.9, 129.6, 129.4, 129.1, 129.0, 128.8, 128.1, 127.7, 126.8, 126.7, 126.4, 126.2, 115.0, 114.8, 113.6 (Ar C), 65.0 (OCH_2), 64.3 (OCH_2), 28.4 (OCH_2CH_2).

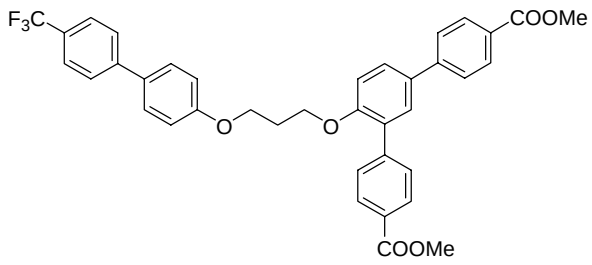
4-(3-Chloro-propoxy)-4'-trifluoromethylbiphenyl (32)



A mixture of 1-bromo-4(3-chloro-propoxy) benzene **22** (2.0 g, 8 mmol), 4-(trifluromethyl)-phenylboronic acid (1.6 g, 9.6 mmol), palladium acetate (0.1 g, 0.4 mmol), potassium carbonate (2.6 g,

16 mmol), triphenylphosphine (0.108g, 0.4 mmol), THF (10 mL), DME (10 mL) and water (5 mL) was degassed three times and then heated at reflux for 16 hours. The reaction mixture was concentrated and the residue was diluted with ethyl acetate and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product which was recrystalized from dichloromethane/petroleum spirit (2.1 g, 85%). m.p. 73-74 ºC; GC-MS showed the purity was >99%; *m/z* 314 (M^+, 45%, $C_{14}H_{14}{}^{35}ClF_3O$), 316 ($(M+2)^+$, 15%, $C_{14}H_{14}{}^{37}ClF_3O$), 238 (100%); ^{1}H NMR δ 7.66-7.70 (m, 4H, ArH), 7.54 (apparent d, *J*= 8.8 Hz, 2H, ArH), 7.01 (apparent d, *J*= 8.8 Hz, 2H, ArH), 4.18 (t, *J*= 6.0 Hz, 2H, OCH_2), 3.76 (t, *J*= 6.0 Hz, 2H, OCH_2), 2.21-2.33 (m, 2H, OCH_2CH_2); ^{13}C NMR 159.7 (C4), 144.9, 133.1, 129.1, 127.8, 127.6, 126.4 (q, *J*= 3.6 Hz, CF_3), 115.7 (Ar C), 65.1 (OCH_2), 42.1 (CH_2Cl), 32.9 (OCH_2CH_2). Some signals are coincidental with each other.

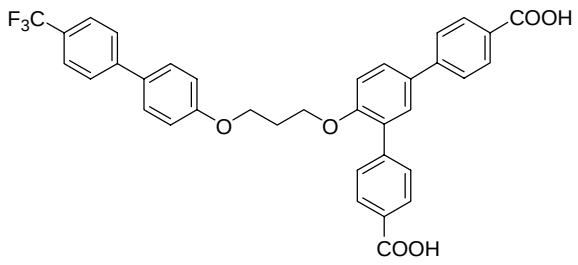
4'-[3-(4'-Trifluoromethyl-biphenyl-4-yloxy)-propoxy]-[1,1';3',1'']terphenyl-4,4″-dicarboxylic acid dimethyl ester (33)



A mixture of the chloride **32** (1.05 g, 3.3 mmol), sodium iodide (2.5 g, 15.5 mmol) and actonitrile (30 mL) was heated at reflux overnight. To the reaction mixture was added the diester **10** (1.2 g, 3.3 mmol) and potassium carbonate (0.91 g, 6.6 mmol)

and the mixture was heated at reflux for 12 hours. The residue was then concentrated *in vacuo* and the residue was diluted with ethyl acetate and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (15% ethyl acetate in petroleum spirit) to afford the desired product as a white solid which was recrystalized from dichloromethane/petroleum spirit (0.41 g, 20%). m.p. 159-160 ºC; Found **C** 70.9, **H** 4.9%; $C_{38}H_{31}F_3O_6$ requires **C** 71.2, **H** 4.9%; ^{1}H NMR δ 8.04-8.11 (m, 4H, ArH), 7.27-7.67 (m, 12H, ArH), 7.13 (apparent d, *J*= 8.1 Hz, 1H, ArH), 6.90-6.95 (m, 2H, ArH), 4.23 (t, *J*= 5.9 Hz, 2H, OCH_2), 4.08 (t, *J*= 5.9 Hz, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.23-2.26 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.7 (C=O), 159.7, 156.6, 145.5, 143.7, 133.7, 133.0, 131.2, 130.9, 130.0, 129.4, 129.3, 129.0, 128.8, 127.6, 127.2, 126.3 (q, *J*= 3.9 Hz, CF_3), 126.3, 115.6, 113.7 (Ar C), 65.7 (OCH_2), 64.9 (OCH_2), 52.8 (2 x OCH_3), 29.7 (OCH_2CH_2). Some signals are coincident to each other.

4'-[3-(4'-Trifluoromethyl-biphenyl-4-yloxy)-propoxy]-[1,1';3',1'']terphenyl-4, 4''-dicarboxylic acid (28)



A solution of the diester **33** (200 mg, 0.31 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 M, 5 mL) with stirring at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the

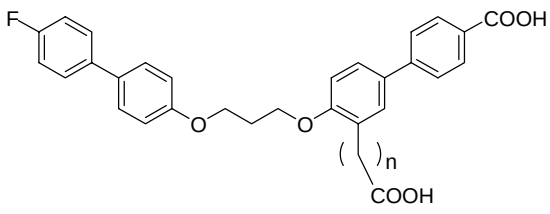
residue was diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystalized from acetone/petroleum spirit to afford a white solid (160 mg, 83%). m.p. 280-281 ºC; Found **C** 67.8, **H** 4.3%; $C_{36}H_{27}F_3O_6 \cdot H_2O$ requires **C** 68.6, **H** 4.6%; ^{1}H NMR δ 8.00-7.96 (m, 5H, ArH), 7.64-7.89 (m, 11H), 7.32 (apparent d, *J*= 8.8 Hz, 1H, ArH), 7.00 (apparent d, *J*= 8.8 Hz, 2H, ArH), 4.26 (t, *J*= 5.9 Hz, 2H, OCH_2), 3.33 (t, *J*= 5.9 Hz, 2H, OCH_2), 2.16-2.23 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.1 (C=O), 158.8, 155.6, 143.7, 143.6, 142.2, 131.8, 130.8, 130.0, 129.9, 129.5, 129.3, 129.0, 128.2, 127.3, 126.8, 126.3, 125.6 (q, *J*= 3.9 Hz), 115.0, 113.5 (Ar C), 65.0 (OCH_2), 64.4 (OCH_2), 28.3 (OCH_2CH_2).

Chapter III Synthesis of biphenyl-biphenyl analogues

3.1 Introduction

The two amino acid residues in insulin, A21 (C-terminal asparagine) and B21 (glutamic acid) have been shown to be critical in the binding of insulin to the insulin receptor. Therefore, in order to have a better understanding of the impact of the two carboxylic acids groups in **IM140**, a series of analogues were prepared in which the position of the two carboxylic acid on the inner and outer rings were systematically changed. This section will focus on the synthesis of analogues with carboxylic acids in different positions on a biphenyl-biphenyl framework.

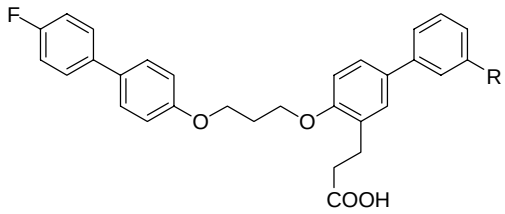
The flexibility of the side chain and reach of the carboxylic acids were of concerns to the computer modeling team because the methylene chain is so flexible that it might lose specificity. Through synthesizing a series of different length side chain analogues (**Figure 3.1**) and testing their biological activity, a structure-activity relationship (SAR) between the length of the chain and the biological affect could be better understood. The feedback from these results will allow the model to be modified, which will in turn provide better predictive power.



n= 0-2

Figure 3.1

As the importance of the carboxylic acid on the outer ring of the right hand side biphenyl was still unknown in binding to the insulin receptor, analogues with changes to this ring will be synthesized. The strategy is to shift or remove the carboxylic acid group on the outer ring of the right hand biphenyl (**Figure 3.2**).



R= COOH, H

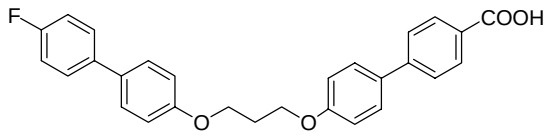
Figure 3.2

In this chapter two types of analogues will be discussed: 1) analogues with different length carboxylic acid side chains and 2) analogues with change to the position of the carboxylic acid on the outer ring.

3.2 Results and discussion

3.2.1 Comparison analogue

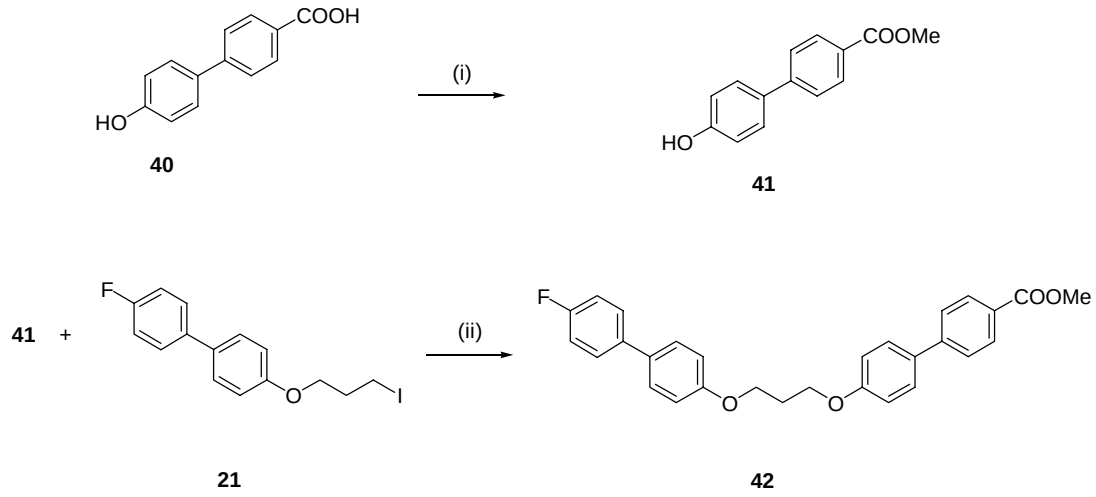
The comparison analogue **39** has the basic biphenyl-biphenyl skeleton but without the side chain acid group. This was chosen to demonstrate the importance of side chain acid (**Figure 3.3**).



39

Figure 3.3

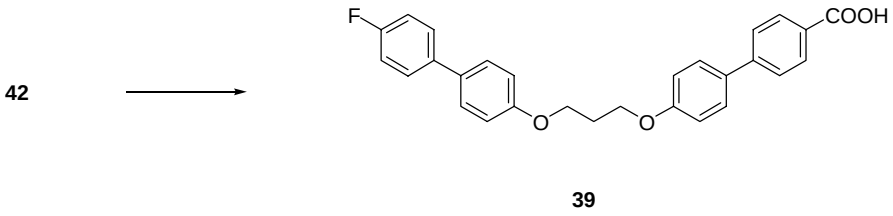
The synthesis of **39** is very straight forward compared to the other analogues. The methodology still followed the convergent method to prepare the left and right hand side separately and then couple them together. Treatment of 4'-hydroxy-biphenyl-4-carboxylic acid (**40**) with methanol/H_2SO_4 produced the methyl ester **41**, which was then coupled with the simplified left hand side **21** to yield the ester **42** in moderate yield (60%) (**Scheme 3.1**).



Scheme 3.1 *Reagents*: (i) MeOH, H_2SO_4; (ii) K_2CO_3, MeCN

The ^1H and ^{13}C NMR spectra confirmed the formation of **42**. In the ^1H NMR spectrum two overlapping triplets at δ_H 4.20-4.27 were assigned to the oxymethylenes which confirmed the formation of the chain. The integration showed 16 aromatic protons relative to three protons from methoxy group (δ_H 3.94), which was consistent with the structure. In the ^{13}C NMR spectrum the long range fluorine coupling was observed as usual, which indicated the presence of the left hand side.

Hydrolysis with sodium hydroxide in methanolic THF, followed by acidification provided the carboxylic acid **39** in good yield (84%) (**Scheme 3.2**). The absence of signals due to the methoxy group in the ^1H and ^{13}C NMR spectra clearly indicates the success of the hydrolysis.



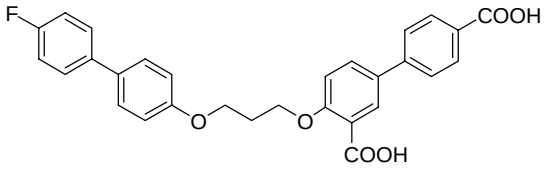
Scheme 3.2 *Reagents*: NaOH, THF, MeOH; HCl

3.2.2 Analogues with different side chains

In this section modification was carried out on the length of the carboxylic acid chain on the inner ring ranging from zero methylenes to two methylenes.

3.2.2.1 Synthesis of analogues with no methylenes in the side chain

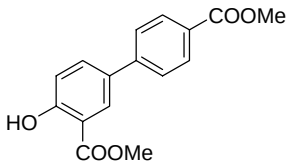
Analogue **43** (**Figure 3.4**) was the first analogue in the series used to determine the impact of the length of the side chain acid on structure activity relationship.



43

Figure 3.4

The initial synthesis of **43** still followed the standard convergent method to prepare both of the sides separately and then couple them. Because the simplified left hand side had been synthesized, the synthesis required only the preparation of the right hand side **44** (**Figure 3.5**).

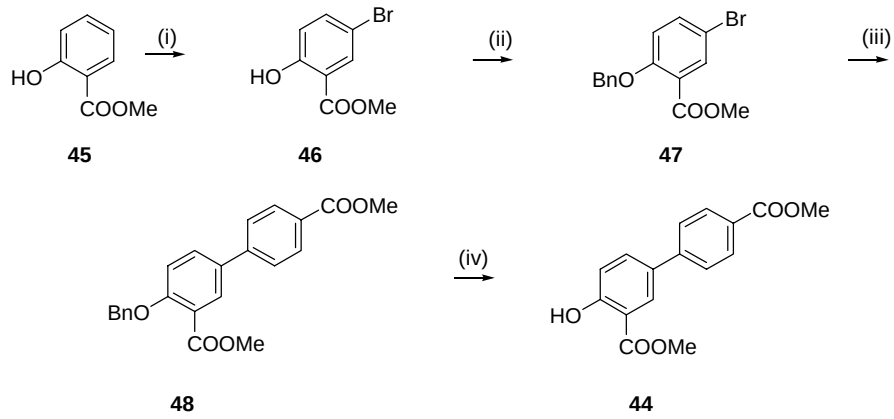


44

Figure 3.5

The first attempt to prepare **44** directly from methyl 5-bromosalicylate *via* a Suzuki coupling reaction was unsuccessful. As described in the previous chapter, the

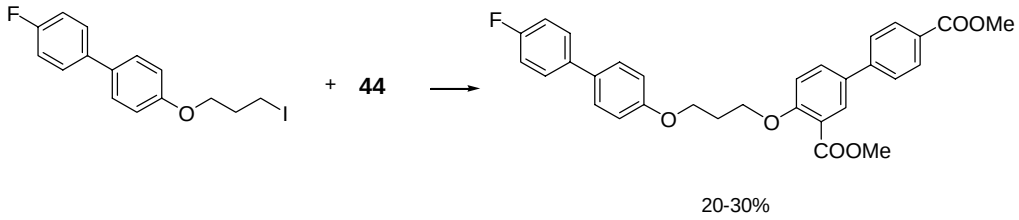
phenol was found unsuitable for the Suzuki coupling reaction. Therefore protection of the phenol was necessary before the Suzuki coupling. Benzylation of compound **46** was successfully performed to give the protected bromide **47**. Subsequent Suzuki coupling reaction introduced the second aromatic ring very smoothly (78%). Debenzylation provided the phenol **44** in good yield (72%) (**Scheme 3.3**).



Scheme 3.3 *Reagents*: (i) Br_2, HOAc; (ii) BnBr, K_2CO_3, acetone; (iii) $(HO)_2BC_6H_4COOMe$, $Pd(OAc)_2$, PPh_3, THF, DME, H_2O, K_2CO_3; (iv) Me_3SiCl, NaI, MeCN

The ^1H and ^{13}C NMR spectra confirmed the synthesis of **44**. The ^1H NMR spectrum showed the typical signals due to the A and X parts of an AMX splitting system. A doublet of doublets at δ_H 7.74 was assigned to the A part and a doublet at δ_H 7.09 was assigned to the X part from AMX system; the M part was masked within the signals of the aromatic protons. Two signals with very similar chemical shifts (δ_H 4.00, 3.94) were assigned to two methoxy groups. The signals for these methoxy groups were also close together in the ^{13}C NMR spectrum (δ_C 53.2, 52.8). The GC-MS showed single peak for the molecular ion *m*/*z* at 286 which was consistent with the formula $C_{16}H_{14}O_5$.

Treatment of **44** with the simplified left hand side **21** and potassium carbonate using the standard coupling procedure described in Chapter II gave the coupled product **45** in poor yield (20-30%) (**Scheme 3.4**). A possible reason is that the intramolecular hydrogen bonding made the deprotonation of the phenol, the critical process of the coupling reaction, much harder than usual.

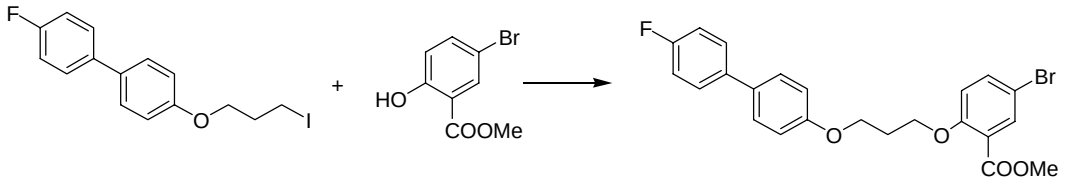


21 **45**

Scheme 3.4 *Reagents*: K_2CO_3, MeCN

The ^1H and ^{13}C NMR spectra confirmed the linkage between both sides. The two triplets (δ_H 4.34 and 4.28) were assigned to the oxymethylenes. Two slightly different methoxy groups could be observed (δ_H 3.94 and 3.90) as well. In the ^{13}C NMR the usual fluorine long distance coupling was observed, which indicated the presence of the left hand side.

In order to shorten the synthetic steps and improve the reaction yield, synthesis of **45** was approached by an alternative method. Instead of coupling the left and right hand sides, the bromosalicylate **46** was coupled with the simplified left hand side (**21**). Since **46** was relatively easy to prepare, five mole equivalents were used in coupling with the simplified left hand side (**Scheme 3.5**). This reaction proceeded in good yield (66%).



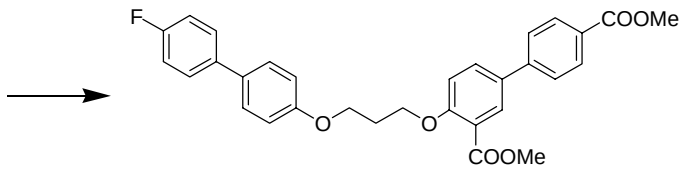
21 **46** **49**

Scheme 3.5 *Reagents*: K_2CO_3, MeCN

Analysis of the ^1H NMR and ^{13}C NMR spectra confirmed the formation of **49**. Two overlapping triplets (δ_H 4.20-4.29) were assigned to the two oxymethylenes, which was an indication of successful coupling of both sides. Integration showed 11 aromatic protons relative to the three protons from the methoxy group (δ_H 3.87) which was consistent with the structure. In the ^{13}C NMR spectrum the usual fluorine long range coupling could be observed, which indicated the presence of left hand side.

The bromide **49** was then subjected to a Suzuki coupling reaction to introduce the final aromatic ring required for **45** in good yield (78%) (**Scheme 3.6**). The ^1H and ^{13}C NMR spectra showed the product was the same as obtained by the previous method. Comparing those two different methods, the first method took 7 steps with an overall yield of 5%; the second route took 5 steps with an overall yield of 23%.

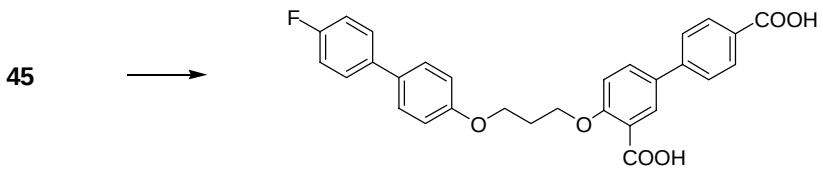
49



45

Scheme 3.6 *Reagents*: 4-$(HO)_2BC_6H_4COOMe$, $Pd(OAc)_2$, PPh_3, THF, DME, H_2O, K_2CO_3

Hydrolysis of the diester **45** provided the final acid derivative **43** in good yield (91%) (**Scheme 3.7**). The disappearance of signals due to the two methoxyl groups in the ^{1}H and ^{13}C NMR spectra confirmed the success of this reaction.

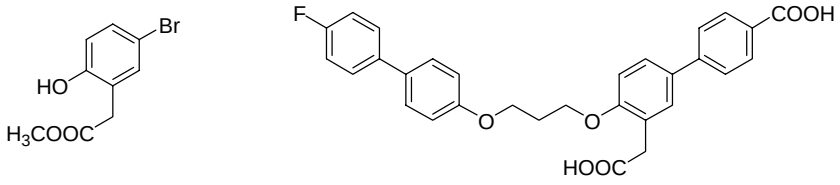


43

Scheme 3.7 *Reagents*: NaOH, THF, MeOH; HCl

3.2.2.2 Synthesis of derivative with one methylene in the side chain

Following the step-wise strategy used in the synthesis of **43**, the bromide **50** was prepared to couple the simplified left hand side in order to synthesize the desired analogue **51** (**Figure 3.6**).

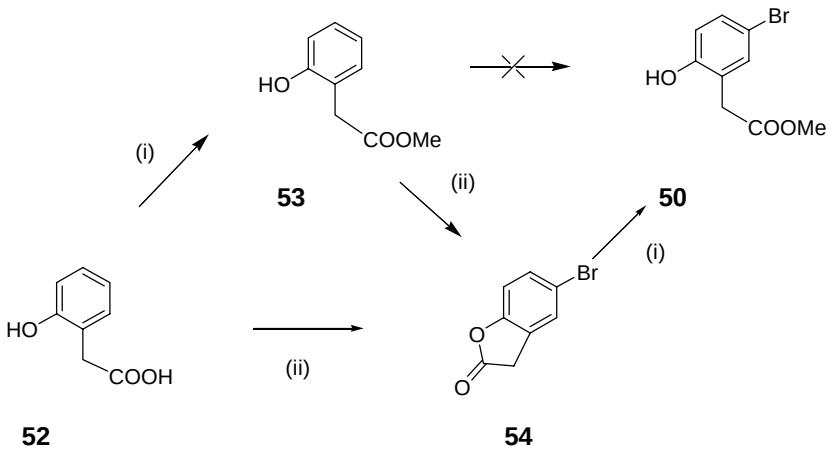


50 **51**

Figure 3.6

Treatment of 2-hydroxyphenylacetic acid with methanol/sulfuric acid afforded the ester **53** in good yield (92%). Bromination with one equivalent of bromine introduced a bromine atom in the *para* position. Surprisingly after bromination, the product obtained was the lactone **54** instead of **50**. Ring opening of the lactone **54** by esterification with methanol provided the methyl ester **50** without any problem. An alternative sequence was investigated in which 2-hydroxyphenylacetic acid was brominated directly and unsurprisingly the final

product was **54** (74%). This clearly indicated that esterification in the first step was not necessary (**Scheme 3.8**).



Scheme 3.8 *Reagents*: (i) H_2SO_4, MeOH; (ii) Br_2, HOAc

The ^1H and ^{13}C NMR spectra confirmed the formation of **50**. Two singlets at δ_H 3.76 and 3.64 were assigned to the methoxy group and the methylene in the chain, respectively. Relative to three protons from the methoxy group, integration of three aromatic protons were observed. When **50** was analyzed by GC-MS, two peaks were observed: one corresponding to **50** and the other to the lactone **54** (**Figure 3.7a**). It was suspected that lactonization either occured when the sample was injected (240 ºC) into the GC-MS, or happened inside the GC column (300 ºC). Therefore cool on column injection was performed, delivering a cold sample of **50** directly to column. The resulting chromatogram showed one peak, corresponding to compound **50**, which clearly indicated that the lactonization did occur when the sample was injected (**Figure 3.7b**).

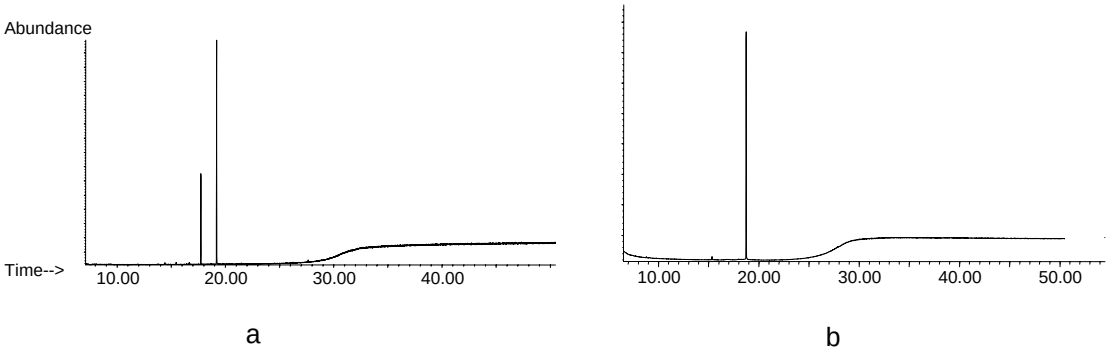
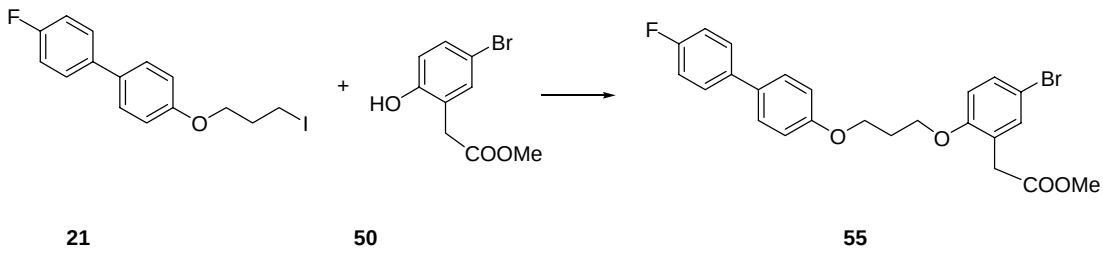


Figure 3.7 GC-MS chromatograms of compound **50** using (a) normal injection and (b) cool-on-column injection

Treatment of the simplified left hand side **21** with five mole equivalents of **50** gave the bromide **55** in reasonable yield (55%) (**Scheme 3.9**).

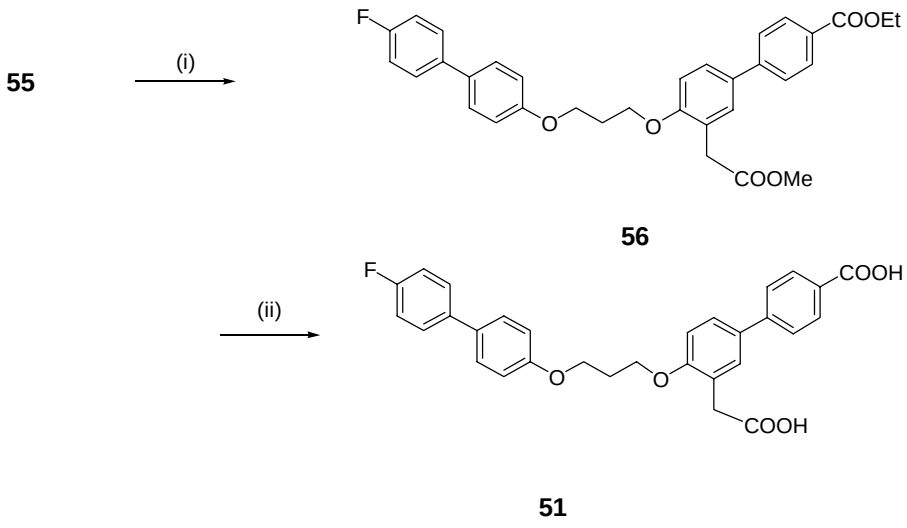


21 **50** **55**

Scheme 3.9 *Reagents*: K_2CO_3, butanone

The bromide **55** was subjected to a Suzuki coupling reaction to introduce the final aromatic ring and subsequent hydrolysis provided the acid analogue **51** in good yield (91%) (**Scheme 3.10**). The ^1H and ^{13}C NMR spectra confirmed the formation of **51**. In the ^1H NMR spectrum the two overlapping triplets were assigned to the oxymethylenes next to the oxygen atoms. Relative to those four protons, an integration of fifteen aromatic protons was consistent with the structure of **51**. The singlet at δ_H 3.58 was assigned to the methylene in the side chain which indicated the presence of right hand side. In the ^{13}C NMR spectrum, the long range fluorine coupling was observed as usual which exhibited the presence of the left hand side.

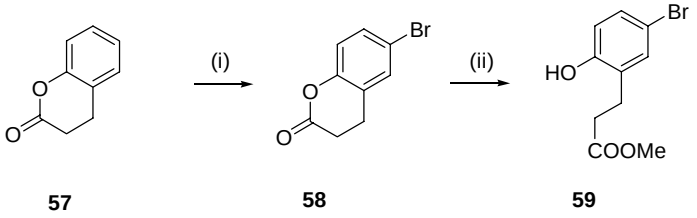
The elemental analysis (**C** 72.0, **H** 5.1%) was consistent with the formula $C_{30}H_{25}FO_6$ (**C** 72.0, **H** 5.1%).



Scheme 3.10 *Reagents*: i) 4-$(HO)_2BC_6H_4COOEt$, $Pd(OAc)_2$, PPh_3, THF, DME, H_2O, K_2CO_3; ii) NaOH, THF, MeOH; HCl

3.2.2.3 Synthesis of analogue with two methylenes in the side chain

The strategy used for the synthesis of compound **51** was applied in synthesizing the analogue with two methylenes in the chain. Bromination of the commercially available starting material, 3,4-dihydrocoumarin, produced the bromide **58** in good yield (73%). Ring opening of the lactone with methanol gave the desired ester **59** (81%) (**Scheme 3.11**).



Scheme 3.11 *Reagents*: (i) Br_2, HOAc; (ii) H_2SO_4, MeOH

The ^1H and ^{13}C NMR spectra confirmed the formation of **59**. In the ^1H NMR spectrum the singlet at δ_H 3.77 was assigned to the methoxy group from the ester.

Two triplets at δ_H 2.85 and 2.71 belong to the two methylenes from the side chain. The ^{13}C NMR spectrum showed 7 signals, between δ_C 100 and 180, representing 6 aromatic carbons and 1 carbonyl carbon. Similar to compound **50**, two peaks were observed in the GC-MS chromatogram (due to compounds **58** and **59**) and again cool on column injection provided a single peak chromatogram (**Figure 3.8**).

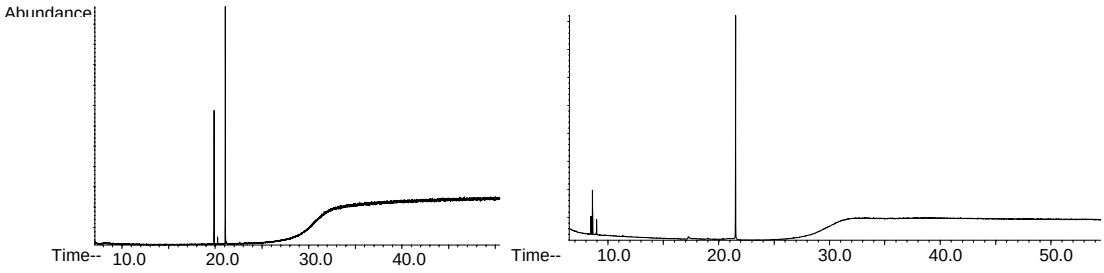
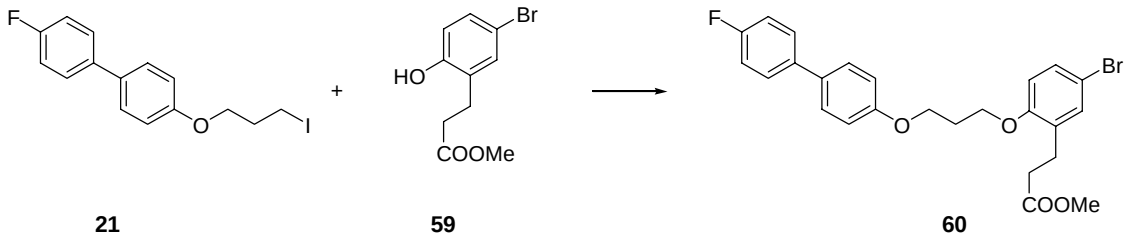


Figure 3.8 GC-MS chromatograms compound **59** using (a) normal injection and (b) cool-on-column injection

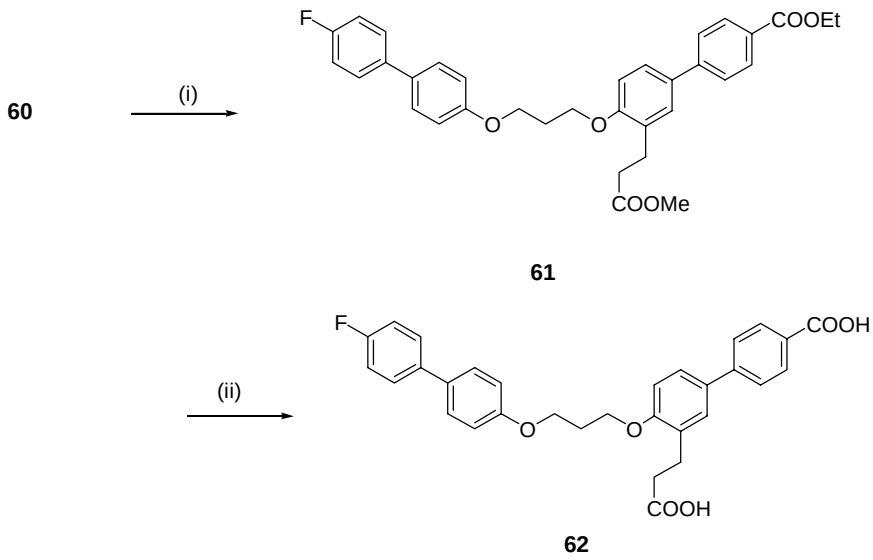
The simplified left hand side **21** was then treated with five equivalents of **59** to afford the bromide **60** in reasonable yield (50%) (**Scheme 3.12**). In the ^1H NMR spectrum two triplets at δ_H 4.20 and 4.16 were assigned to the oxymethylenes, which confirmed the linkage of both sides. The peak at δ_H 3.66 was assigned to the methoxy group and relative to those three protons, an integration for eleven aromatic protons was consistent with the structure of **60**.



21 **59** **60**

Scheme 3.12 Reagents: K_2CO_3, butanone

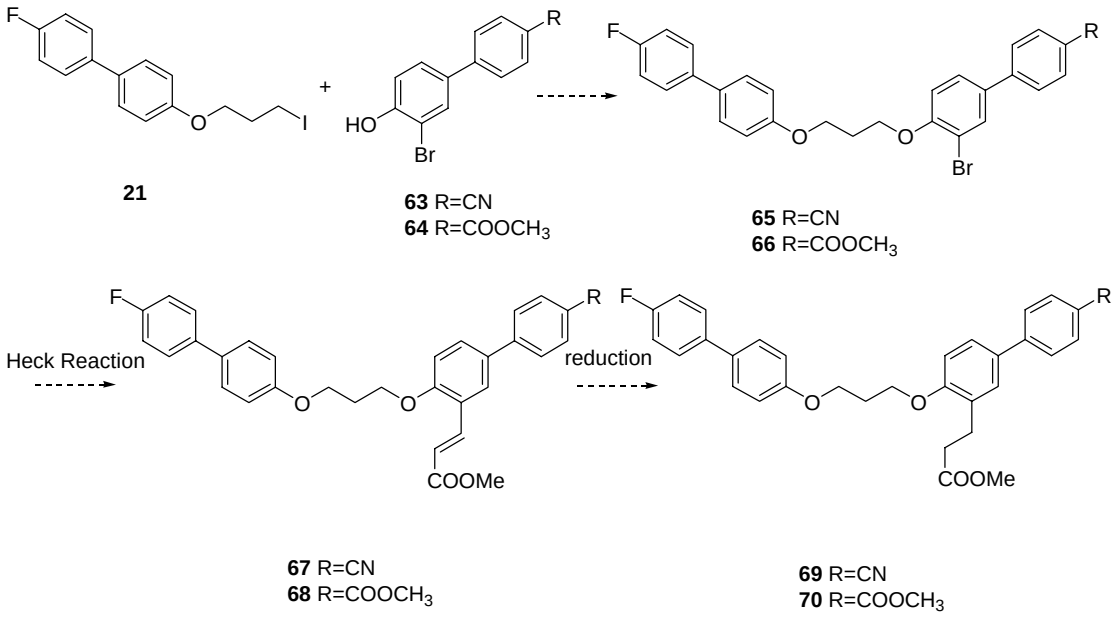
A Suzuki coupling reaction between the bromide **60** and 4-ethoxycarbonylphenylboronic acid introduced the final ring in moderate yield (63%). Hydrolysis of the ester provided the acid derivative **62** in excellent yield (91%) (**Scheme 3.13**).



Scheme 3.13 *Reagents*: (i) 4-$(HO)_2BC_6H_4COOEt$, $Pd(OAc)_2$, PPh_3, THF, DME, H_2O, K_2CO_3; (ii) NaOH, THF, MeOH; HCl

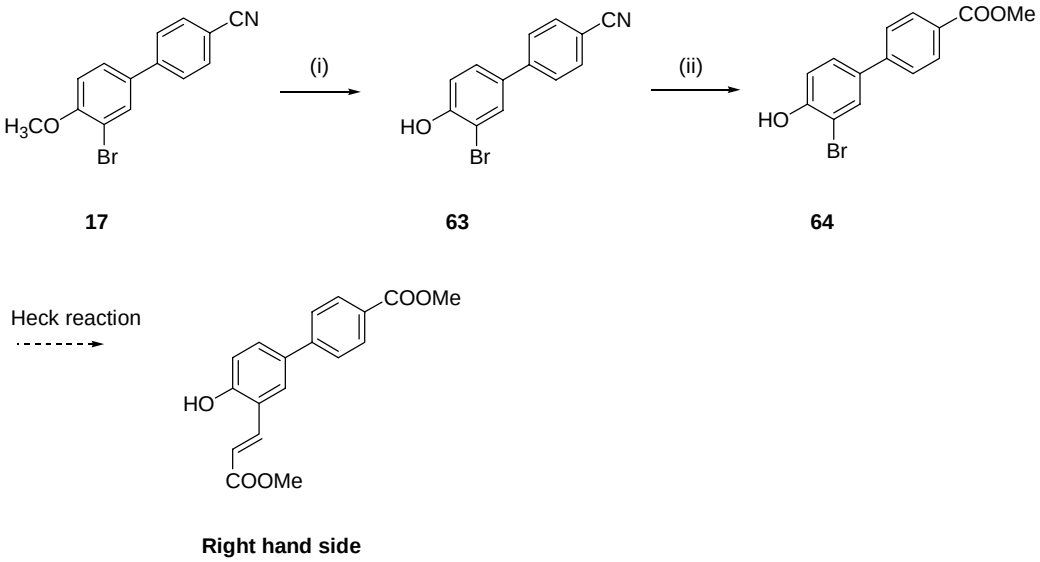
Analysis of the ^1H and ^{13}C NMR spectra confirmed the formation of **62**. In the ^1H NMR spectrum two overlapping triplets at δ_H 4.30-4.33 were assigned to the oxymethylenes. Another two triplets at δ_H 2.64 and 2.95 belong to the methylenes on the side chain. In the ^{13}C NMR spectrum two carbonyl peaks at δ_C 167.0 and 173.8 and the usual fluorine coupling were observed..

An alternative synthesis of **62** would involve coupling the brominated right hand side **64** with the simplified left hand side, **21**, and subsequent Heck reaction to introduce the side chain acid group (**Scheme 3.14**).



Scheme 3.14 Possible alternative synthetic route for **62**

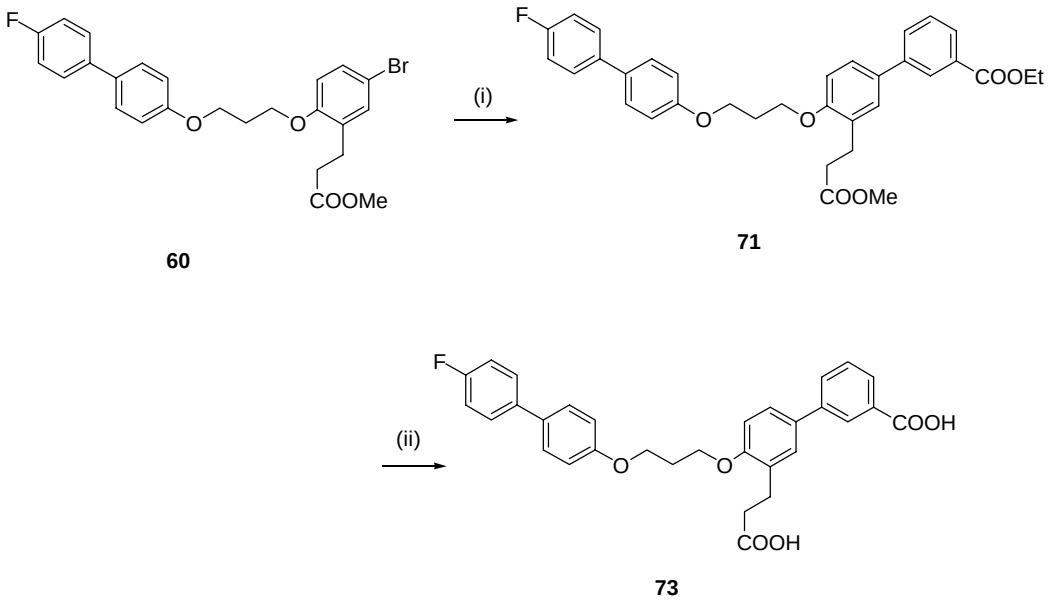
Demethylation of compound **17** afforded the phenol **63** in moderate yield (77%). Hydrolysis of compound **63** followed by esterification then provided the ester **64**. Both **63** and **64** could be coupled with the simplified left hand side and then the side chain could be introduced *via* a Heck reaction (**Scheme 3.15**).[157] This was a reserve plan for **62** and further synthesis will be considered depending on the biological testing of **62**. The unsaturated analogues (**67** and **68**) available through the Heck reaction are also at interest as the side chain is less flexible.



Scheme 3.15 *Reagents*: (i) pyridine hydrochloride, 170-180 ºC; (ii) KOH, MeOH; H_2SO_4, MeOH

3.2.3 Analogues with modification of the outer carboxylic acid

Since the analogues with two-methylenes in the side chain have the same chain length as **IM140**, these types of analogues are more likely to present similar biological activity as **IM140**. The preparation of the bromide **60** provided great opportunities to make derivatives from the key intermediate. By reacting **60** with various boronic acids, a variety of analogues could be easily synthesized. One of the analogues is outlined in **Scheme 3.16**.



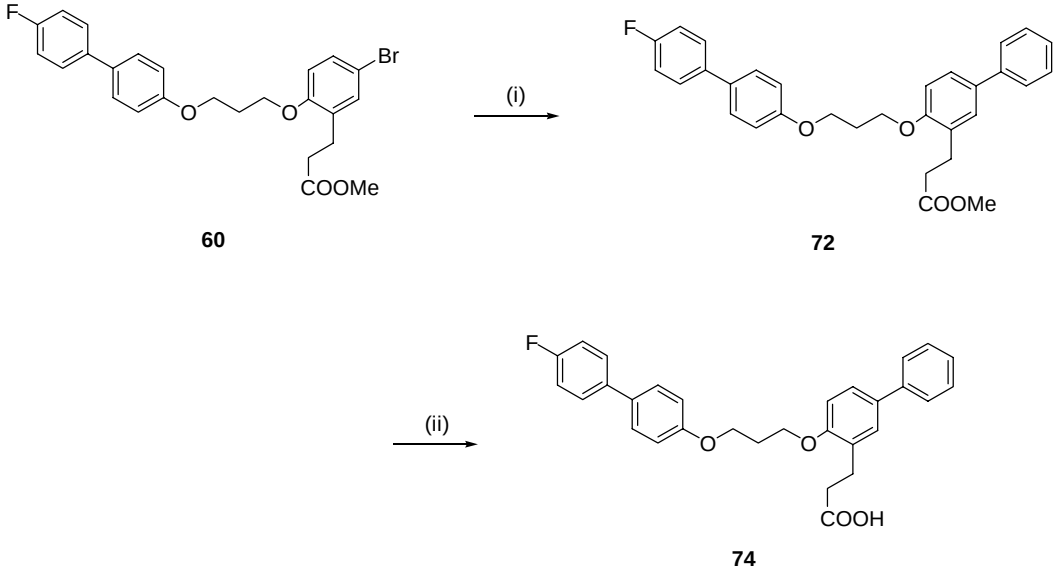
60 **71** **73**

Scheme 3.16 *Reagents*: (i) 3-$(HO)_2BC_6H_4COOEt$, $Pd(OAc)_2$, PPh_3, THF, DME/H_2O, K_2CO_3; (ii) THF, MeOH, NaOH; HCl

Suzuki coupling of **60** with 3-methoxycarbonylphenylboronic acid, using the previous described method, provided the ester **71** smoothly (85%). Hydrolysis of the ester **71** provided the desired acid analogue **73** in moderate yield (69%) (**Scheme 3.17**). The ^1H NMR spectrum of **73** was similar to the *para*-acid derivative **62** except the difference in the aromatic region. The singlet at δ_H 8.23 was assigned to the aromatic proton between the aromatic ring and the *meta* carboxylic acid, which was a typical difference between *para* and *meta* analogues. The elemental analysis (**C** 72.4, **H** 5.4%) was consistent with the formula $C_{31}H_{27}FO_6$ (**C** 72.4, **H** 5.3%).

Suzuki coupling of **60** with phenylboronic acid, using the previous described method, provided the ester **72** in good yield (85%) and subsequent hydrolysis provided the acid **74**. Both **72** and **74** were obtained as viscous oils and consequently it was difficult to obtain satisfactory elemental analysis. Since 80% purity is the

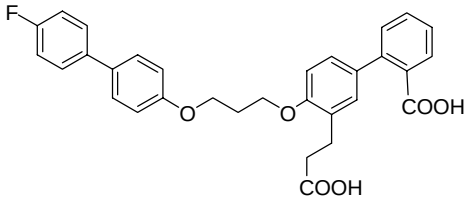
minimum requirement of purity for preliminary biological tests,[‡‡‡‡‡‡‡‡‡] further purification will be carried out only if **74** had moderate to high biological activity.



60 **72** **74**

Scheme 3.17 *Reagents*: (i) $C_6H_5B(OH)_2$, $Pd(OAc)_2$, PPh_3, THF, K_2CO_3, DME/H_2O; ii) NaOH, THF, CH_3OH; (ii) NaOH, THF, MeOH; HCl

The *ortho*- carboxylic acid analogue **75** (**Figure 3.7**) was also a possible target, but it was expected that the hindered carboxylic acid might be less active than the *meta*- and *para*- analogues. The synthesis of the analogue will be carried out only if the *meta* derivative was found to be more active than the *para* derivative.



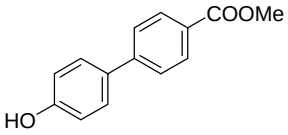
75

Figure 3.7

[‡‡‡‡‡‡‡‡‡] This requirement is from endocrinologists in WABRI, which shows the minimum quality requirement. Once the biology testing shows good activity, further purification will be carried out to minimize the error.

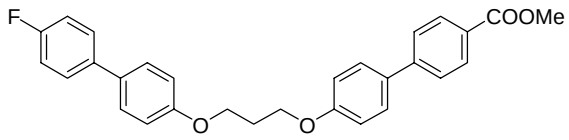
Experimental

4-(4'-Hydroxyphenyl) benzoic acid methyl ester (41)



A mixture of 4-(4'-hydroxyphenyl)benzoic acid (1.14 g, 0.05 mol), methanol (10 mL) and concentrated sulfuric acid (1 mL) was heated at reflux (16 h). The reaction mixture was poured into ice water (300 mL) and the resulting precipitate was collected and dried to afford a white solid which was recrystallized from methanol (0.91 g, 86%). m.p. 219-220 ºC (Lit.[158] m.p. 221-223 ºC); ^{1}H NMR (d_6-acetone) δ 7.95 (apparent d, *J*= 4.0 Hz, 2H, H2,6), 7.79 (apparent d, *J*= 4.0 Hz, 2H, H3,5), 7.66 (apparent d, *J*= 4.0 Hz, 2H, H2',6'), 7.02 (apparent d, *J*= 4.0 Hz, 2H, H3',5'), 3.95 (s, 3H, OCH_3); ^{13}C NMR 166.0 (C=O), 157.7 (C4'), 145.1, 130.6, 129.6, 128.1, 127.9, 125.9, 115.6 (Ar C), 51.1 (OCH_3). The NMR data was consistent with the literature.[158]

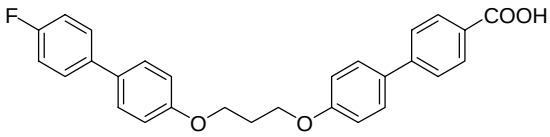
4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]biphenyl-4-carboxylic acid methyl ester (42)



Potassium carbonate (1.38 g, 0.1 mol) was added to a solution of **21** (1.19 g, 3.3 mmol) and **41** (0.76 g, 3.3 mmol) in acetonitrile (20 mL). The reaction mixture was heated at reflux (16 h) and concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford a white solid (0.99 g, 60%). m.p. 165-167 ºC; Found **C** 75.8, **H** 5.3%, $C_{29}H_{25}FO_4$ requires **C** 76.3, **H** 5.5%; ^{1}H NMR δ 8.08

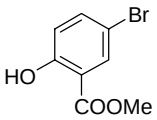
(apparent d, *J*= 8.1 Hz, 2H, ArH), 7.44-7.64 (m, 8H, ArH), 6.97-7.14 (m, 6H, ArH), 4.20-4.27 (m, 4H, 2 x OCH_2), 3.94 (s, 3H, CH_3), 2.32-2.35 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.8 (C=O), 162.7 (d, J_{FC}= -245.8 Hz), 159.8, 159.1, 145.9, 137.6 (d, J_{FCCCC}= 3.3 Hz), 133.6, 133.2, 130.8, 129.1, 128.9 (d, J_{FCCC}= 8.0 Hz), 128.7, 127.2, 116.2 (d, J_{FCC}= 21.4 Hz), 115.6, 115.5 (Ar C), 65.2 (2 x OCH_2), 52.8 (OCH_3), 30.0 (OCH_2CH_2), some signals are coincident with each other.

4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]biphenyl-4-carboxylic acid (39)



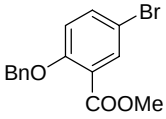
Sodium hydroxide solution (9 M, 10 ml) was added to a solution of **42** (0.20 g, 0.45 mmol) in THF (10 mL) and methanol (10 mL). The reaction mixture was stirred at room temperature (2 h). The residue was poured into water (100 mL), acidified with HCl (5 M) until pH<1 and the resulting white precipitate was collected, washed with dichloromethane and then dried in a desiccator to afford a white solid (165 mg, 84%). m.p. 201-203 ºC; Found **C** 74.7, **H** 4.8%; $C_{28}H_{23}FO_4$ requires **C** 76.0, **H** 5.2%; ^1H NMR (d_6-DMSO) δ 8.00 (apparent d, *J*= 8.4 Hz, 2H, ArH), 7.55-7.76 (m, 8H, ArH), 7.02-7.24 (m, 6H, ArH), 4.16-4.24 (m, 4H, 2 x OCH_2), 2.18-2.25 (m, 2H, OCH_2CH_2); ^{13}C (d_6-DMSO) 167.3 (C=O), 161.4 (d, J_{FC}= -243.4 Hz), 158.7, 158.1, 143.8, 136.3 (d, J_{FCCCC}= 3.1 Hz), 131.6, 131.4, 129.9, 129.3, 128.1 (d, J_{FCCC}= 8.0 Hz), 126.1, 115.6 (d, J_{FCC}= 21.4 Hz), 115.1, 115.0 (Ar C), 64.3 (2 x OCH_2), 28.6 (OCH_2CH_2). Some signals are coincident with each other.

5-Bromo-2-hydroxybenzoic acid methyl ester (46)



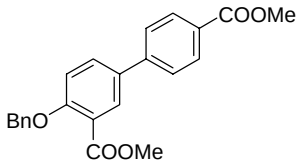
5-Bromo-2-hydroxybenzoic acid methyl ester was prepared by a variation of the procedure used by Mao *et al.*[159] Bromine (16 g, 0.1 mol) was slowly added to a warm (50-60 ºC) solution of methyl salicylate (14 g, 0.1 mol) in acetic acid (40 mL). After all the bromine was added, the mixture was stirred for another half an hour. Then the residue was poured into icy water (200 mL) with sodium metabisulfite (10 g). The resulting precipitate was collected and dried in desiccator to afford a white solid (19.2 g, 83%). m.p. 62-64 ºC; ^{1}H NMR δ 10.7 (s, 1H, OH), 7.95 (apparent d, *J*= 2.6 Hz, 1H, H6), 7.53 (dd, *J*= 9.0, 2.6 Hz, 1H, H4), 6.88 (apparent d, *J*= 9.0 Hz, 1H, H3), 3.96 (s, 3H, OCH_3). The NMR data were consistent with the literature.[159]

2-Benzyloxy-5-bromobenzoic acid methyl ester (47)



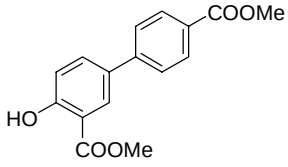
A mixture of **46** (1.15 g, 0.005 mol) , benzyl bromide (0.86 g, 0.005 mol), anhydrous potassium carbonate (1.38 g, 0.01 mol) and anhydrous acetone (10 mL) were heated at reflux (8 h). The resulting mixture was concentrated and the residue was acidified with hydrochloric acid (2 M, 10 mL) and extracted with ether. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to afford a clear liquid (1.25 g, 78%). GC-MS showed the purity was 96%, *m*/*z* 320 (M^+, 5%, $C_{15}H_{13}{}^{79}BrO_3$), 322 (M^+, 5%, $C_{15}H_{13}{}^{81}BrO_3$), 91 (100%); ^{1}H NMR δ 7.93-7.95 (m, 1H, H6), 7.31- 7.54 (m, 6H, ArH), 6.89 (apparent d, *J*= 8.7 Hz, 1H, H3), 5.2 (s, 2H, OCH_2), 3.90 (s, 3H, OCH_3); ^{13}C NMR 166.0 (C=O), 157.9 (C2), 139.1, 136.9, 136.6, 135.0, 129.3, 128.6, 127.5, 116.5, 113.4 (Ar C), 71.6 (OCH_2), 52.9 (OCH_3). The NMR data were consistent with the literature.

4-Benzyloxybiphenyl-3, 4'-dicarboxylic acid dimethyl ester (48)



A mixture of **47** (0.52 g, 1.38 mmol), 4-methoxylcarbonylphenylboronic acid (0.29 g, 1.52 mmol), $Pd(OAc)_2$ (20 mg, 0.08 mmol), triphenylphosphine (15 mg, 0.058 mmol), potassium carbonate (0.48 g, 3.46 mmol) was dissolved in a mixture of dimethoxyethane (5 mL), THF (10 mL) and water (6 mL). The reaction mixture was heated at reflux (16 h) and the resulting mixture was concentrated *in vacuo*. The residue was diluted with dichloromethane and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford a white solid (0.40 g, 78%). m.p. 91-93 ºC; GC-MS showed the purity was 97%, *m*/*z* 376 (M^+, 20%, $C_{23}H_{20}O_5$), 91 (100%); ^{1}H NMR δ 8.07- 8.11 (m, 3H, ArH), 7.30- 7.72 (m, 8H, ArH), 7.10 (apparent d, *J*= 8.8 Hz, 1H, H5), 5.2 (s, 2H, OCH_2), 3.94 (s, 6H, 2 x OCH_3); ^{13}C NMR 166.0 (C=O), 165.9 (C=O), 157.8, 143.8, 137.0, 131.7, 131.6, 131.5, 129.9, 129.5, 128.8, 128.3, 127.5, 126.9, 121.7, 114.5 (Ar C), 70.1 (OCH_2), 51.3 (2 x OCH_3).

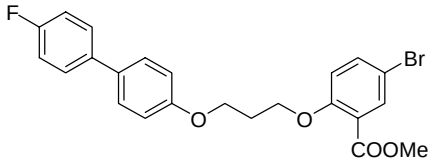
4-Hydroxybiphenyl-3, 4'-dicarboxylic acid dimethyl ester (44)



A mixture of **48** (0.58 g, 2.5 mmol), trimethylsilyl chloride (1.83 g, 12.5 mmol), sodium iodide (3.75 g, 25 mmol) and acetonitrile (40 mL) was heated at reflux overnight. The reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was separated, dried ($MgSO_4$) and concentrated. The resulting solid was purified by chromatography (5% ethyl acetate in petroleum spirit) to afford

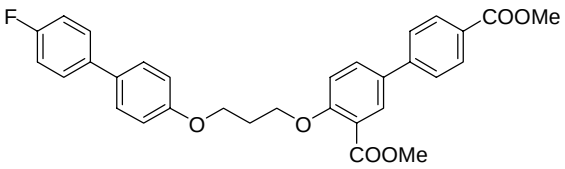
a white solid (0.52 g, 72%). m.p. 100-101 ºC; GC-MS showed the purity was 96%, *m/z* 286 (M^+, 70%, $C_{16}H_{14}O_5$), 254 (100%); ^{1}H NMR δ 10.9 (s, 1H, OH), 8.07-8.12 (m, 3H, ArH), 7.74 (dd, *J*= 8.6, 2.4 Hz, 1H, H6), 7.62 (apparent d, *J*= 8.1 Hz, 2H, ArH), 7.09 (apparent d, *J*= 8.6 Hz, 1H, H5), 4.00 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C 171.1 (C=O), 167.6 (C=O), 162.3, 144.9, 135.1, 131.8, 130.9, 129.4, 129.2, 127.1, 119.0, 113.4 (Ar C), 53.2 (OCH_3), 52.8 (OCH_3).

5-Bromo-2-[3-(4'-fluoro-biphenyl-4-yloxy)propoxy]benzoic acid methyl ester (49)



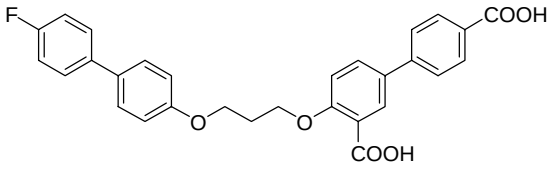
A solution of the left hand side iodide **21** (0.75 g, 2.1 mmol), 5-bromo-2-hydroxybenzoic acid methyl ester, **46**, (2.42 g, 10.5 mmol) in acetonitrile (15 mL) was added potassium carbonate (1.45 g, 10.5 mol) and heated at reflux overnight. The reaction mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate and washed with water once. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (0.64 g, 66%). m.p. 81-83 ºC; Found **C** 59.6, **H** 4.4%, $C_{23}H_{20}BrFO_4$ requires **C** 60.1, **H** 4.4%; ^{1}H NMR δ 7.91 (d, *J*= 2.6 Hz, 1H, H6), 7.43- 7.56 (m, 5H, ArH), 6.86-7.13 (m, 5H, ArH), 4.20-4.29 (m, 4H, 2 x OCH_2), 3.87 (s, 3H, OCH_3), 2.29-2.32 (m, 2H, OCH_2CH_2); ^{13}C NMR 165.9 (C=O), 162.7 (d, J_{FC}= -245.3 Hz), 159.0, 158.2, 137.6 (d, J_{FCCCC}= 3.1 Hz), 136.7, 134.9, 133.6, 128.8 (d, J_{FCCC}= 8.0 Hz), 128.7, 122.7, 116.2 (d, J_{FCC}= 21.4 Hz), 115.8, 115.5, 113.0 (Ar C), 66.3 (OCH_2), 64.9 (OCH_2), 52.8 (OCH_3), 29.9 (OCH_2CH_2).

4-[3-(4'-Fluoro-biphenyl-4-yloxy)propoxy]biphenyl-3,4'-dicarboxylic acid dimethyl ester (45)



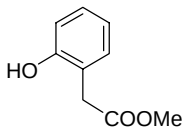
A mixture of the bromide **49** (630 mg, 1.38 mmol), 4-methoxycarbonylphenylboronic acid (290 mg, 1.52 mmol), $Pd(OAc)_2$ (20 mg, 0.08 mmol), triphenylphosphine (15 mg, 0.058 mmol), potassium carbonate (480 mg, 3.46 mmol) was dissolved in a mixture of DME (5 mL), THF (10 mL) and water (6 mL). The reaction mixture was heated at reflux for 16 hours and concentrated *in vacuo*. The residue was diluted with dichloromethane and washed once with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (550 mg, 78%). m.p. 101-102 ºC; Found **C** 72.1, **H** 5.3%, $C_{31}H_{27}FO_6$ requires **C** 72.4, **H** 5.3%; ^{1}H NMR δ 8.07- 8.11 (m, 3H, ArH), 7.74 (dd, *J*= 8.8, 2.6 Hz, 1H, ArH), 7.63 (apparent d, *J*= 8.1 Hz, 2H, ArH), 7.43-7.65 (m, 4H, ArH), 6.97-7.13 (m, 5H, ArH), 4.34 (t, *J*= 5.9 Hz, 2H, OCH_2), 4.28 (t, *J*= 5.5 Hz, 2H, OCH_2), 3.94 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 2.33-2.38 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.6 (C=O), 167.1 (C=O), 162.8 (d, J_{FC} = -245.6 Hz), 159.2, 159.1, 144.8, 137.6 (d, J_{FCCCC}= 3.1 Hz), 133.6, 132.8, 132.7, 131.1, 130.9, 129.4, 128.9 (d, J_{FCCC}= 8.1 Hz), 128.7, 127.2, 121.5, 116.4, 115.8 (d, J_{FCC}= 21.0 Hz), 114.4 (Ar C), 66.2 (OCH_2), 65.0 (OCH_2), 52.8 (2 x OCH_3), 29.9 (OCH_2CH_2).

4-[3-(4'-Fluoro-biphenyl-4-yloxy)propoxy]biphenyl-3,4'-dicarboxylic acid (43)



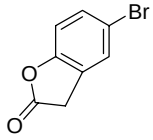
Sodium hydroxide solution (5 M, 10 mL) was added to a solution of **45** (0.20 g, 3.89 mmol) in THF (10 mL) and methanol (10 mL) and the reaction mixture was stirred at room temperature for 2 hours. The residue was poured into water (100 mL) and acidified with HCl (5 M). The resulting precipitate was collected and dried in desiccator. The crude product was recrystalized from THF/hexane to afford a white solid (172 mg, 91%); m.p. 231-232 ºC; Found **C** 70.4%, **H** 4.7%; $C_{29}H_{23}FO_6$ requires **C** 71.6, **H** 4.8%; ^{1}H NMR δ 7.80-8.02 (m, 4H, ArH), 7.78 (apparent d, *J*= 8.6 Hz, 2H, ArH), 7.20-7.68 (m, 7H, ArH), 7.04 (apparent d, *J*=8.6 Hz, 2H, ArH), 4.22-4.28 (m, 4H, 2 x OCH_2), 2.18-2.24 (m, 2H, OCH_2CH_2); ^{13}C NMR 167.0 (2 x C=O), 161.4 (d, J_{FC}= -243.3 Hz), 158.0, 157.4, 142.9, 136.3 (d, J_{FCCCC}= 3.0 Hz), 131.5, 131.2, 130.8, 130.0, 129.2, 128.8, 128.0 (d, J_{FCCC}= 8.4 Hz), 127.7, 126.2, 122.2, 115.5 (d, J_{FCC}= 21.4), 114.9, 114.1 (Ar C), 65.1(OCH_2), 64.2 (OCH_2), 28.5 (OCH_2CH_2).

2-Hydroxyphenylacetic acid methyl ester (53)



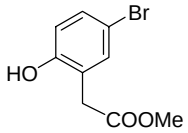
2-Hydroxyphenylacetic acid (6.84 g, 0.045 mol) was dissolved in methanol (60 mL) and concentrated sulfuric acid (10 mL). The reaction mixture was heated at reflux for 12 hours and the resulting mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with sodium bicarbonate and water. The organic layer was separated, dried ($MgSO_4$) and concentrated to afford the desired product as white solid (6.87 g, 92%). m.p. 71-74ºC (Lit.[160] m.p. 69-71 ºC); ^{1}H NMR δ 7.07-7.24 (m, 2H, ArH), 6.84-6.96 (m, 2H, ArH), 3.75 (s, 3H, OCH_3), 3.69 (s, 2H, $ArCH_2$). The NMR data were consistent with the literature.[160]

5-Bromo-3H-benzofuran-2-one (54)



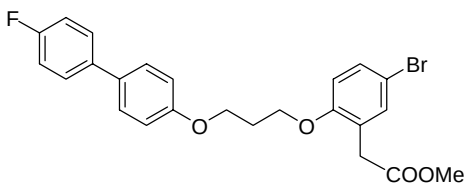
Bromine (9.6 g, 0.06 mol) was slowly added to a warm solution (50-60 ºC) of 2-hydroxyphenylacetic acid (9.12 g, 0.06 mol) in acetic acid (40 mL). After all the bromine was added, the mixture was stirred for half an hour. The residue was poured into a solution of ice (50 g), water (100 g) and sodium metabisulfite (10 g). The precipitate was collected and dried in vacuum desiccator to afford a white solid (9.5 g, 74%). m.p. 147-149 ºC; GC-MS showed the purity was >99%, *m*/*z* 212 (M^+, 89%, $C_8H_5{}^{79}BrO_2$), 214 (M^+, 89%, $C_8H_5{}^{81}BrO_2$), 77 (100%); ^{1}H NMR δ 7.42-7.46 (m, 2H, ArH), 7.00 (apparent d, *J*= 8.8 Hz, 1H, H3), 3.75 (s, 2H, $ArCH_2$). ^{13}C NMR 173.7 (C=O), 154.3 (C2), 132.6, 128.5, 125.8, 117.3, 113.0 (Ar C), 33.6 ($ArCH_2$).

5-Bromo-2-hydroxyphenylacetic acid methyl ester (50)



Bromide **54** (9.5 g, 0.045 mol) was dissolved in methanol (40 mL) and concentrated sulfuric acid (5 mL). The reaction mixture was heated at reflux for 12 hours and the resulting mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with sodium bicarbonate and water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired product as white solid (10.1 g, 92%). m.p. 74-76 ºC; GC-MS §§§§§§§§§ showed the purity was >99%, *m*/*z* 244 (M^+, 45%, $C_9H_9{}^{79}BrO_3$), 246 (M^+, 45%, $C_9H_9{}^{81}BrO_3$), 212, 214 (100%); ^{1}H NMR δ 7.21-7.31 (m, 2H, H3,4), 6.81 (apparent d, *J*= 8.4 Hz, 1H, H6), 3.76 (s, 3H, OCH_3), 3.64 (s, 2H, $ArCH_2$); ^{13}C NMR 174.6 (C=O), 155.1 (C2), 134.1, 132.7, 123.3, 120.1, 113.4 (Ar C), 53.6 (OCH_3), 38.0 ($ArCH_2$).

{5-Bromo-2-[3-(4'-fluoro-biphenyl-4-yloxy)propoxy]phenyl}acetic acid methyl ester (55)

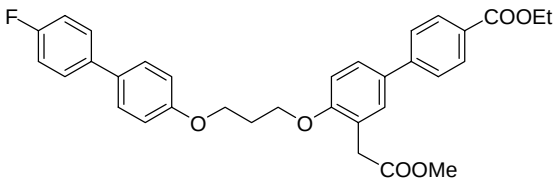


Potassium carbonate (4.9 g, 35 mmol) was added to a solution of the left hand side iodide **21** (2.50 g, 7 mmol), and the phenol **50** (8.50 g, 35 mmol) in butanone (80 mL). The reaction mixture was heated at reflux overnight and concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford the desired product as white needles (1.81 g, 55%). m.p. 81-83 ºC;

§§§§§§§§§ This GC-MS analysis was carried out using the cool on column injection technique

Found **C** 60.7, **H** 4.7%, $C_{24}H_{22}FO_4Br$ requires **C** 60.9%, **H** 4.9%; ^{1}H NMR δ 7.36-7.52 (m, 6H, ArH), 6.95-7.14 (m, 4H, ArH), 6.77 (apparent d, *J*= 8.4 Hz, 1H, H6), 4.12-4.21 (m, 4H, 2 x OCH_2), 3.63 (s, 3H, CH_3), 3.59 (s, 2H, $ArCH_2$), 2.23-2.29 (m, 2H, OCH_2CH_2); ^{13}C NMR 172.2(C=O), 162.8 (d, J_{FC}= -245.3 Hz), 159.0, 156.6, 137.6 (d, J_{FCCCC}= 3.4 Hz), 134.4, 133.7, 131.9, 128.9 (d, J_{FCCC}= 8.0 Hz), 128.7, 126.0, 116.2 (d, J_{FCC}= 21.4 Hz), 115.5, 113.6, 113.4 (Ar C), 65.5 (OCH_2), 65.0 (OCH_2), 52.6 (OCH_3), 36.5 ($ArCH_2$), 29.9 (OCH_2CH_2).

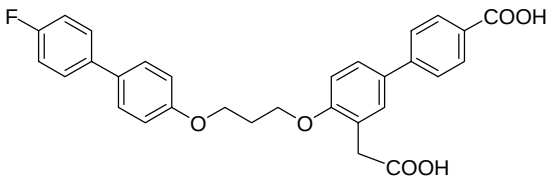
4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-3'-methoxycarbonylmethyl biphenyl-4-carboxylic acid ethyl ester (56)



A mixture of **55** (1.20 g, 2.5 mmol), 4-ethoxycarbonylphenylboronic acid (0.55 g, 2.7 mmol), palladium acetate (30 mg, 0.135 mmol), triphenylphosphine (25 mg, 0.096 mmol) and potassium carbonate (0.61 g, 4.4 mmol) were dissolved in a mixture of DME (10 mL), THF (20 mL) and water (10 mL). The reaction mixture was degassed three times and then heated at reflux for 16 hours. The resulting mixture was concentrated *in vacuo* and the residue was diluted in dichloromethane and washed with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (0.76 g, 63%). m.p. 95-97 ºC; Found **C** 73.1, **H** 5.6%; $C_{33}H_{31}FO_6$ requires **C** 73.1, **H** 5.8%; ^{1}H NMR δ 8.08 (d, *J*= 8.4 Hz, 2H, ArH), 7.44-7.64 (m, 8H, ArH), 6.96-7.14 (m, 5H, ArH), 4.39 (q, *J*= 7.1

Hz, 2H, OC*H*$_2$CH$_3$), 4.18-4.27 (m, 4H, 2 x OCH$_2$), 3.70 (s, 2H, ArCH$_2$), 3.65 (s, 3H, OCH$_3$), 2.24-2.36 (m, 2H, OCH$_2$C*H*$_2$), 1.41 (t, *J*= 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR 172.7 (C=O), 167.2 (C=O), 162.7 (d, J_{FC}= -245.3 Hz), 159.1, 157.7, 145.6, 137.6 (d, J_{FCCCC}= 3.0 Hz), 133.6, 133.2, 130.7, 130.65, 129.4, 128.9 (d, J_{FCCC}= 8.0 Hz), 128.7, 128.1, 127.2, 124.4, 116.2 (d, J_{FCC}= 21.4 Hz), 115.5, 112.3 (Ar C), 65.4 (OCH$_2$), 65.1 (OCH$_2$), 61.6 (O*C*H$_2$CH$_3$), 52.6 (OCH$_3$), 36.9 (ArCH$_2$), 30.0 (OCH$_2$*C*H$_2$), 15.0 (CH$_2$*C*H$_3$).

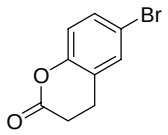
3'-Carboxymethyl-4'-[3-(4'-fluoro-biphenyl-4-yloxy)propoxy]biphenyl-4-carboxylic acid (51)



A solution of diester **56** (200 mg, 0.36 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 3 hour. The residue was concentrated *in vacuo* and acidified with hydrochloric acid (5 M). The resulting precipitate was collected and dried in vacuum desiccator to afford a white solid which was recrystalized from acetone/petroleum spirit (168 mg, 91%). m.p. 201-203 ºC; Found **C** 72.0, **H** 5.1%; $C_{30}H_{25}FO_6$ requires **C** 72.0, **H** 5.0%; ^{1}H NMR (d_6-DMSO) δ 8.00 (apparent d, J= 8.4 Hz, 2H, ArH), 7.55-7.76 (m, 8H, ArH), 7.02-7.29 (m, 5H, ArH), 4.17-4.23 (m, 4H, 2 x OCH$_2$), 3.62 (s, 2H, ArCH$_2$), 2.16-2.22 (m, 2H, OCH$_2$C*H*$_2$); ^{13}C NMR 172.4 (C=O), 167.1 (C=O), 161.4 (d, J_{FC}= -243.0 Hz), 158.0, 156.9, 143.9, 136.3 (d, J_{FCCCC}= 3.0 Hz), 131.5, 130.8, 129.9, 129.7, 128.8, 128.0 (d, J_{FCCC}= 8.0 Hz), 127.7, 126.7, 126.0, 124.6,

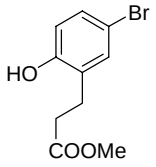
115.5 (d, J_{FCC}= 21.4 Hz), 114.9, 111.9 (Ar C), 64.5 (OCH_2), 64.3 (OCH_2), 35.8 ($ArCH_2$), 28.7 (OCH_2CH_2).

6-Bromo-2,3-dihydrocoumarin (58)



6-Bromo-2,3-dihydrocoumarin was prepared by a variation of the method of Davies.[161] Bromine (24.0 g, 0.15 mol) was slowly added to a warm (50-60 ºC) solution of 3,4-dihydrocoumarin (22.2 g, 0.15 mol) in acetic acid (50 mL). After all the bromine was added, the reaction mixture was stirred for half an hour. The residue was poured into a mixture of ice (50 g), water (100 g) and sodium metabisulfite (10 g). The resulting precipitate was collected and dried in a desiccator to afford a white solid which was recrystallized from dichloromethane/petroleum (25.0 g, 73%). m.p. 106- 107 ºC (Lit.[161] m.p. 104-105 ºC), ^{1}H NMR δ 7.27- 7.40 (m, 2H, ArH), 6.94 (apparent d, *J*= 8.8 Hz, 1H, H6), 3.00 (t, *J*= 7.4 Hz, 2H, $OCCH_2$), 2.77 (m, 2H, $ArCH_2$). The NMR data were consistent with the literature.

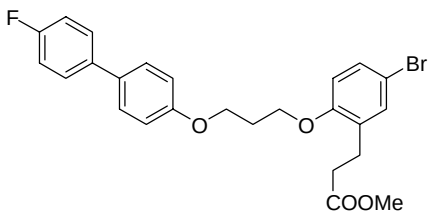
3-(5-Bromo-2-hydroxyphenyl)propanoic acid methyl ester (59)



A solution of **58** (15 g, 66 mmol) in methanol (40 mL) was added concentrated sulfuric acid (5 mL) and heated at reflux (12 h). The resulting mixture was concentrated *in vacuo*, diluted with ethyl acetate and washed with sodium bicarbonate and water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (16.2 g) which was purified by chromatography (dichloromethane) (13.4 g, 81%). m.p. 59- 61 ºC; Found

C 46.4%, **H** 4.4%, $C_{10}H_{11}BrO_3$ requires **C** 46.4, **H** 4.3%; GC-MS********** showed the purity was > 99%, *m/z* 258 (M^+, 14%, $C_{10}H_{11}{}^{79}BrO_3$), 260 ($(M+2)^+$, 14%, $C_{10}H_{11}{}^{81}BrO_3$), 226, 228 (100%); ^{1}H NMR δ 7.17-7.22 (m, 2H, ArH), 6.76 (apparent d, *J*= 9.1 Hz, 1H, H3), 3.77 (s, 3H, OCH_3), 2.85 (t, *J*= 6.6 Hz, 2H, $ArCH_2$), 2.71 (t, *J*= 6.6 Hz, 2H, $ArCH_2CH_2$); ^{13}C NMR 176.6 (C=O), 154.2, 133.7, 131.5, 130.2, 119.7, 113.3 (Ar C), 53.0 (OCH_3), 35.4 ($ArCH_2$), 25.2 ($ArCH_2CH_2$).

3-{5-Bromo-2-[3-(4'-fluoro-biphenyl-4-yloxy)-propoxy]-phenyl}-propanoic acid methyl ester (60)

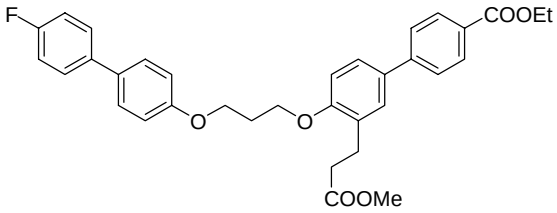


The simplified left hand side moiety **21** (1.78 g, 5.28 mmol) was added to a mixture of **59** (6.7 g, 26 mmol) and potassium carbonate (3.6 g, 26 mmol) in acetonitrile (45 mL). The reaction mixture was heated at reflux overnight and the resulting mixture was concentrated *in vacuo*. The residue was diluted in ethyl acetate and washed with water. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford a white solid (1.29 g, 50%). m.p. 65-67 ºC; Found **C** 61.4, **H** 5.1%, $C_{25}H_{24}BrFO_4$ requires **C** 61.6, **H** 5.0%; ^{1}H NMR δ 7.44-7.52 (m, 4H, ArH), 7.29 (apparent d, *J*= 2.5 Hz, 1H, ArH), 6.95-7.14 (m, 4H, ArH), 6.74 (apparent d, *J*= 8.8 Hz, ArH), 4.20 (t, *J*= 6.2 Hz, 2H, OCH_2), 4.16 (t, *J*= 6.2 Hz, 2H, OCH_2), 3.66 (s, 3H, OCH_3), 2.91 (t, *J*= 8.1 Hz, 2H, $ArCH_2$), 2.58 (t, *J*= 8.1 Hz, 2H, CH_2COO), 2.27-2.34 (m, 2H, OCH_2CH_2); ^{13}C NMR 174.0 (C=O), 162.8 (d, J_{FC}= -245.6 Hz), 160.0, 156.5, 137.6 (d, J_{FCCCC}= 3.4

********** This GC-MS analysis was carried out using the cool on column injection technique

Hz), 133.5, 133.3, 131.9, 130.9, 128.9 (d, J_{FCCC}= 8.0 Hz), 128.7, 116.2 (d, J_{FCC}= 21.4 Hz), 115.5, 113.5, 113.4 (Ar C), 65.4 (OCH_2), 65.1 (OCH_2), 52.3 (OCH_3), 34.5 (CH_2COO), 30.0 (OCH_2CH_2), 26.5 ($ArCH_2$);

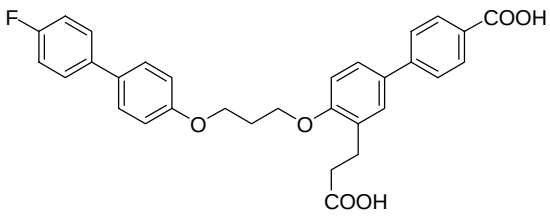
4'-[3-(4'-Fluoro-biphenyl-4-yloxy)propoxy]-3'-(2-methoxycarbonyl-ethyl)biphenyl-4-carboxylic acid ethyl ester (61)



A mixture of **60** (1.08 g, 2.2 mmol), 4-ethoxycarbonylphenylboronic acid (0.50 g, 2.5 mmol), palladium acetate (30 mg, 0.135 mmol), triphenylphosphine (25 mg, 0.096 mmol) and potassium carbonate (612 mg, 4.4 mmol) were dissolved in a mixture of dimethoxyethane (10 mL), THF (20 mL) and water (10 mL). The reaction mixture was degassed three times and heated at reflux for 16 hours. The resulting mixture was concentrated *in vacuo* and the residue was diluted in dichloromethane and washed with water. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a white solid (1.04 g, 85%). m.p. 82-83 ºC; Found **C** 72.94, **H** 5.9, $C_{34}H_{33}FO_6$ requires **C** 73.36%, **H** 6.0%; ^{1}H NMR δ 8.13 (apparent d, *J*= 8.0 Hz, 2H, ArH), 7.50-7.67 (m, 7H, ArH), 7.02-7.20 (m, 6H, ArH), 4.39 (q, *J*= 7.2 Hz, 2H, $COOCH_2$), 4.28 (m, 4H, 2 x OCH_2), 3.71 (s, 3H, OCH_3), 3.06 (t, *J*= 4.2 Hz, 2H, CH_2COO), 2.72 (t, *J*= 4.2 Hz, 2H, $ArCH_2$), 2.40- 2.43 (m, 2H, OCH_2CH_2), 1.46 (t, *J*= 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR 174.3 (C=O), 167.3 (C=O), 162.8 (d, J_{FC}= -245.3 Hz), 159.0, 157.6, 145.8, 137.6 (d, J_{FCCCC}= 3.4 Hz), 133.7, 133.0, 130.7,

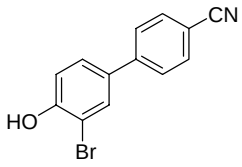
130.2, 129.6, 129.3, 128.8 (d, J_{FCCC}= 8.0 Hz), 128.7, 127.1, 116.2 (d, J_{FCC}= 21.3 Hz), 116.2, 115.5, 112.2 (Ar C), 65.2 (OCH_2), 65.1 (OCH_2), 61.6 (OCH_2CH_3), 52.3 (OCH_3), 34.8 (CH_2COO), 30.0 (OCH_2CH_2), 27.0 ($ArCH_2$), 15.0 (OCH_2CH_3).

3'-(2-Carboxy-ethyl)-4'-[3-(4'-fluoro-biphenyl-4-yloxy)propoxy]biphenyl-4-carboxylic acid (62)



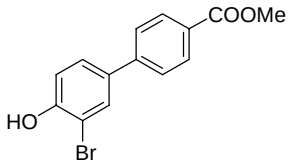
A solution of diester **61** (200 mg, 0.36 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 3 hours. The residue was concentrated *in vacuo* and acidified with hydrochloric acid (5 M). The resulting precipitate was collected and dried in a desiccator to afford a white solid (168 mg) which was recrystalized from acetone/petroleum (144 mg, 78%). m.p. 207–208 ºC; Found **C** 70.9, **H** 5.3%; $C_{31}H_{27}FO_6 \cdot H_2O$ requires **C** 69.9, **H** 5.5%; ^{1}H NMR (d_6-DMSO) δ 8.07 (apparent d, splitting 8.0 Hz, 2H, ArH), 7.65- 7.85 (m, 7H, ArH), 7.12- 7.39 (m, 6H, ArH), 4.30-4.33 (m, 4H, OCH_2), 2.95 (t, *J*= 8.1 Hz, 2H, CH_2COO), 2.64 (t, *J*= 8.1 Hz, 2H, $ArCH_2$), 2.34-2.38 (m, 2H, OCH_2CH_2), ^{13}C NMR 173.8 (C=O), 167.0 (C=O), 161.3 (d, J_{FC}= -243.3 Hz), 157.9, 156.5, 143.9, 136.1 (d, J_{FCCCC}= 3.1 Hz), 131.4, 130.8, 129.7, 129.2, 128.6, 128.2, 127.9 (d, J_{FCCC}= 8.0 Hz), 127.6, 125.9, 115.4 (d, J_{FCC}= 21.4 Hz), 114.7, 111.8 (Ar C), 64.3 (2 x OCH_2), 33.5 ($ArCH_2CH_2$), 28.5 (OCH_2CH_2), 25.4 ($ArCH_2$). Some signals are coincidental with each other.

3'-Bromo-4'-hydroxy-biphenyl-4-carbonitrile (63)



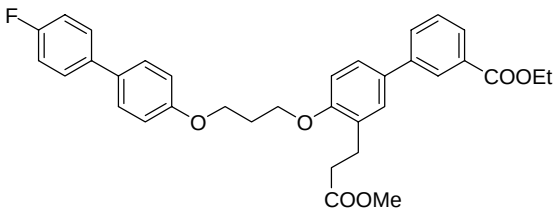
A mixture of methyl ether **17** (0.28 g, 1 mmol) and pyridine hydrochloride (1.2 g, 10 mmol) was heated at 170-180 ºC (3 h). The residue was diluted with water (50 mL) and the resulting precipitate was collected and dried in a desiccator. The crude product was purified by chromatography (30% ethyl acetate in petroleum spirit) to afford a pale yellow solid (0.21 g, 77%). m.p. 201-203 ºC (Lit.[162] m.p. 202-203 ºC); ^{1}H NMR δ 7.69-7.73 (m, 3H), 7.59-7.63 (m, 2H), 7.47 (dd, *J*= 2.2, 8.4 Hz, 1H, ArH), 7.12 (d, *J*= 8.4 Hz, 1H, H2'). The NMR data were consistent with the literature.[162]

3'-Bromo-4'-hydroxy-biphenyl-4-carboxylic acid methyl ester (64)



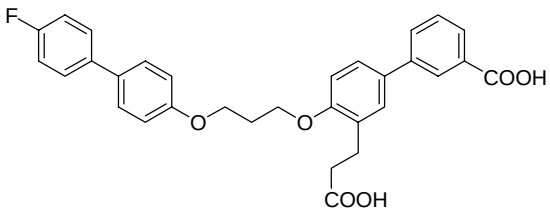
A solution of **63** (0.20 g, 0.72 mmol) and potassium hydroxide (2 g, 36 mmol) in methanol (15 mL) was heated at reflux for three days. The residue was diluted with water and concentrated in vacuo. The resulting mixture was diluted with ethyl acetate and the organic layer was collected, dried and concentrated. The crude solid was dissolved in methanol (20 mL) and concentrated sulfuric acid (4 mL) and heated at reflux overnight. The reaction mixture was poured into ice water (100 mL) and the precipitate was collected and dried in desiccator. The crude product was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford a white solid (0.13 g, 59%). m.p. 132-134 ºC; ^{1}H NMR δ 8.06-8.11 (m, 2H, ArH), 7.74 (d, *J*= 2.2 Hz, 1H, H2'), 7.56-7.60 (m, 2H, ArH), 7.50 (dd, *J*= 2.2, 8.5 Hz, 1H, H6'), 7.10 (d, *J*= 8.6 Hz, H5'); ^{13}C NMR 167.0 (C=O), 155.1, 144.7, 133.6, 132.4, 130.8, 129.6, 128.4, 127.3, 117.7, 111.0 (Ar C), 52.3 (OCH_3).

4'-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-3'-(2-methoxycarbonyl-ethyl)-biphenyl-3-carboxylic acid ethyl ester (71)



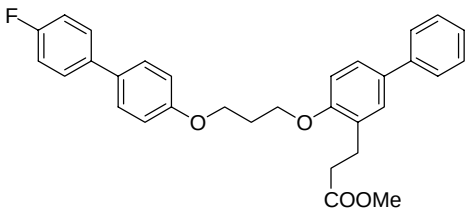
A mixture of the bromide **60** (1.08 g, 2.2 mmol), 3-ethoxycarbonylphenylboronic acid (0.50 g, 2.5 mmol), palladium acetate (30 mg, 0.135 mmol), triphenylphosphine (25 mg, 0.096 mmol) and potassium carbonate (612 mg, 4.4 mmol) were dissolved in a mixture of dimethoxyethane (10 mL), THF (20 mL) and water (10 mL). The reaction mixture was degassed three times and then heated at reflux for 16 hours. The resulting mixture was concentrated *in vacuo* and the residue was diluted in dichloromethane and washed with water. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a clear glass (1.04 g, 85%). ^{1}H NMR δ 7.49-7.58 (m, 7H, ArH), 7.00-7.35 (m, 6H, ArH), 6.79 (apparent d, *J*= 8.8 Hz, 2H, ArH), 4.19-4.30 (m, 6H, 3 x OCH_2), 3.71 (s, 3H, OCH_3), 2.97 (t, *J*= 7.4 Hz, 2H, $ArCH_2$), 2.64 (t, *J*= 7.4 Hz, 2H, CH_2COO), 2.33-2.39 (m, 2H, OCH_2CH_2), 1.33 (m, 3H, OCH_2CH_3); The crude product was used in next step without further purification.

3'-(2-Carboxy-ethyl)-4'-[3-(4'-fluoro-biphenyl-4-yloxy)-propoxy]-biphenyl-3-carboxylic acid (73)



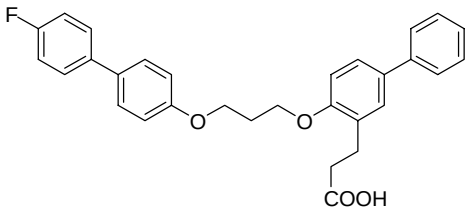
A solution of the diester **71** (800 mg, 0.14 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 3 hours. The residue was concentrated *in vacuo* and acidified with hydrochloric acid (5 M). The resulting precipitate was collected and dried in vacuum desiccator to afford a white solid (0.71 g, 98%) which was recrystalized from acetone/petroleum (0.50 g, 69%). m.p. 182-183 ºC; Found **C** 72.4, **H** 5.4%, $C_{31}H_{27}FO_6$ requires **C** 72.4, **H** 5.3%; ^{1}H NMR (d_6-DMSO) δ 8.23 (s, 1H, ArH), 7.61-7.99 (m, 10H, ArH), 7.22-7.39 (m, 2H, ArH), 7.13-7.17 (m, 2H, ArH), 4.32-4.34 (m, 4H, 2 x OCH_2), 2.99 (t, *J*= 7.3 Hz, 2H, $ArCH_2$), 2.64 (t, *J*= 7.3 Hz, 2H, Ar CH_2CH_2, half was coincidental with the DMSO signal), 2.32-2.37 (m, 2H, OCH_2CH_2); ^{13}C NMR 174.0 (C=O), 167.3 (C=O), 161.4 (d, J_{FC}= -243.4 Hz), 160.0, 158.1, 156.3, 140.3, 136.3 (d, J_{FCCCC}= 3.0 Hz), 131.6, 131.5, 131.3, 130.5, 129.4, 128.1 (d, J_{FCCC}= 8.0 Hz), 127.8, 127.5, 126.7, 125.8, 115.5 (d, J_{FCC}= 21.3 Hz), 114.9, 111.9 (Ar C), 64.4 (2 x OCH_2), 33.7 ($ArCH_2CH_2$), 28.7 (OCH_2CH_2), 25.5 ($ArCH_2$). Some signals are coincidental with each other.

3-{4-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-biphenyl-3-yl}-propionic acid methyl ester (72)



A mixture of the bromide **60** (1.08 g, 2.2 mmol), phenylboronic acid (0.24 g, 2.5 mmol), palladium acetate (30 mg, 0.135 mmol), triphenylphosphine (25 mg, 0.096 mmol) and potassium carbonate (612 mg, 4.4 mmol) were dissolved in a mixture of dimethoxyethane (10 mL), THF (20 mL) and water (10 mL). The reaction mixture was degassed three times and heated at reflux for 16 hours. The resulting mixture was concentrated *in vacuo* and the residue was diluted in dichloromethane and washed with water. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in petroleum spirit) to afford the desired product as a clear viscous oil (1.04 g, 85%). ^{1}H NMR δ 7.32-7.69 (m, 10H, ArH), 7.00-7.20 (m, 5H, ArH), 6.80 (apparent d, *J*= 8.7 Hz, ArH), 4.13-4.33 (m, 4H, 2 x OCH_2), 3.71 (s, 3H, OCH_3), 2.97 (t, *J*= 7.3 Hz, 2H, $ArCH_2$), 2.64 (t, *J*= 7.3 Hz, CH_2COO), 2.33-2.39 (m, 2H, OCH_2CH_2); ^{13}C NMR 173.9 (C=O), 162.7 (d, J_{FC}= -245.7 Hz), 158.9, 156.4, 137.5 (d, J_{FCCCC}= 3.1 Hz), 133.5, 133.2, 131.8, 130.8, 129.4, 129.3, 128.8 (d, J_{FCCC}= 8.0 Hz), 128.6, 127.3, 126.8, 116.2 (d, J_{FCC}= 21.3 Hz), 115.4, 113.4, 112.0 (Ar C), 65.3 (OCH2), 65.0 (OCH_2), 52.1 (OCH_3), 34.4 ($ArCH_2CH_2$), 29.9 (OCH_2CH_2), 26.4 ($ArCH_2$).

3-{4-[3-(4'-Fluoro-biphenyl-4-yloxy)-propoxy]-biphenyl-3-yl}-propionic acid (74)



The solution of **72** (1.04 g, 0.21 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 3 hours. The residue was concentrated *in vacuo* and acidified with hydrochloric acid (5 M). The resulting precipitate was collected and dried in vacuum desiccator to afford a viscous oil (0.95 g, 96%). ^{1}H NMR δ 7.24-7.53 (m, 9H, ArH), 6.95-7.13 (m, 6H, ArH), 6.72 (apparent d, *J*= 9.5 Hz, 1H, ArH), 4.11-4.25 (m, 4H, 2 x OCH_2), 2.91 (t, *J*= 7.4 Hz, 2H, $ArCH_2$), 2.62 (t, *J*= 7.4 Hz, 2H, CH_2COO), 2.25-2.28 (m, 2H, OCH_2CH_2); ^{13}C NMR 179.8 (C=O), 162.8 (d, J_{FC}= -245.7 Hz), 159.0, 158.9, 156.9, 156.4, 141.4, 137.6 (d, J_{FCCCC}= 3.0 Hz), 134.3, 133.6, 133.2, 131.5, 131.0, 129.5, 129.4, 128.8 (d, J_{FCCC}= 8.0 Hz), 128.7, 127.4, 126.9, 116.2 (d, J_{FCC}= 21.0 Hz), 115.9, 115.5, 113.5, 113.4, 112.1 (Ar C), 65.4 (OCH_2), 65.1 (OCH_2), 34.5 (CH_2COO), 30.0 (OCH_2CH_2), 26.7 ($ArCH_2$).

Chapter IV Analogues with different linkers

4.1 Introduction

The linker group is also an important component in insulin mimetic analogues. Although it is not involved in the binding directly, its length and flexibility are expected to significantly influence binding to the insulin receptor. The impact of alternative linkers was predicted by computer modeling carried out by the WABRI molecular modeling team, which suggests a less flexible linker would increase the "fit" of the four binding groups to the insulin receptor. Thus, more rigid linkers, such as amide or xylene linkers, were considered in the first generation analogues. The successful synthesis will provide useful information for modifying the binding model and aid in developing further leading candidates.

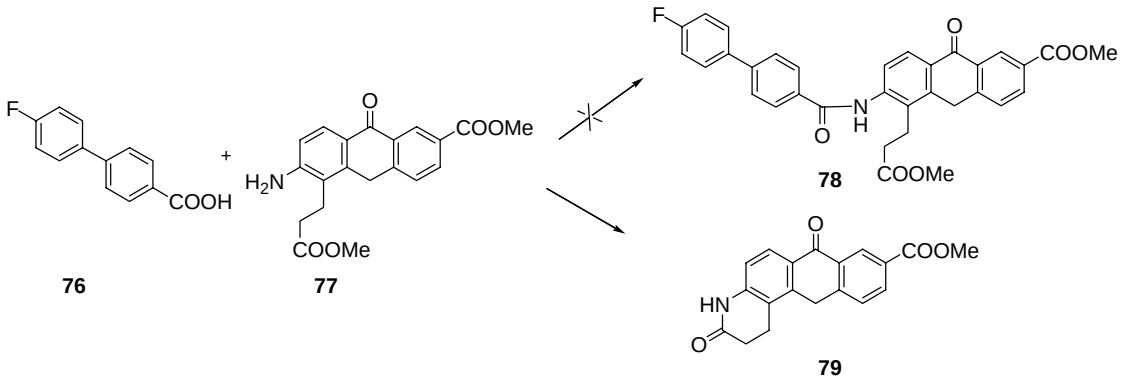
There are three types of analogues in this chapter: 1) analogues with an amide linker; 2) symmetric analogues with a xylene linker and 3) binaphthol derivatives.

4.2 Results and discussion

4.2.1 Amide linker analogues

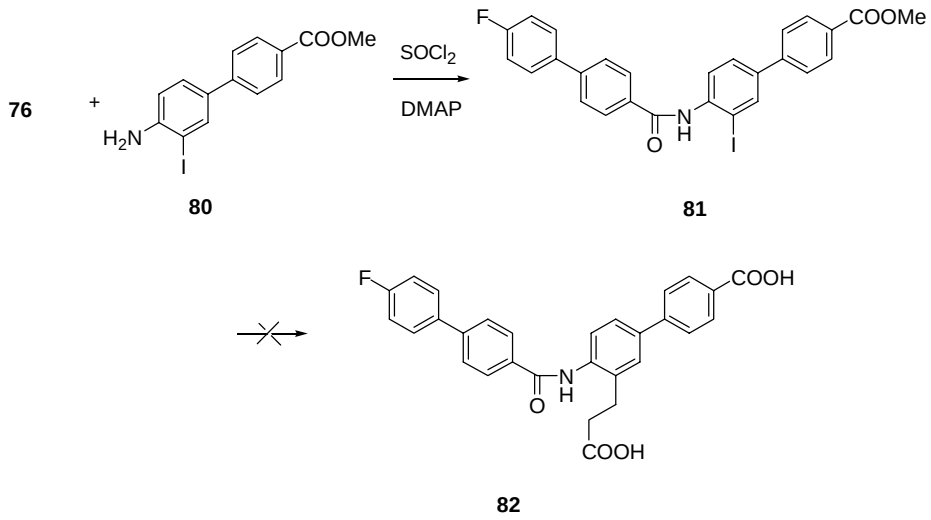
Computer modelling suggests that an amide linked analogue was "the best fit target" among all the analogues with a predicted activity ten times better than **IM140**. However the synthesis of amide linked analogues proved to be much more difficult target than anticipated by synthetic chemists. Two commercial contract synthesis companies, one from India and the other from Australia, were under contract to synthesize amide linked analogues, but neither of them succeeded in the synthesis of their target molecules.

The Indian company was assigned the analogue with the same left and right hand sides as **IM140** except linked by an amide linker. They had difficulty in synthesizing the left hand side with carboxylic acid containing the ethyl and hydroxyl group, so they simplified the target to the carboxylic acid **76**. They did synthesize the seemingly more complex amino xanthone **77**, however all attempts to couple the two sides resulted in formation of the lactam **79**, and none of the desired compound **78** was obtained (**Scheme 4.1**).[163]



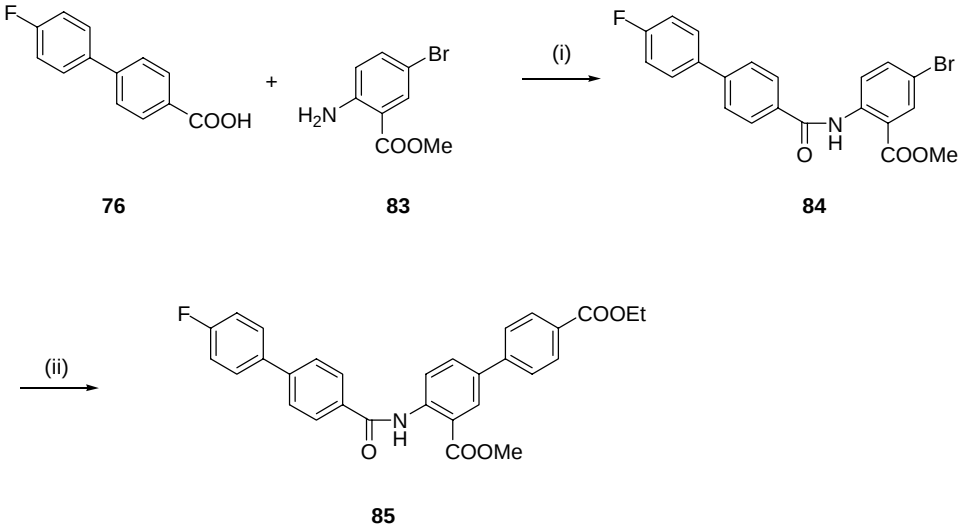
Scheme 4.1

The Australian company was assigned the synthesis of the amide linked biphenyl-biphenyl derivative. They also had difficulty in preparing the fully functionalized left hand side and opted for the simplified left hand side **76**. Their strategy was to assemble the aromatic framework and then introduce the side chain acid *via* a Heck reaction (**Scheme 4.2**). The two components **76**, **80** were coupled to provide the key precursor **81**. However they were unable to introduce the side chain, possibly due to the extremely poor solubility of **81**.[163]



Scheme 4.2

Based on these previous attempts, an alternative strategy for the introduction of the side chain was sought. The strategy was to introduce an ester group on the ring which could be used to extend the side chain later. Condensation of the acid chloride of 4'-fluorobiphenyl-4-carboxylic acid with methyl 2-amino-5-bromobenzoate (**83**) gave the intermediate amide **84** in moderate yield (53%). Suzuki coupling then produced the biphenyl-biphenyl intermediate **85** in good yield (76%) (**Scheme 4.3**).



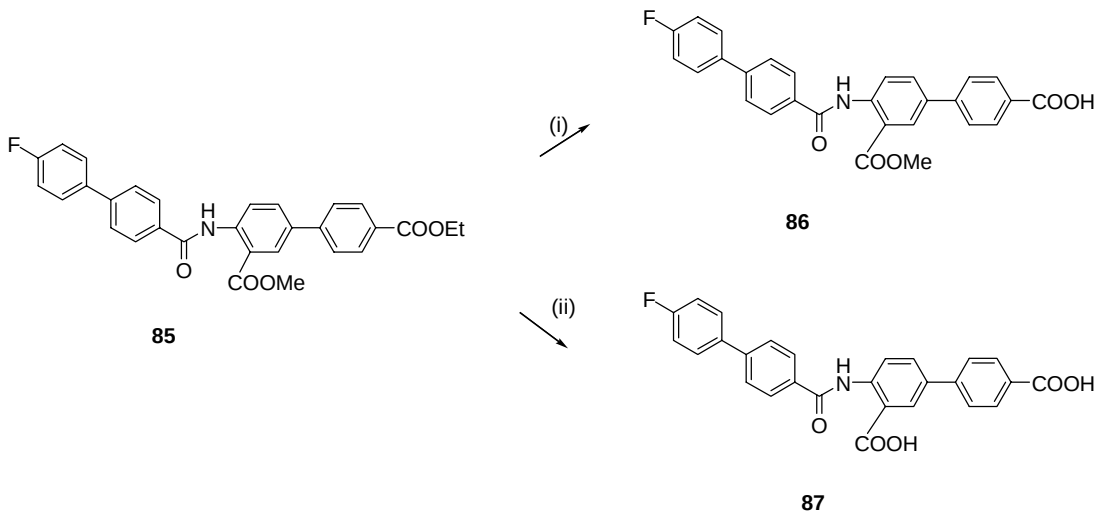
76 **83** **84** **85**

Scheme 4.3 *Reagents*: **(**i) $SOCl_2$, pyridine; (ii) 4-$(HO)_2BC_6H_4COOEt$, $Pd(OAc)_2$, PPh_3, K_2CO_3, THF, DME/H_2O

The ^1H and ^{13}C NMR spectra confirmed the formation of **85**. The typical amide peak (NH) appeared at δ_H 12.2 in the ^1H NMR spectrum. The singlet at δ_H 4.47 was assigned to the methoxy group while the quartet at δ_H 4.42 and triplet at δ_H 1.43 were assigned to the ethoxy group which indicated the successful formation of biphenyl on the right hand side. In the ^{13}C NMR spectrum the regular fluorine long range coupling indicated the presence of left hand side biphenyl. The methoxy group (δ_C 53.4) and ethoxy group (δ_C 61.7 and 15.1) indicated the presence of the two aromatic rings on the right hand side.

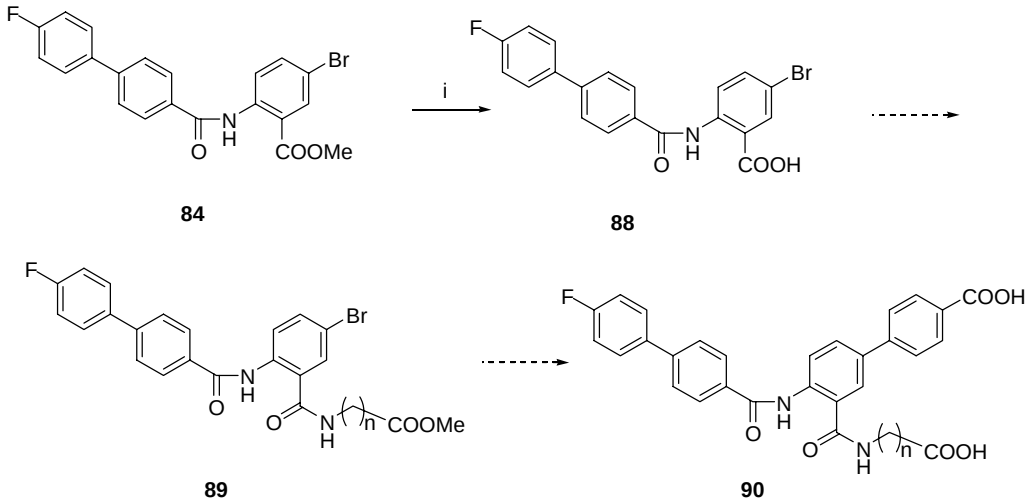
A few methods for selective hydrolysis at the diester **85** were investigated to provide the diacid analogue without cleaving the amide linker. A recently reported method for mild hydrolysis using lithium bromide and triethyl amine[164] was unsuccessful for this analogue. The use of potassium carbonate and methanol provided selective hydrolysis of the ethyl ester only while potassium hydroxide resulted in the hydrolysis of both esters without cleaving the amide (**Scheme 4.4**).

The absence of signals for the methoxy and ethoxy groups in both the ^{1}H and ^{13}C NMR spectra confirmed the completion of hydrolysis. The elemental analysis (**C** 66.1, **H** 4.0, **N** 2.8%) was consistent with the formula $C_{27}H_{18}FNO_5.2H_2O$ (**C** 66.0, **H** 4.5, **N** 2.9%).



Scheme 4.4 *Reagents*: (i) K_2CO_3, MeOH; HCl (ii) KOH, MeOH; HCl

The ester **84** was readily hydrolyzed to the acid **88** (93%), which provides a good opportunity to synthesize a series of amide linked analogues. The acid **88** could be easily coupled with a variety of amino acids to extend the side chain, and subsequent Suzuki coupling reactions followed by selective hydrolysis should afford many analogues (**Scheme 4.5**).



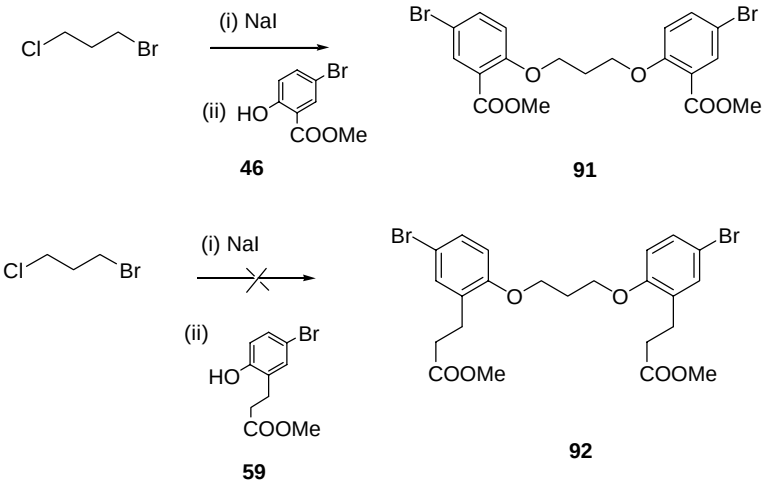
Scheme 4.5 *Reagents*: KOH, MeOH; HCl

4.2.2 Symmetric xylene linker analogues

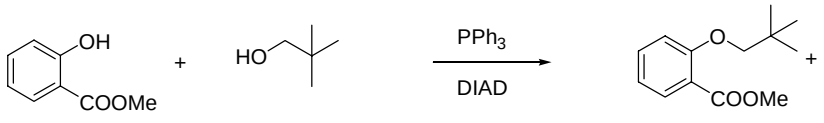
Biphenyl-biphenyl analogues were the preferred candidates from a synthetic point of view and computer modeling suggests their biological activities would be similar to the biphenyl-xanthone analogue. However, it is possible that the biphenyls from both the left and right hand sides are able to mimic the function of phenylalanine (B24) and phenylalanine (B25) binding to the insulin receptor, which could result in significant loss of activity or specificity. Under this assumption it might be a drawback to put biphenyl moieties on both sides. But from another point of view, fully symmetrical targets with biphenyl and carboxylic acid on both sides are synthetically very simple to prepare and should provide insight into the value of the left hand side biphenyl. Hence, symmetric targets were included in the first generation analogues.

The initial plan was to synthesize the symmetric biaryl targets based on the propanediol linker. However the synthesis of symmetric analogues based on this

linker was unsuccessful. Although some coupled product was obtained in low yield (5%) from the reaction between 1-bromo-3-chloropropane and 5-bromosalicylate (**46**), the coupling of two methylene chain analogue (**59**) provided only starting material (**Scheme 4.6**). Other coupling reactions, such as Mitsunobu reaction[165], were consided to increase the yield. In the Mistsunobu reaction alcohols can be coupled with carboxylic acid or phenols by the use of dialkyl azodicarboxylates to produce esters or ethers. Recently the Mitstunobu reaction has been used to produce a series of alkyl-aryl ethers on good yield (**Scheme 4.7**).[166] However, as an aim of this project was to generate a variety of analogues with different types of linkers, we chose not to pursue these options but instead investigated a more reactive linker based on ortho-xylene to produce symmetrical analogues.



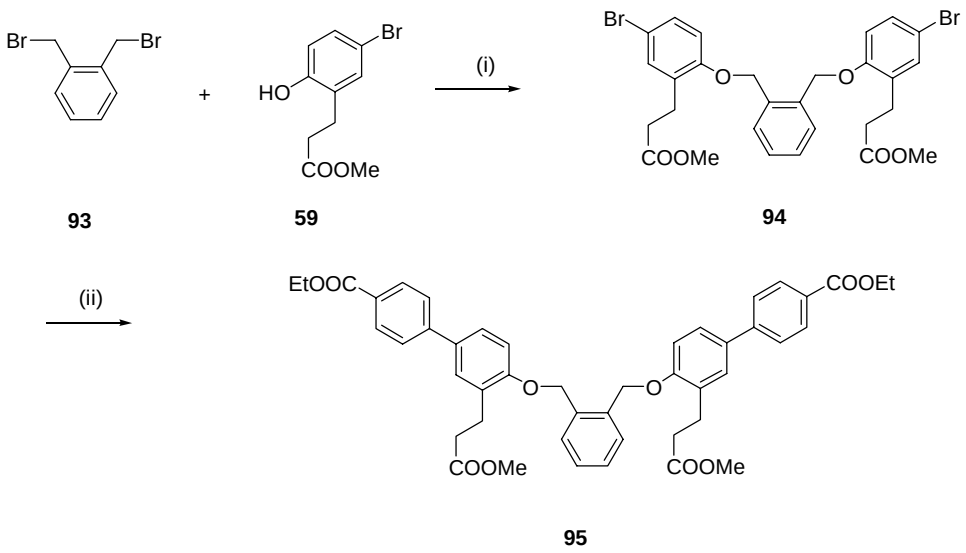
Scheme 4.6 *Reagents*: (i) K_2CO_3, butanone; (ii) K_2CO_3, butanone



DIAD=diisopropyl azodicarboxylate

Scheme 4.7 possible synthetic route via Mitunobu reaction[166]

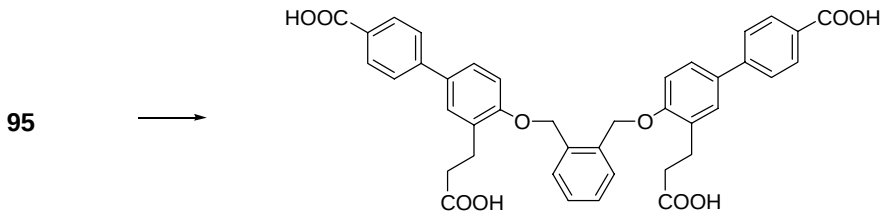
α,α'-Dibromo-ortho-xylene (**93**) was initially activated by potassium iodide and then treated with the phenol **59** to provide the symmetrical precursor **94**. A double Suzuki coupling reaction introduced the two aromatic rings onto both sides to afford the symmetric tetraester **95** in a moderate yield (20%) (**Scheme 4.8**).



Scheme 4.8 *Reagents:* (i) K_2CO_3, KI, butanone; (ii) $(HO)_2BC_6H_4COOEt$, $Pd(OAc)_2$, PPh_3, K_2CO_3, THF, DME, water

The ^1H and ^{13}C NMR spectra confirmed the formation of **95**. In the ^1H NMR spectrum the singlet at δH 3.63 was assigned to the methoxy group. Relative to those six protons, integration of four protons at δ_H 5.27 was assigned to the benzylic hydrogens of the xylene. The quartet at δ_H 4.39 and the triplet at δ_H 1.41 belong to the ethoxy group. In the ^{13}C NMR spectrum the two different carbonyl peaks at δ_C 174.2 and 167.2 were due to the aliphatic and aromatic ester carbonyls. δ_C= 174.2 is alky ester and the 167.2 is the aryl ester. The assignment was according to the additively rule for estimating ^{13}C chemical shifts for carboxyl carbon atom: R-COOH $\delta_{C=O}$ = 166.0 + ΣZi; When R=alkyl; Zi=11.0; when R=phenyl, Zi=6.0. So the signal for the carbonyl carbon atom of an alkanoic acid is shifted further downfield that of the benzenecarboxylic acid.

Hydrolysis of **95** provided the desired acid **96** (**Scheme 4.9**). The absence of the signals for the methoxy and ethoxy groups from both the ^{1}H and ^{13}C NMR spectra clearly confirmed the success of the hydrolysis reaction. The elemental analysis data were not collected for the final product **96**, further purification will be carried out only if **96** had moderate to high biological activity.



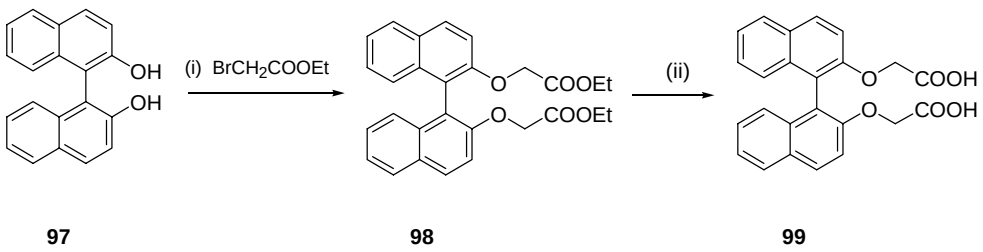
96

Scheme 4.9 *Reagents*: NaOH, MeOH and THF; HCl

4.2.3 Binaphthol analogues

Since **IM25** (**Figure 1.9**) showed activity (although poor), was symmetrical and was based on two naphthol groups, we considered a symmetrical binaphthol derivative. Carboxylic acids could be easily introduced to the naphthyl ring to produce an analogue in one step. In addition binaphthol is readily available in racemic and both chiral forms thus allowing the investigation of stereochemical effects. If the racemic analogue was found to be active (even moderately), the enantiomerically pure binaphthols will be used to generate the enantiomerically pure analogues. The length of the acid chain could be very variable ranging from one methylene group to many. In the first generation the short chain was selected and synthesized to measure the biological activity.

Treatment of 1,1'-binaphthol with ethyl bromoacetate produced the diester **98** in good yield (82%) and subsequent hydrolysis provided the desired acid **99** (92%) (**Scheme 4.10**). The ^{1}H and ^{13}C NMR spectra then confirmed the formation of the acid. The singlet at δ_H 4.83 was assigned to the two oxymethylenes of the linker which indicated the successful linkage between naphthol and the ethylbromoacetate. This is somewhat surprising given that hydrogens on the chain are pro-chiral hydrogens and one would expect to observe two doublets. For example binol bis(methoxymethyl ether) those two protons are different giving signals at δ_H=5.03 and 5.16 as a doublet of doublet, *J*= 6.7 Hz (**Figure 4.1**).[167] However in our case it appears as singlet. The lack of signals due to the ethoxy group indicated successful hydrolysis. The elemental analysis (**C** 71.6, **H** 4.5%) was consistent with the formula $C_{24}H_{18}O_6$ (**C** 71.6, **H** 4.5%).



97 **98** **99**

Scheme 4.10 *Reagents*: (i) NaI, CH_3CN; K_2CO_3, butanone;
(ii) NaOH, MeOH, THF; HCl

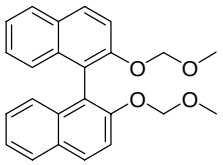
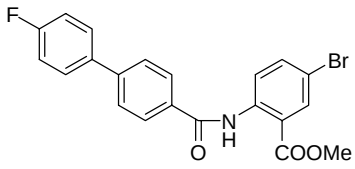


Figure 4.1 structure of binol bis(methoxymethyl ether)[167]

The binaphthol analogues are still under investigation, the preparation of homologous analogues could be achieved by reacting binaphthol with ω-halocarboxylic acid ester [$Br(CH_2)_nCOOEt$] type of reagents. Further synthesis will be subject to the results of biological activity data.

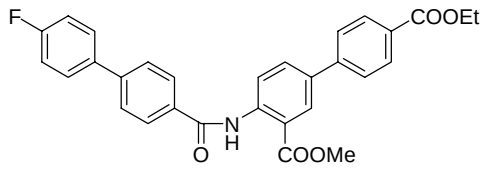
Experimental

5-Bromo-2-[(4'-fluoro-biphenyl-4-carbonyl)-amino]-benzoic acid methyl ester (84)



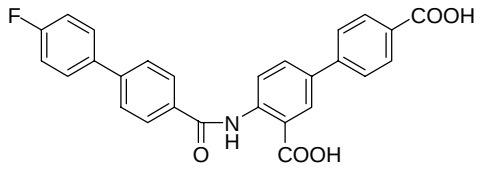
A mixture of 4'-fluorobiphenyl-4-carboxylic acid (0.54 g, 2.5 mmol) and thionyl chloride (5 mL) was heated at reflux (3 h). The excess thionyl chloride was removed by distillation and the residue was dissolved in anhydrous pyridine (15 mL). To the complex mixture was slowly added to a solution of methyl 5-bromo-2-aminobenzoate (0.58 g, 2.5 mmol) in pyridine (20 mL) and the reaction mixture was stirred overnight. The resulting precipitate was collected (0.52 g) and the filtrate was diluted with dichloromethane, washed with water, hydrochloric acid, sodium bicarbonate and water. The organic layer was collected, dried ($MgSO_4$) and concentrated to provide a grey solid (0.21 g). Two batches of solid were combined and recrystalized from dichloromethane/petroleum spirit to provide a white solid (0.57 g, 53%); m.p. 182-183 ºC; Found **C** 59.5, **H** 3.3, **N** 2.9%; $C_{21}H_{15}BrFNO_3$ requires **C** 58.9, **H** 3.5, **N** 3.3%; ^{1}H NMR δ 12.0 (s, 1H, NH), 8.88 (apparent d, *J*= 9.1 Hz, 1H, ArH), 8.07-8.22 (m, 3H, ArH), 7.57-7.74 (m, 5H, ArH), 7.12-7.21 (m, 2H, ArH), 3.99 (s, 3H, OCH_3); ^{13}C NMR 168.7 (C=O), 166.1 (C=O), 163.6 (d, J_{FC}= -242.6 Hz), 144.6, 141.6, 138.3, 136.8, 136.7 (d, J_{FCCCC}= 3.0 Hz), 134.2, 131.4, 129.6 (d, J_{FCCC}= 8.4 Hz), 128.7, 128.1, 122.8, 117.4, 116.6 (d, J_{FCC}= 21.4 Hz), 115.7 (Ar C), 53.5 (OCH_3).

4-[(4'-Fluoro-biphenyl-4-carbonyl)-amino]-biphenyl-3,4'-dicarboxylic acid 4'-ethyl ester 3-methyl ester (**85**)



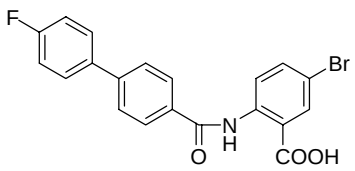
A mixture of the bromide **84** (0.59 g, 1.38 mmol), 4-ethoxycarbonylphenyl boronic acid (0.40 g, 1.52 mmol), palladium acetate (20 mg, 0.08 mmol), potassium carbonate (0.48 g, 3.46 mmol) and triphenylphosphine (20 mg, 0.08 mmol) in THF (20 mL), DME (20 mL) and water (10 mL) was degassed three times and then heated at reflux (16 h). The resulting mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate. The organic layer was washed once with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the product as a white solid (0.52 g, 76%). m.p. 166-168 ºC; Found **C** 72.4, **H** 4.7, **N** 2.7%, $C_{30}H_{24}NFO_5$ requires **C** 72.4, **H** 4.9, **N** 2.8%; ^{1}H NMR δ 12.2 (s, 1H, NH), 9.07 (apparent d, *J*= 9.0 Hz, 1H, ArH), 8.38 (apparent d, *J*= 2.2 Hz, 1H, ArH), 8.11-8.16 (m, 4H, ArH), 7.90 (dd, *J*= 2.2, 9.0 Hz, 1H, ArH), 7.58-7.74 (m, 6H, ArH), 7.17 (m, 2H, ArH), 4.42 (q, *J*= 7.0 Hz, 2H, OCH_2CH_3), 4.03 (s, 3H, OCH_3), 1.43 (t, *J*= 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR 169.7 (C=O), 167.1 (C=O), 166.1 (C=O), 163.6 (J_{FC}= -244.9 Hz), 144.5, 142.4, 136.8 (J_{FCCCC}= 3.1 Hz), 134.9, 134.1, 134.0, 130.9, 130.2, 129.5 (d, J_{FCCC}= 8.0 Hz), 128.7, 128.0, 127.3, 121.7, 116.6 (d, J_{FCC}= 21.4 Hz), 116.3 (Ar C), 61.7 (OCH_2CH_3), 53.4 (OCH_3), 15.1 (OCH_2CH_3). Some signals are coincidental with each other.

4-[(4'-Fluoro-biphenyl-4-carbonyl)-amino]-biphenyl-3,4'-dicarboxylic acid (87)



A solution of diester **85** (200 mg, 0.4 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide (10 mL, 5 M) with stirring at room temperature overnight. The residue was concentrated *in vacuo* and acidified with HCl (5 M). The resulting precipitate was collected, washed with dichloromethane and dried in a desiccator to afford a solid (160 mg, 88%). m.p. 295-297 ºC; Found **C** 66.1, **H** 4.0, **N** 2.8%; $C_{27}H_{18}FNO_5 \cdot 2H_2O$ requires **C** 66.0, **H** 4.5, **N** 2.9%; ^{1}H NMR (d_6-DMSO) δ 12.37 (s, 1H, NH), 8.86 (apparent d, *J*= 8.7 Hz, 1H, ArH), 8.39 (apparent d, *J*= 2.3 Hz, 1H, ArH), 8.02-8.14 (m, 5H, ArH), 7.80-7.92 (m, 6H, ArH), 7.31 (m, 2H, ArH); ^{13}C NMR 169.8 (C=O), 167.0 (C=O), 164.3 (C=O), 162.3 (d, J_{FC}= -245.7 Hz), 142.7, 142.6, 141.0, 135.3, 133.1 (d, J_{FCCCC}= 2.9 Hz), 132.5, 130.1, 129.6, 129.3, 129.1 (d, J_{FCCC}= 8.4 Hz), 127.7, 127.1, 126.4, 120.5, 117.3, 116.1 (d, J_{FCC}= 21.4 Hz), 115.6 (Ar C).

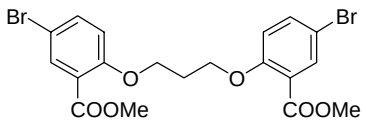
5-Bromo-2-[(4'-fluoro-biphenyl-4-carbonyl)-amino]-benzoic acid (88)



A solution of ester **84** (2.80 g, 6.5 mmol) in methanol (20 mL) was treated with potassium hydroxide (30 g) in methanol (80 mL) with stirring at room temperature overnight. The reaction mixture was diluted with water, concentrated and then acidified with hydrochloric acid (5 M). The precipitate was filtered and dried in desiccator to afford a white solid which was recrystalized from acetone/petroleum spirit (2.51 g, 93%). m.p. 278-281 ºC; Found **C** 55.2, **H** 3.1, **N** 3.1%;

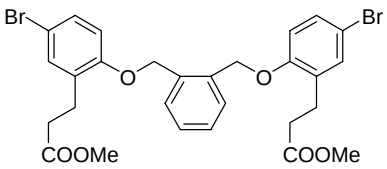
$C_{20}H_{13}BrFNO_3 \cdot H_2O$ requires **C** 55.6, **H** 3.5 **N** 3.2%; ^{1}H NMR (d_6-DMSO) δ 12.18 (s, 1H, NH), 8.68 (apparent d, *J*= 8.8 Hz, 1H, ArH), 8.13 (apparent d, *J*= 2.5 Hz, 1H, ArH), 8.03 (apparent d, *J*= 8.1 Hz, 2H, ArH), 7.79 -8.05 (m, 5H, ArH), 7.31-7.39 (m, 2H, ArH); ^{13}C NMR 168.6 (C=O), 164.3 (C=O), 162.3 (d, J_{FC}= -245.7 Hz), 142.7, 140.2, 136.7, 135.3 (d, J_{FCCCC}=3.0 Hz), 133.2, 132.9, 129.1 (d, J_{FCCC}= 8.4 Hz), 127.7, 127.1, 122.1, 118.9, 115.9 (d, J_{FCC}= 21.4 Hz), 114.3 (Ar C).

5-Bromo-2-[3-(4'-bromo-2'-methoxycarbony)propoxy]benzoic acid methyl ester (91)



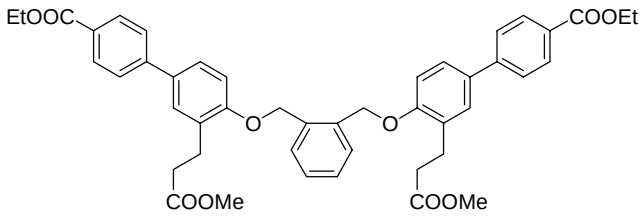
A mixture of 1-bromo-3-chloropropane (2.86 g, 0.02 mol), sodium iodide (15.1 g, 0.1 mol) and butanone (60 mL) was heated at reflux (3 h). To the resulting mixture was added methyl 5-bromosalicylate (9.2 g, 0.04 mol) and potassium carbonate (6.9 g, 0.05 mol). The mixture was heated at reflux overnight. The reaction mixture was concentrated in *vacuo* and diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water, dried and concentrated *in vacuo*. The crude product was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford a white solid (0.47 g, 4.7%). m.p. 95-96 ºC; Found **C** 45.8, **H** 3.7%, $C_{19}H_{18}Br_2O_6$ requires **C** 45.4, **H** 3.6%; ^{1}H NMR δ 7.89 (d, *J*= 2.6 Hz, 2H, H6,3'), 7.53 (dd, *J*= 8.8, 2.6 Hz, 2H, H4, 5'), 6.91 (d, *J*= 8.8 Hz, 2H, H3, 6'), 4.27 (t, *J*= 5.9 Hz, 4H, 2 x OCH_2), 3.84 (s, 6H, 2 x OCH_3), 2.29-2.36 (m, 2H, OCH_2CH_2); ^{13}C NMR 165.8 (C=O), 158.3, 136.8, 134.9, 122.6, 115.9, 113.0 (Ar C), 66.1 (2 x OCH_2), 52.8 (2 x OCH_3), 29.7 (OCH_2CH_2)

3-(5-Bromo-2-{2-[4-bromo-2-(2-methoxycarbonyl-ethyl)-phenoxymethyl]-benzyloxy}phenyl) propionic acid methyl ester (94)



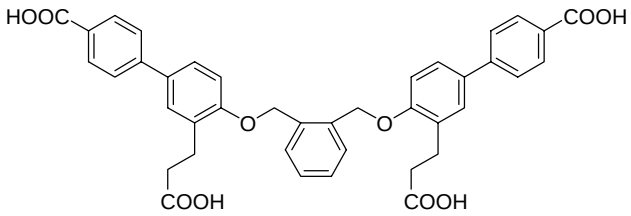
A mixture of α-α'-dibromo-*o*-xylene (2.64 g, 0.01 mol), sodium iodide (6.0 g, 0.04 mol) and butanone (60 mL) was heated at reflux (3 h). To the mixture was then added methyl (5-bromo-2-hydroxyphenyl)propanoate (5.18 g, 0.02 mol) and potassium carbonate (5.5 g, 0.04 mol). The mixture was heated at reflux for overnight. The residue was concentrated in *vacuo* and diluted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford a clear liquid which slowly crystallized to white needles (4.2 g, 67%). m.p. 64-66 ºC; Found **C** 53.9, **H** 4.6%, $C_{28}H_{28}Br_2O_6$ requires **C** 54.2%, **H** 4.6%; ^{1}HNMR δ 7.24-7.52 (m, 8H, ArH), 6.74-6.79 (m, 2H, ArH), 5.14 (s, 4H, 2 x $ArCH_2O$), 3.64 (s, 6H, 2 x OCH_3), 2.92 (t, *J*=7.5 Hz, 4H, 2 x $ArCH_2$), 2.59 (t, *J*=7.5 Hz, 4H, 2 x $ArCH_2CH_2$); ^{13}C NMR 173.8 (2 x C=O), 156.2, 135.3, 133.5, 132.1, 131.0, 129.4, 129.3, 114.0 (Ar C), 68.8 (2 x $ArCH_2O$), 52.3 (2 x OCH_3), 34.4 (2 x $ArCH_2$), 26.3 (2 x $ArCH_2CH_2$). Some signals are coincident with each other.

4'-{2-[4'-Ethoxycarbonyl-3-(2-methoxycarbonyl-ethyl)biphenyl-4-yloxymethyl] benzyloxy}biphenyl-4-carboxylic acid ethyl ester (95)



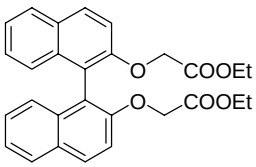
A mixture of the diester **94** (2.25 g, 4 mmol), 4-ethoxylcarbonylphenylboronic acid (1.84 g, 9.6 mmol), palladium acetate (0.1 g, 0.4 mmol), potassium carbonate (2.6 g, 16 mmol) and triphenylphosphine (0.11 g, 0. 4 mmol), THF (10 mL), DME (10 mL) and water (5 mL) was degassed three times and then heated at reflux (16 h). The resulting mixture was concentrated and the residue was diluted with ethyl acetate. The organic layer was washed once with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (20% ethyl acetate in petroleum spirit) to afford the product as a white solid (0.61 g, 20%). m.p. 111-113 ºC; Found **C** 72.4, **H** 6.2%; $C_{46}H_{46}O_{10}$ requires **C** 72.8, **H** 6.1%; ^{1}H NMR δ 8.06-8.10 (m, 4H, ArH), 7.40-7.63 (m, 12H, ArH), 7.01 (apparent d, *J*= 9.1 Hz, 2H, ArH), 5.27 (s, 4H, 2 x OCH_2Ar), 4.39 (q, *J*= 7.1 Hz, 4H, 2 x OCH_2CH_3), 3.63 (s, 6H, 2 x OCH_3), 3.06 (t, *J*= 7.6 Hz, 4H, 2 x $ArCH_2CH_2$), 2.67 (t, *J*= 7.6 Hz, 4H, 2 x $ArCH_2CH_2$), 1.41 (t, *J*= 7.1 Hz, 6H, 2 x OCH_2CH_3); ^{13}C NMR 174.2 (C=O), 167.2 (C=O), 157.4, 145.7, 135.5, 133.5, 130.7, 129.7, 129.4, 129.2, 127.1, 116.3, 112.7 (Ar C), 68.7 (2 x OCH_2Ar), 61.6 (2 x OCH_2CH_3), 52.2 (2 x OCH_3), 34.8 (2 x $ArCH_2CH_2$), 26.9 (2 x CH_2COO), 15.0 (2 x OCH_2CH_3). Some signals are coincident with each other.

4'-{2-[4'-Ethoxycarbonyl-3-(2-methoxycarbonyl-ethyl)biphenyl-4-yloxymethyl] benzyloxy}biphenyl-4-carboxylic acid (96)



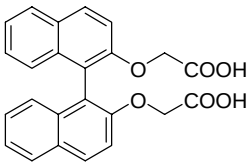
A solution of the tetraester **95** (200 mg, 0.26 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The desired product was collected as a white solid and recrystalized from acetone/petroleum spirit (149 mg, 84%). m.p. 301-303 ºC; ^{1}H NMR δ 8.02 (apparent d, *J*= 8.5 Hz, 4H, ArH), 7.78 (apparent d, *J*= 8.5 Hz, 4H, ArH), 7.43-7.64 (m, 8H, ArH), 7.24 (apparent d, *J*=9.5 Hz, 2H, ArH), 5.42 (s, 4H, 2 x OCH_2Ar), 2.98 (t, *J*= 7.5 Hz, 4H, 2 x $ArCH_2$), 2.63 (d, *J*= 7.5 Hz, 4H, 2 x CH_2COO); ^{13}C NMR 173.9 (C=O), 167.1 (C=O), 156.3, 144.0, 135.0, 131.2, 129.8, 129.5, 129.0, 128.3, 128.0, 127.9, 126.1, 126.0, 112.4 (Ar C), 67.1 (2 x OCH_2), 33.6 (2 x CH_2COO), 25.4 (2 x $ArCH_2$).

2,2'-Di(ethoxycarbonylmethoxy)-[1,1']-binaphthol (98)



A mixture of ethyl bromoacetate (1.67 g, 0.1 mol), sodium iodide (7.5 g, 0.5 mol) and acetonitrile (20 mL) was heated at reflux overnight. After cooling, 1,1'-binaphthol (1.4 g, 0.05 mol) and potassium carbonate (1.38 g, 0.1 mol) were added to this mixture and heated at reflux for 8 hours. The mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (10% ethyl acetate in petroleum spirit) to afford a white solid (1.88 g, 82%). m.p. 107-108 ºC; Found **C** 73.0, **H** 5.9%, $C_{28}H_{26}O_6$ requires **C** 73.4, **H** 5.7%; ^{1}H NMR δ 8.02 (d, *J*= 8.8 Hz, 2H, ArH), 7.93 (d, *J*= 8.1 Hz, 2H, ArH), 7.26-7.45 (m, 8H, ArH), 4.55 (s, 4H, 2 x OCH_2CO), 4.15 (q, *J*= 6.9 Hz, 4H, 2 x OCH_2CH_3), 1.23 (t, *J*= 6.9 Hz, 6H, 2 x CH_3); ^{13}C NMR 170.0 (C=O), 154.5, 134.7, 130.5, 130.3, 128.6, 127.2, 126.4, 124.8, 121.1, 116.4 (Ar C), 68.0 (2 x OCH_2CO), 61.7 (2 x OCH_2CH_3), 14.7 (2 x OCH_2CH_3).

(2'-Carboxymethoxy-[1, 1']binaphthalenyl-2-yloxy)-acetic acid (99)



A solution of the diester **98** (200 mg, 0.44 mmol) in THF (10 mL) and methanol (10 mL) was treated with sodium hydroxide solution (5 mL, 5 M) with stirring at room temperature for 1 hour. The residue was concentrated *in vacuo*, diluted with water, acidified with hydrochloric acid (5 M) and extracted with ethyl acetate. The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The desired product was collected as a white solid and recrystalized from acetone/petroleum spirit (162 mg,

92%). m.p. 208-209 ºC; Found **C** 71.6, **H** 4.5%; $C_{24}H_{18}O_6$ requires **C** 71.6, **H** 4.5%; ^{1}H NMR δ 8.08 (d, *J*= 8.1 Hz, 2H, ArH), 7.66 (d, *J*= 9.1 Hz, 2H, ArH), 7.24- 7.54 (m, 8H, ArH), 4.83 (s, 4H, 2 x OCH_2); ^{13}C NMR 174.0 (2 x C=O), 158.3, 138.4, 134.2, 133.8, 132.3, 130.6, 129.7, 128.2, 124.3, 119.8 (Ar C), 70.5 (2 x OCH_2).

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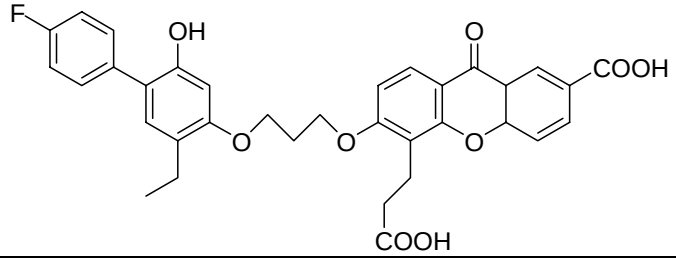
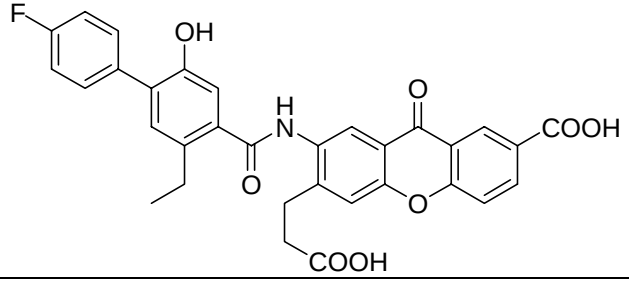
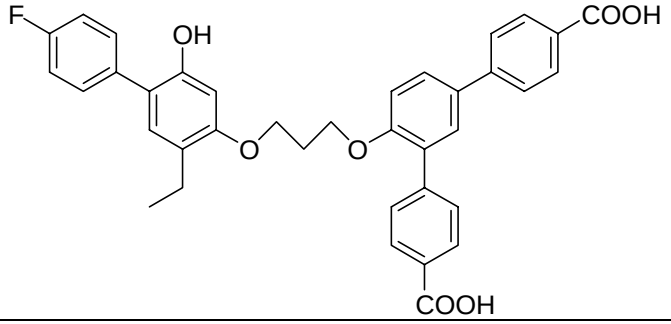
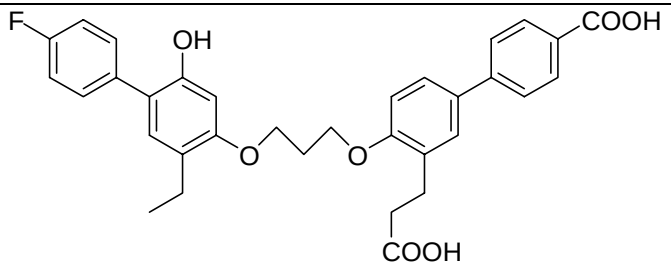
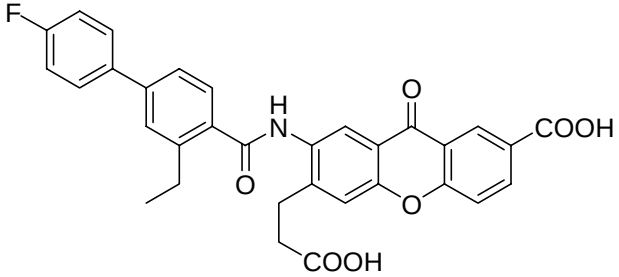
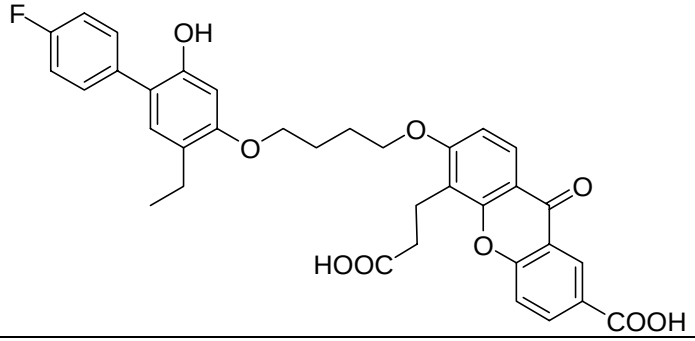
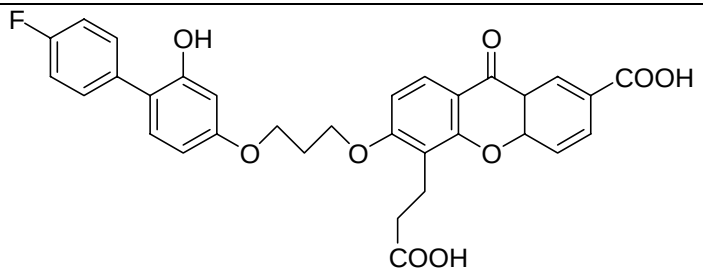
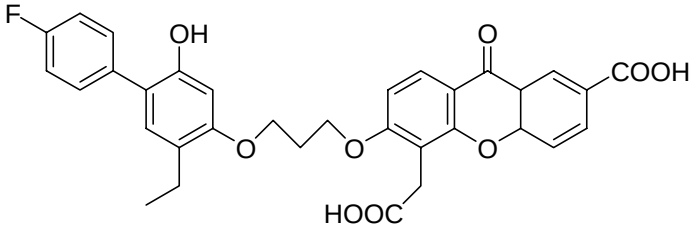
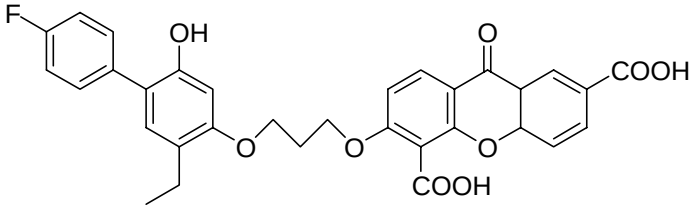
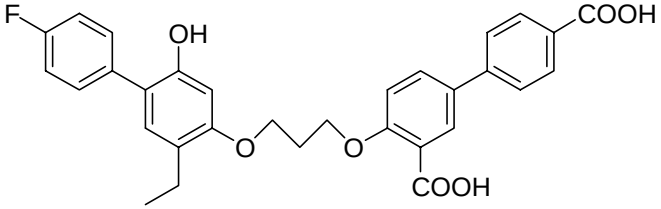
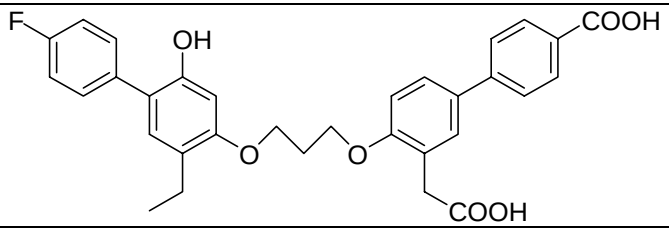
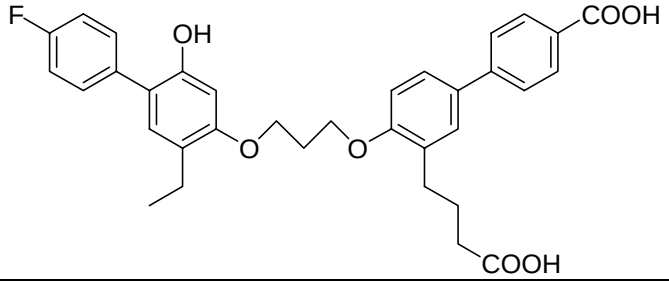
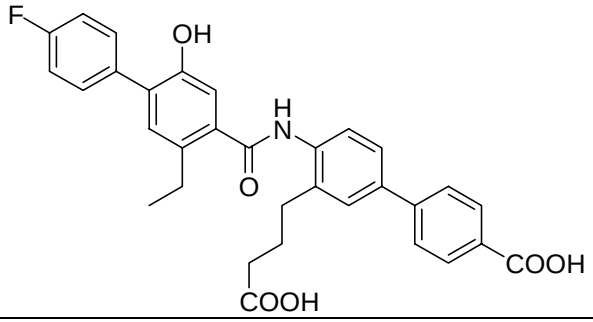
Appendix

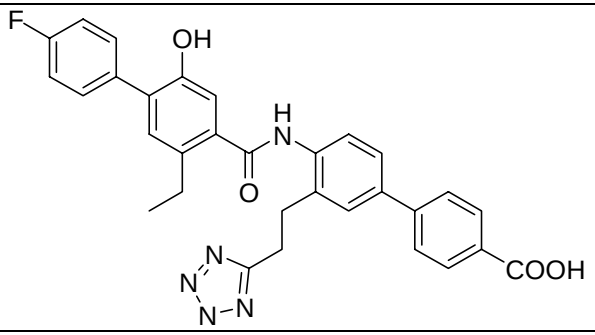
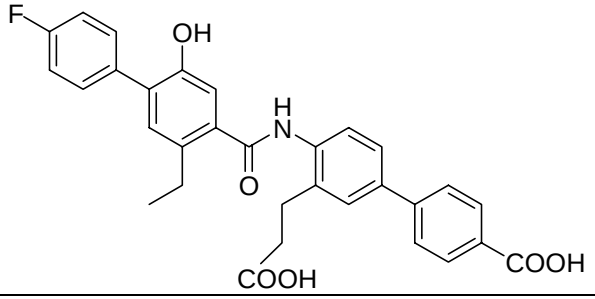
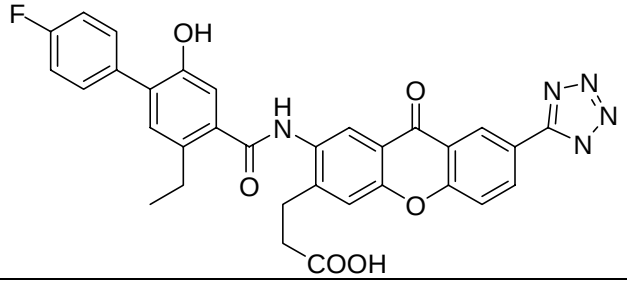
Computational calculations for **IM140** and some analogues

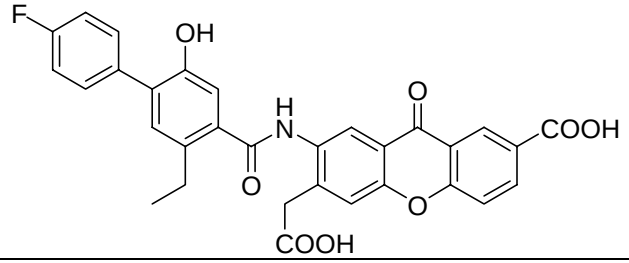
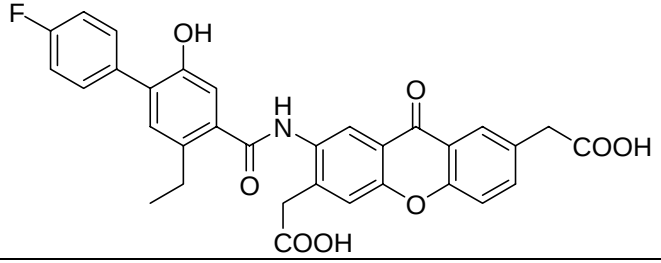
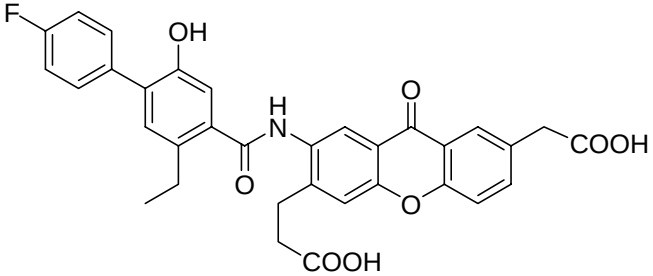
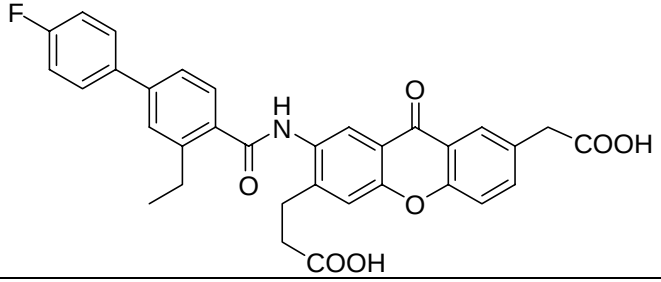
Code	Structure	ClogP	%HIA	Ame's MI	Pharm, Fit (RMSD)	Calc. Ki (µM)	Specific (IR/IGFR)	Mol. Wt (di-ion)
IM140		-.450	40.01	1	2.868	4.906	276	598.57
WAB2		1.91	63.0	0	2.875	0.352	115	567.5
WAB54		1.74	63.0	1	2.74			604.63

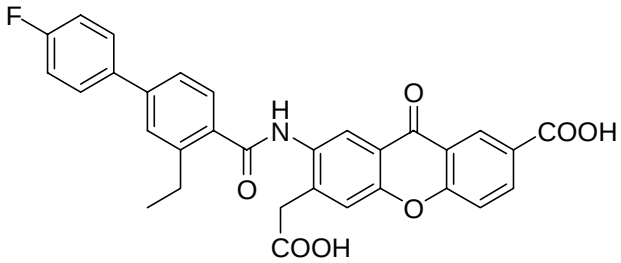
WAB49		-0.23	64.0	1	2.89			556.58
WAB6		2.90	57.9	0	2.87	0.502		551.52
WAB69		-0.02	40.3	1				612.61

WAB71		0.12	23.0	0				582.58
WAB66		0.02	38.4	1	3.351			584.55
WAB67		1.85	34.3	1				570.52
WAB55		1.09	57.5	1	3.38			528.53

WAB56		-0.20	62.3	1	2.83			542.55
WAB51		0.31	64.5	1	2.68			570.61
WAB59		3.09	73.8	1	2.46			539.55

WAB60		5.45	75.3	0	3.26			549.56
WAB57		2.55	73.7	1	2.70			525.53
WAB8		3.58	72.9	0	2.89			575.55

WAB38		2.01	61.5	0	3.18			553.49
WAB40		0.90	62.2	0	3.03			567.52
WAB10		0.80	63.8	0	2.80	0.69		581.55
WAB14		1.79	60.4	0	2.76			565.55

WAB36		2.99	52.1	0	3.19	1.56		537.49