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PYRAZOLO[1,5-*a*][1,3,5]TRIAZINES (5-AZA-9-DEAZAPURINES): SYNTHESIS AND BIOLOGICAL ACTIVITY[1]

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Abstract – The present review gives an account on the synthetic routes to pyrazolo[1,5-*a*][1,3,5]triazine system, which is an isostere of purine, and polyfused systems bearing this heterocyclic core. Data concerning biological activity of compounds with pyrazolo[1,5-*a*][1,3,5]triazine skeleton are also discussed.

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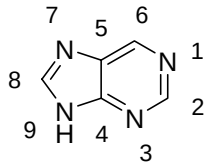
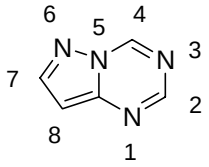
1. INTRODUCTION

The pyrazolo[1,5-*a*][1,3,5]triazine (5-aza-9-deazapurine) heterocyclic system is an isostere of purine (Figure 1), and a number of investigations particularly in the area of nucleoside chemistry have been inspirited by this fact. The close structural resemblance between pyrazolo[1,5-*a*][1,3,5]triazine and purine nuclei rationalized the development of the pyrazolo[1,5-*a*][1,3,5]triazines as biologically active agents that would target the purinergic signaling receptors and enzymes involved in the metabolism of biogenic purines.



purine



pyrazolo[1,5-a][1,3,5]triazine
(5-aza-9-deazapurine)

Figure 1

For the first time, the pyrazolo[1,5-*a*][1,3,5]triazine system was synthesized by Checchi and Ridi 50 years ago in 1957[2] (*vide infra* Scheme 18). In this review, we aim to summarize the methods developed since that time for the preparation of compounds with the pyrazolo[1,5-*a*][1,3,5]triazine scaffold. The information on the biological activity of pyrazolo[1,5-*a*][1,3,5]triazine derivatives are also included. The

syntheses and pharmacological data on the more interesting examples of bioactive compounds are discussed separately in the Section 6 of this review.

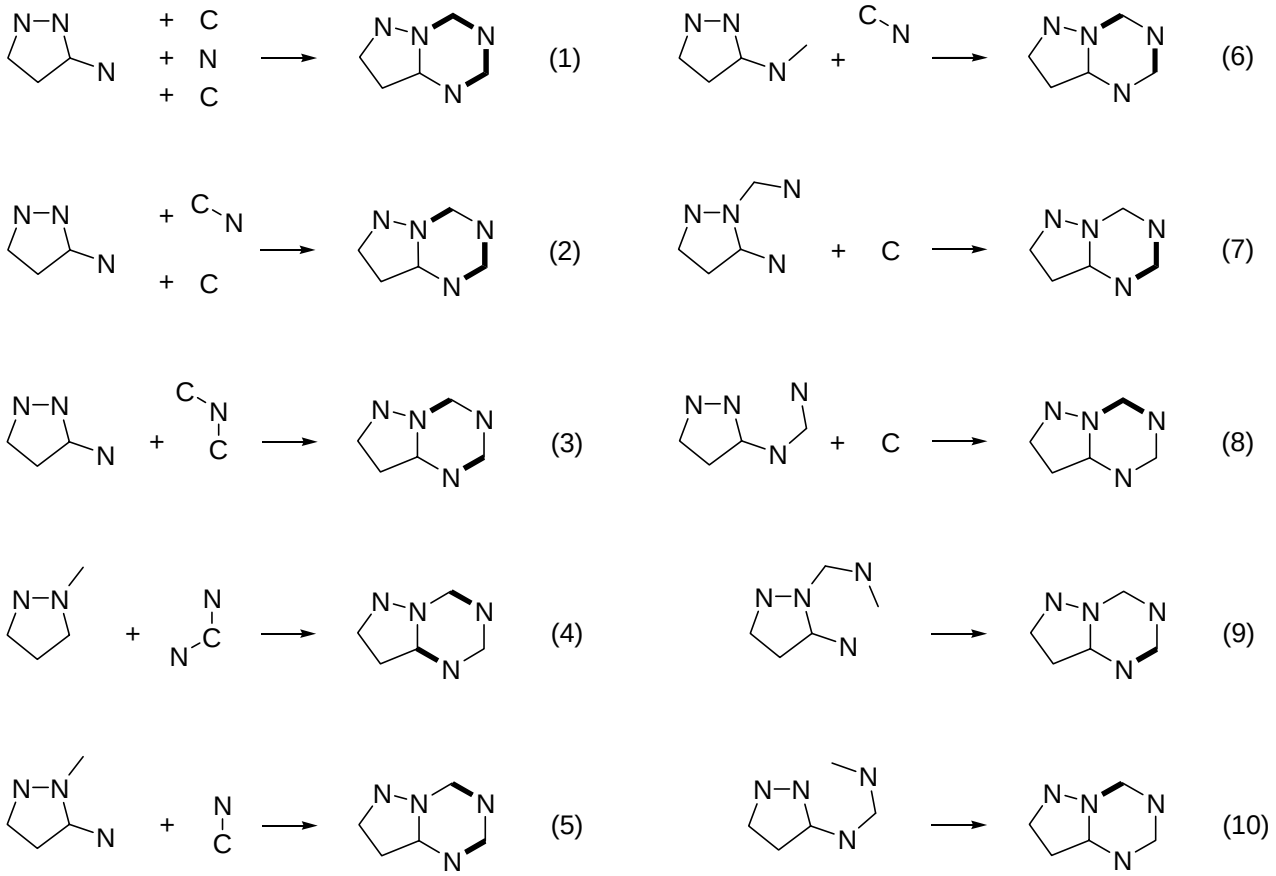
Within the review we collectively categorized the common approaches to the synthesis of pyrazolo[1,5-*a*][1,3,5]triazines into: (A) annelation of the 1,3,5-triazine ring onto a pyrazole scaffold; (B) annelation of the pyrazole ring onto a 1,3,5-triazine scaffold; (C) concurrent formation of both the 1,3,5-triazine and pyrazole ring; (D) syntheses *via* ring transformation reactions.

2. SYNTHESIS BY ANNELATION OF THE 1,3,5-TRIAZINE RING ONTO A PYRAZOLE SCAFFOLD

The 1,3,5-triazine ring annelation strategy is a very versatile synthetic approach for the preparation of pyrazolo[1,5-*a*][1,3,5]triazines. This strategy represents the most frequently utilized route to the formation of the pyrazolo[1,5-*a*][1,3,5]triazine ring system.

Suitably functionalized pyrazoles can be cyclized to pyrazolo[1,5-*a*][1,3,5]triazines according to the following schematically represented plan (Scheme 1):

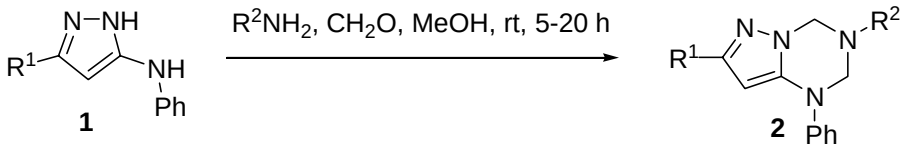
1. Four-bond formation (3+1+1+1) through cyclization of 3(5)-aminopyrazoles with two carbon and one nitrogen atoms.
2. Three-bond formation (3+2+1) through cyclization of 3(5)-aminopyrazoles with reagents introducing C-N fragment and one carbon atom.
3. Two-bond formation (3+3) through cyclization of 3(5)-aminopyrazoles with reagents introducing C-N-C fragment.
4. Two-bond formation (3+3) through cyclization of 1-acylpyrazolidinediones with reagents introducing N-C-N fragment.
5. Two-bond formation (4+2) through cyclization of 5-aminopyrazoles having carbon atom at N1 with reagents introducing C-N fragment.
6. Two-bond formation (4+2) through cyclization of pyrazoles having N-C appendage at C3(5) with reagents introducing C-N fragment.
7. Two-bond formation (5+1) through cyclization of 5-aminopyrazoles having C-N appendage at N1 with one carbon atom.
8. Two-bond formation (5+1) through cyclization of pyrazoles having N-C-N appendage at C3(5) with one carbon atom.
9. One bond formation through intramolecular cyclization of 5-aminopyrazoles having C-N-C appendage at N1.
10. One bond formation through intramolecular cyclization of pyrazoles having N-C-N-C appendage at C3(5).



Scheme 1

2.1. Four-bond formation through (3+1+1+1) atoms heterocyclization of 3(5)-aminopyrazoles with two carbon and one nitrogen atoms.

The condensation of 3(5)-phenylaminopyrazoles (**1**) with two equivalents of formaldehyde and one equivalent of primary amines was reported to proceed regioselectively affording 1,2,3,4-tetrahydropyrazolo[1,5-*a*][1,3,5]triazines (**2**) (Scheme 2).[3] It should be mentioned that using of 3(5)-alkylaminopyrazoles under identical conditions resulted in the cyclization to carbon atom of pyrazole ring with the formation of pyrazolo[3,4-*d*]pyrimidine system.

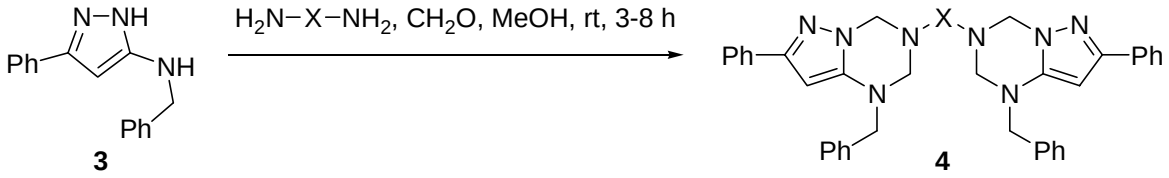


R^1 = Ph, R^2 = Me, 87% (**2a**); Et, 83% (**2b**); Bn, 92% (**2c**); C_6H_4OMe-4, 95% (**2d**);
R^1 = C_6H_4Me-4, R^2 = Et, 94% (**2e**)

Scheme 2

When similar condensation with formaldehyde was performed using 3(5)-benzylaminopyrazole (**3**) and diamines, bis(1,2,3,4-tetrahydropyrazolo[1,5-*a*][1,3,5]triazinyl) derivatives **4** were formed (Scheme 3).[4] However, the type of substituent at the exocyclic nitrogen atom also played a role in the regioselectivity

of ring closure. Thus, the annelation of tetrahydropyrimidine ring was observed when 3(5)-methylaminopyrazoles were used as starting materials.

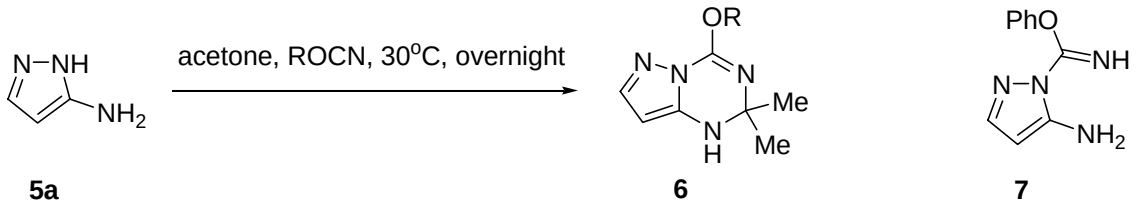


X = -$(CH_2)_2$-, 51% (**4a**); -$(CH_2)_4$-, 50% (**4b**); 1,4-C_6H_4, 55% (**4c**)

Scheme 3

2.2. Three-bond formation (3+2+1) through cyclization of 3(5)-aminopyrazoles with reagents introducing C-N fragment and one carbon atom.

The reaction of 3(5)-aminopyrazole (**5a**) and aryl cyanates in acetone was reported to afford 4-aryloxy-2,2-dimethyl-2,3-dihydropyrazolo[1,5-*a*][1,3,5]triazines (**6**) (Scheme 4).[5] When DMF was used as a solvent in the reaction of **5a** with phenyl cyanate, unstable adduct **7** was obtained.



R = Ph, 41% (**6a**); C_6H_4Me-4, 34% (**6b**)

Scheme 4

2.3. Two-bond formation (3+3) through cyclization of 3(5)-aminopyrazoles with reagents introducing C-N-C fragment.

This synthetic approach provides an excellent opportunity for the preparation of a variety of functionalized pyrazolo[1,5-*a*][1,3,5]triazines using 3(5)-aminopyrazoles, wide spectrum of which are readily available[6] as building blocks. The triatomic C-N-C synthons used in the cyclization determined substitution pattern at the formed 1,3,5-triazine ring. The substituted imidates[7] are excellent examples of this type of synthons. Thus, the reactions of 3(5)-aminopyrazoles (**5**) with *N*-acyl- (**8**), *N*-cyano- (**9**) and *N*-carbethoxyimidates (**10**) (Figure 2) provided an accessible source for the preparation of pyrazolo[1,5-*a*][1,3,5]triazines with alkyl-, aryl-, amino-, oxo- and alkylthio- substituents at the positions 2 and 4 of the triazine ring. The cyclization reactions within each section of the review are arranged based on the type of substituents at 1,3,5-triazine ring of the products. It should be also mentioned that regiochemistry of the ring closure was not always unambiguous and the structure assignments were often uncertain and therefore require further verification.

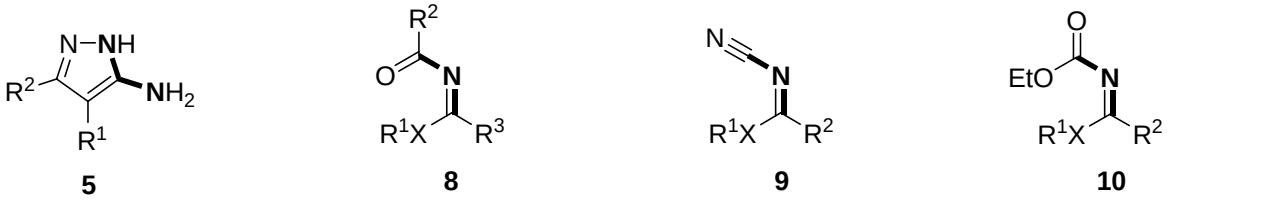
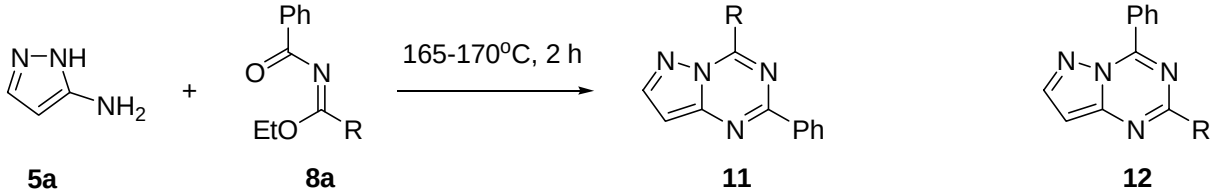


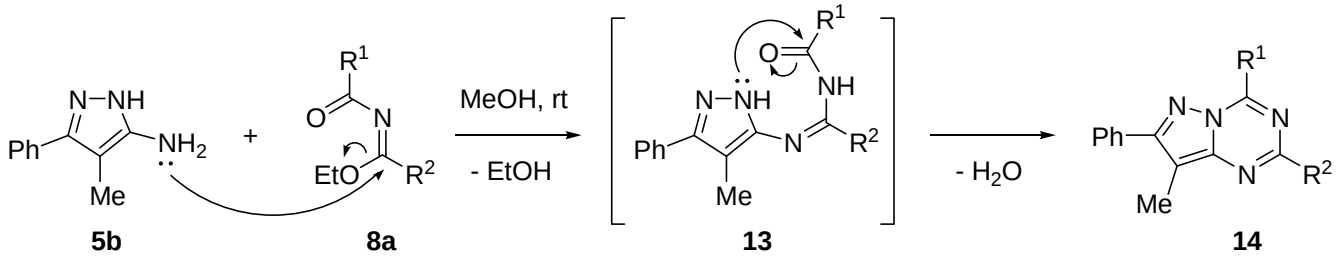
Figure 2

It was reported that the reaction of 3(5)-aminopyrazole (**5a**) with ethyl *N*-benzoylimidates (**8a**) afforded 2,4-diarylpyrazolo[1,5-*a*][1,3,5]triazines (**11**) (Scheme 5).[8] The regioselectivity of this reaction was not discussed in the original paper[8] even though formation of the isomer **12** would be preferred over **11b** because of higher nucleophilicity of exocyclic nitrogen atom of 3(5)-aminopyrazole (**5a**). In view of this fact, more rational mechanism of similar heterocyclization was proposed in the reaction of the substituted 3(5)-aminopyrazole (**5b**) with ethyl *N*-acylimidates (**8a**) *via* intermediate **13** resulting in the formation of **14** (Scheme 6).[9]



R = Ph, 83% (**11a**); C_6H_4Me-4, 85% (**11b**)

Scheme 5

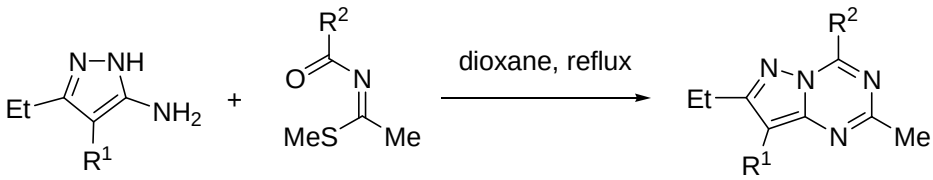


R^1 = Me, R^2 = Ph, 85% (**14a**); R^1 = *i*-Pr, R^2 = $CH_2C_6H_4Cl$-4, 85% (**14b**)

Scheme 6

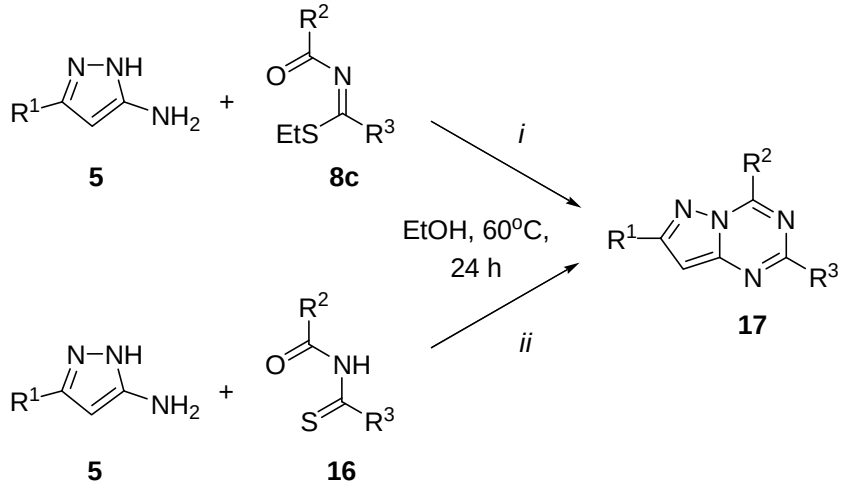
The reaction of 3(5)-aminopyrazoles (**5**) with methyl *N*-aroylthioacetimidates (**8b**) effected annelation to 4-aryl-2-methyl-1,3,5-triazine ring, exclusively (Scheme 7).[10] The structure of the product **15** (R^1 = $CHEt_2$, R^2 = $C_6H_3Cl_2$-2,4) was supported by X-ray crystallography data.

Similarly, the 2,4-diarylpyrazolo[1,5-*a*][1,3,5]triazines **17** were synthesized by the reaction of 3(5)-aminopyrazoles (**5**) with ethyl *N*-aroylthioimidates (**8c**) (Scheme 8).[11] It was shown that *N*-acylthioamides (**16**) could be as effective in this reaction as their *S*-ethyl derivatives **8c**. The X-ray crystallography data were used to confirm the structure of **17** (R^1 = Me, R^2 = $C_6H_4CF_3$-4, R^3 = Ph).



5 **8b** **15**

Scheme 7



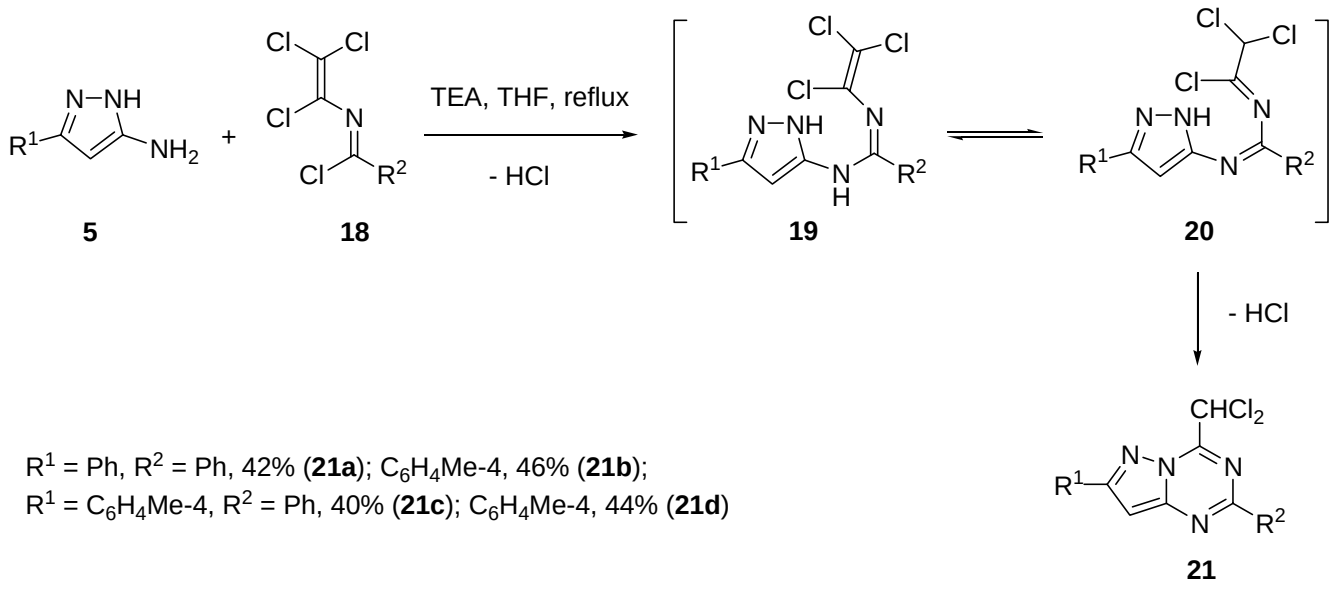
5 **8c** **17**

5 **16**

R^1 = H, Me, Ph, C_6H_4OMe-3, 2-furyl, 2-thienyl;
i: R^2 = $C_6H_4CF_3$-4; R^3 = Ph, C_6H_4Cl-4 (65-81%);
ii: R^2 = Me, $C_6H_4CF_3$-4; R^3 = Me, Ph, C_6H_4F-4 (51-93%)

Scheme 8

It was found that the reaction of 1-aryl-1,3,4,4-tetrachloro-2-azabuta-1,3-dienes (**18**) with 3(5)-aminopyrazoles (**5**) afforded the 2-aryl-4-dichloromethylpyrazolo[1,5-*a*][1,3,5]triazines **21** *via* intermediates **19** and **20** (Scheme 9).[12] The structural assignments were confirmed using NMR data, including HMBC experiment for **21b**.



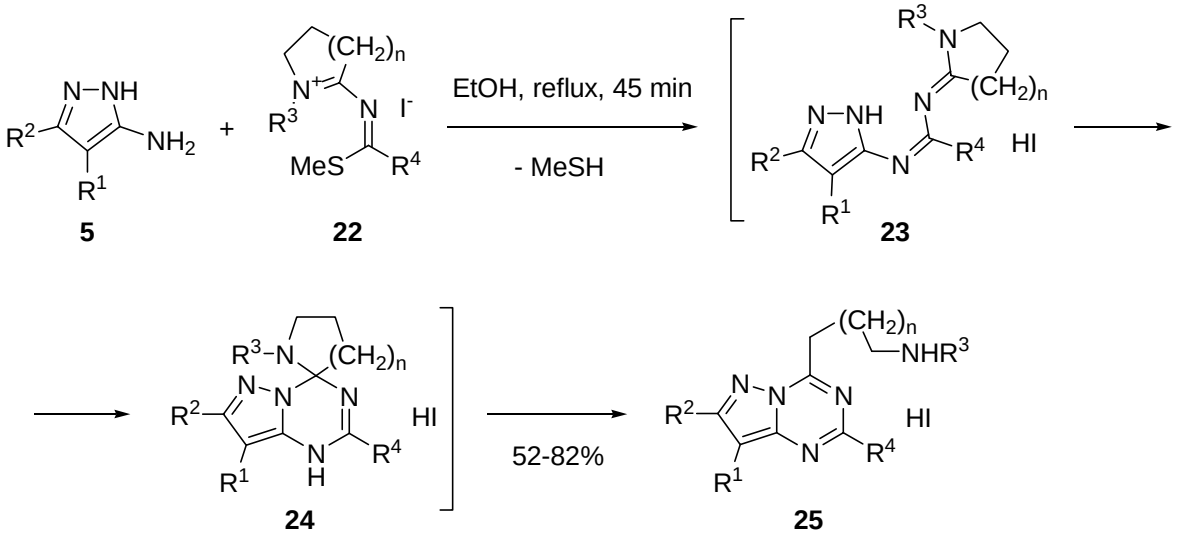
5 **18** **19** **20**

21

R^1 = Ph, R^2 = Ph, 42% (**21a**); C_6H_4Me-4, 46% (**21b**);
R^1 = C_6H_4Me-4, R^2 = Ph, 40% (**21c**); C_6H_4Me-4, 44% (**21d**)

Scheme 9

The annelation of the 2-aryl-4-aminoalkyl-1,3,5-triazine ring onto 3(5)-aminopyrazoles (**5**) using *N*-substituted methyl thioimidates **22** (Scheme 10) was reported[13] *via* the formation of intermediate **23** followed by the ring-chain transformation: the 1,3,5-triazine ring closure affording **24** with subsequent ring opening of the spiro-ring providing pyrazolo[1,5-*a*][1,3,5]triazines **25**.

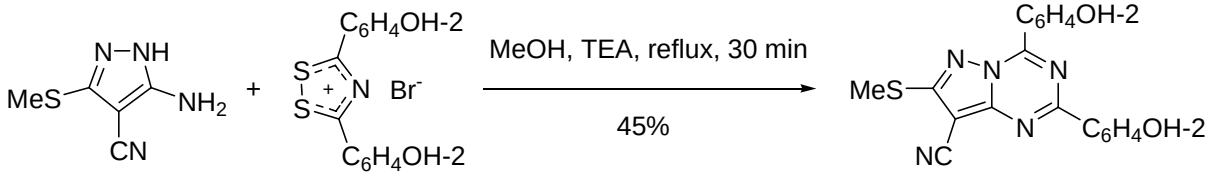


5 **22** **23** **24** **25**

R^1 = H, Ph; R^2 = H, Me, *t*-Bu, Ph, C_6H_4Me-4, C_6H_4Cl-4, C_6H_4Br-4, 2-thienyl;
R^3 = Me, Et, $C_{16}H_{33}$; R^4 = C_6H_4OMe-4, C_6H_4Cl-4, 2-thienyl; n = 1-3

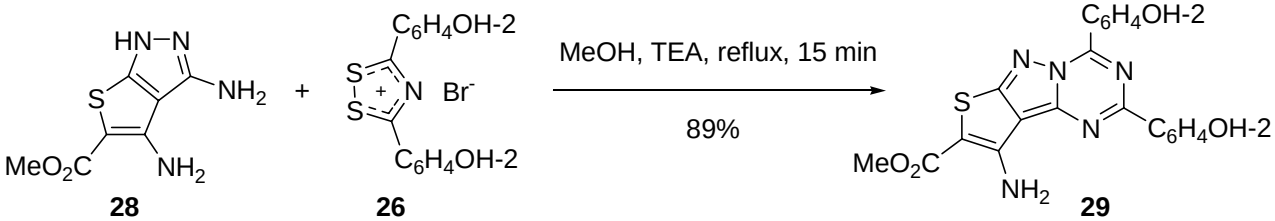
Scheme 10

3,5-Bis(2-hydroxyphenyl)-1,2,4-dithiazolium bromide (**26**) was used as a triatomic synthon for the preparation of 2,4-bis(2-hydroxyphenyl)pyrazolo[1,5-*a*][1,3,5]triazine (**27**) from **5c** (Scheme 11).[14] Analogously, tricyclic system **29** was synthesized from thieno[2,3-*c*]pyrazole **28** using **26** (Scheme 12).



5c **26** **27**

Scheme 11

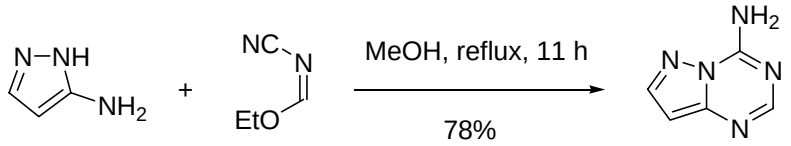


28 **26** **29**

Scheme 12

The preparation of 4-aminopyrazolo[1,5-*a*][1,3,5]triazine (5-aza-9-deazaadenine, **30a**) from 3(5)-aminopyrazole (**5a**) using ethyl *N*-cyanoformimidate (**9a**) (Scheme 13) was reported.[15] In order to confirm the structure of **30a**, an independent synthesis of this compound was also performed. The

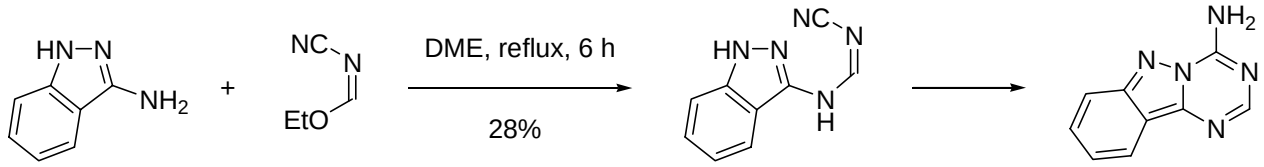
reactions of substituted 3(5)-aminopyrazole (**5**) with methyl or ethyl *N*-cyanoformimidates (*e.g.* **9a**) were found to be useful for the preparation of corresponding adenosine isostere[15] as well as a number of other 4-aminopyrazolo[1,5-*a*][1,3,5]triazine *C*-nucleosides[16-18] and their analogues.[19]



5a **9a** **30a**

Scheme 13

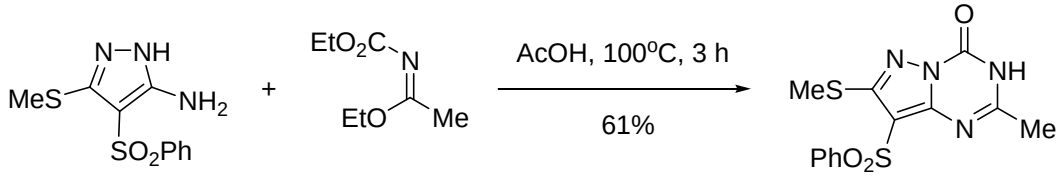
Similarly, the reaction of 3-aminoindazole (**31**) with ethyl *N*-cyanoformimidate (**9a**) afforded the benzoanalogue of **30a** *viz.* 4-amino[1,3,5]triazino[1,2-*b*]indazole (**33**) (Scheme 14).[20] Reducing the reaction time to 0.5 h allowed to isolate compound **32**.



31 **9a** **32** **33**

Scheme 14

It was reported that ethyl *N*-carbethoxyacetimidate (**10a**) was an effective reagent for the annelation of the 2-methyl-4-oxo-1,3,5-triazine ring onto 3(5)-aminopyrazole **5d** (Scheme 15).[21] The product of this reaction, compound **34** was claimed to be an intermediate in the synthesis of the compounds with high affinity to 5-HT_6 receptors (*vide infra* Section 6).

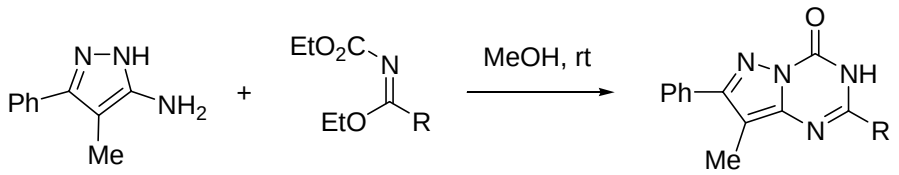


5d **10a** **34**

Scheme 15

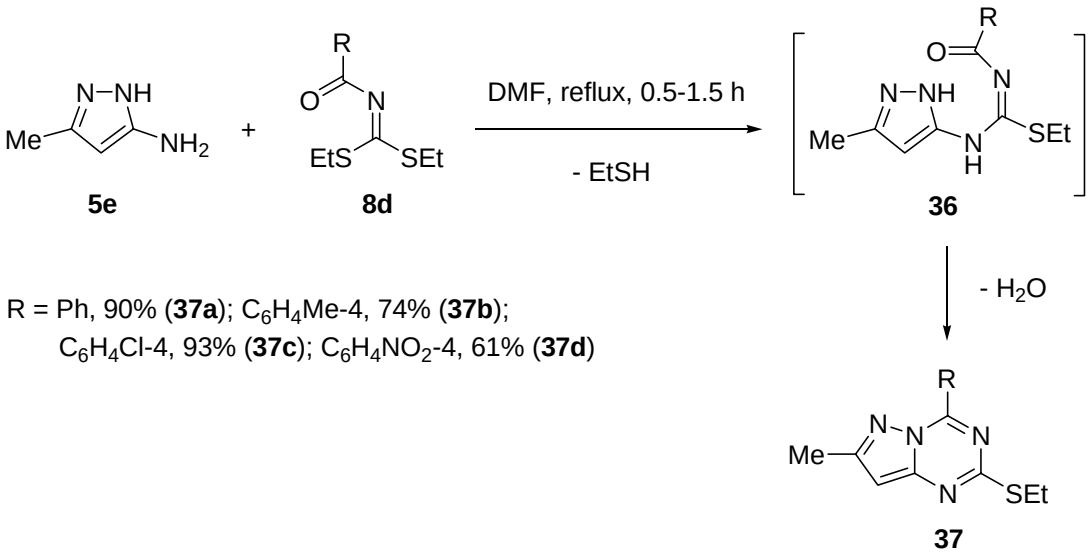
The synthesis of the 2-benzyl(phenyl)-4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**35**) was reported to be achieved upon treatment of 3(5)-aminopyrazole **5b** with ethyl *N*-carbethoxyimidates (**10b,c**) in methanol at ambient temperature (Scheme 16).[9]

The heterocyclization of 3(5)-amino-5(3)-methylpyrazole (**5e**) with diethyl *N*-aroyldithiocarbonimidate (**8d**) was found to give 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*][1,3,5]triazines (**37**) (Scheme 17).[22] The regioselectivity of the ring closure was established by the preparation of **37** *via* an alternative synthetic pathway (*vide infra* Scheme 63)[22] and X-ray crystallographic study of **37b,d**.[23] The isolation of intermediate **36** was shown to be possible when the reaction was carried out at room temperature.



R = Bn, 85% (**35a**); Ph, 85% (**35b**)

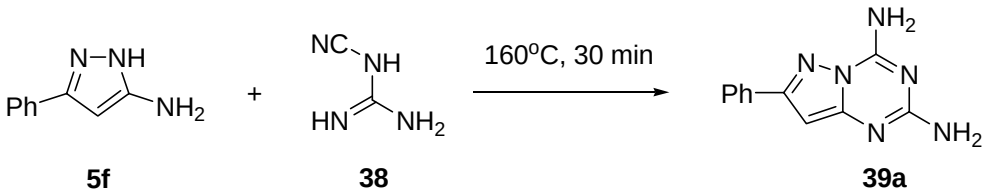
Scheme 16



R = Ph, 90% (**37a**); C_6H_4Me-4, 74% (**37b**);
C_6H_4Cl-4, 93% (**37c**); $C_6H_4NO_2$-4, 61% (**37d**)

Scheme 17

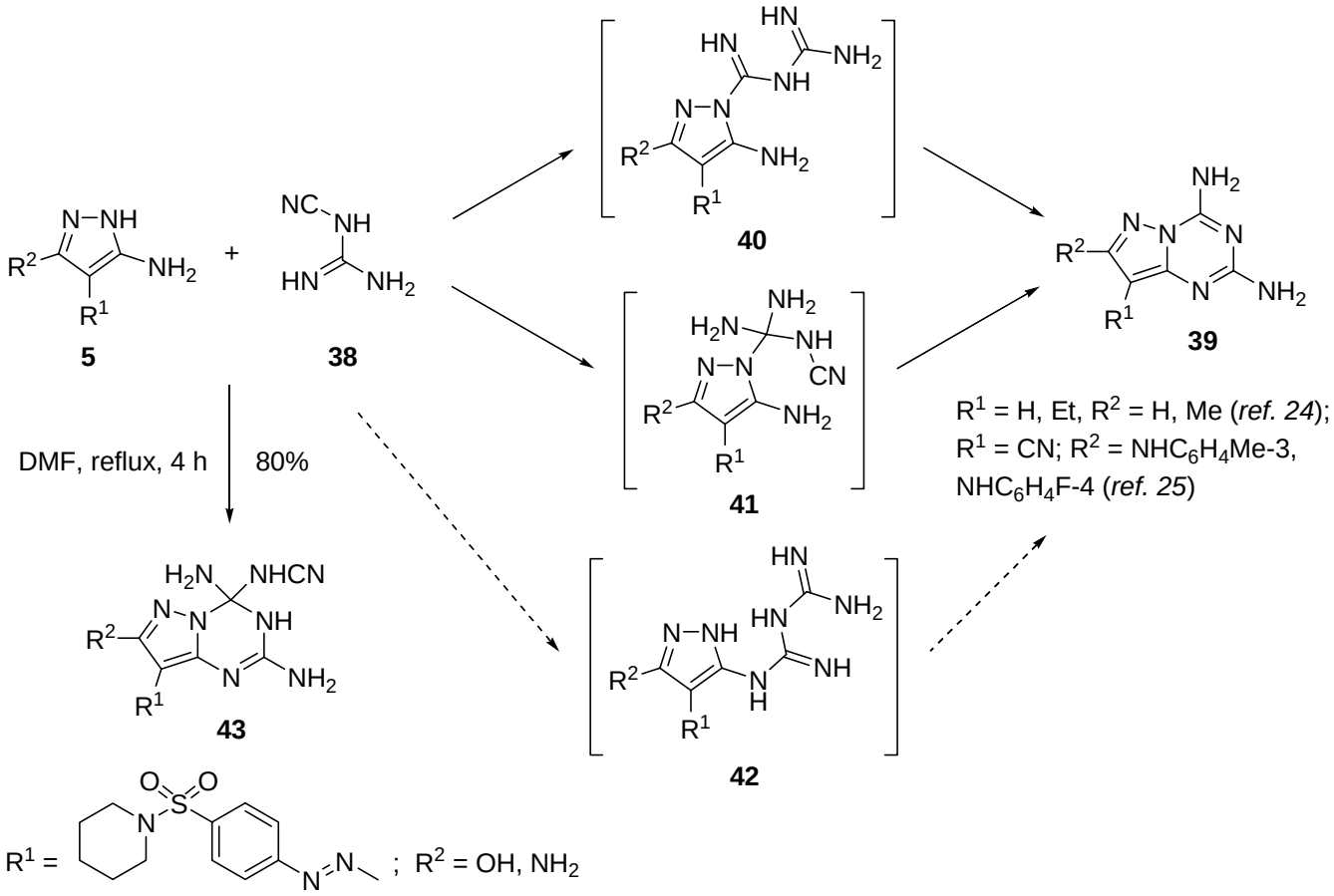
The reaction of 3(5)-aminopyrazole **5f** with cyanoguanidine (**38**) was the first report[2] on the synthesis of the pyrazolo[1,5-*a*][1,3,5]triazine ring system providing 2,4-diamino-7-phenyl-pyrazolo[1,5-*a*][1,3,5]triazine (**39a**) (Scheme 18).



Scheme 18

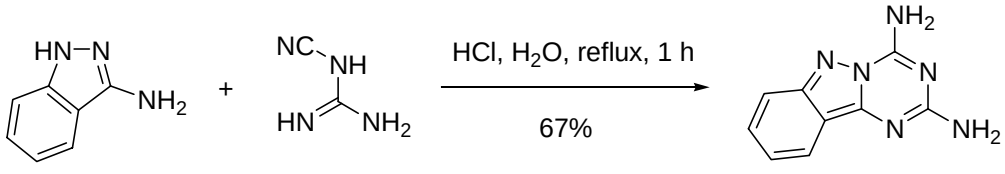
The reaction of 3(5)-aminopyrazoles (**5**) with cyanoguanidine (**38**) has a long history, and it was found to be a good tool for the preparation of a variety of the 2,4-diaminopyrazolo[1,5-*a*][1,3,5]triazines (**39**) (Scheme 19).[24,25] However, controversial mechanisms of the reaction were reported. Thus, two types of adducts *i.e.* **40**[24] and **41**[25] formed at the initial stage of the reaction were proposed, and intermediates **41** were said[25] to be isolated when 3(5)-aminopyrazoles (**5**) and cyanoguanidine (**38**) were heated in ethanol instead of DMF. At the same time, no evidence has been available to confirm the formation of sp^3 hybridized carbon atom (adducts **41**) as well as the initial addition of **38** to endocyclic rather than exocyclic nitrogen of 3(5)-aminopyrazoles (**5**) with formation of possible intermediate **42**. Moreover, it

was reported[26,27] that pyrazolo[1,5-*a*][1,3,5]triazines **43** were products of the reaction between some 3(5)-aminopyrazoles (**5**) and 1.5 equivalent of **38**, but the spectral data provided were limited and not sufficient for conclusive structural assignments. Therefore, this old reaction is open as a subject for further detail investigation.



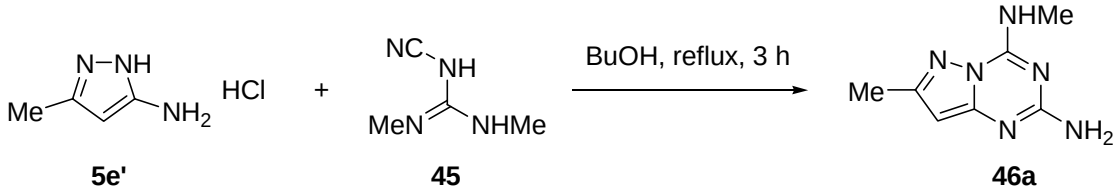
Scheme 19

The cyclocondensation of 3(5)-aminopyrazoles (**5**) with cyanoguanidine (**38**) required heating at high temperature (melting at 160 °C[2] or refluxing in DMF[25-27]). However, other solvents such as water or butanol were found to be suitable when 3(5)-aminopyrazoles (**5**) were used as salts (*e.g.* hydrochloride or mesylate),[24] or acid was added to facilitate the reaction. Analogously, 3-aminoindazole (**31**) was found to react with **38** in the presence of hydrochloric acid affording benzofused 2,4-diaminopyrazolo[1,5-*a*][1,3,5]triazine (**44a**) (Scheme 20).[20]



Scheme 20

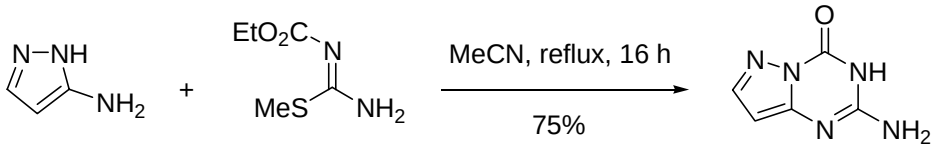
The reaction of 3(5)-amino-5(3)-methylpyrazole hydrochloride (**5e′**) with *N',N''*-dimethylcyanoguanidine (**45**) was reported to result in the annelation of the 2-amino-4-methylamino-1,3,5-triazine ring (Scheme 21).[24] It should be noted that no data was provided to support the regioselective formation of **46a**.



5e' **45** **46a**

Scheme 21

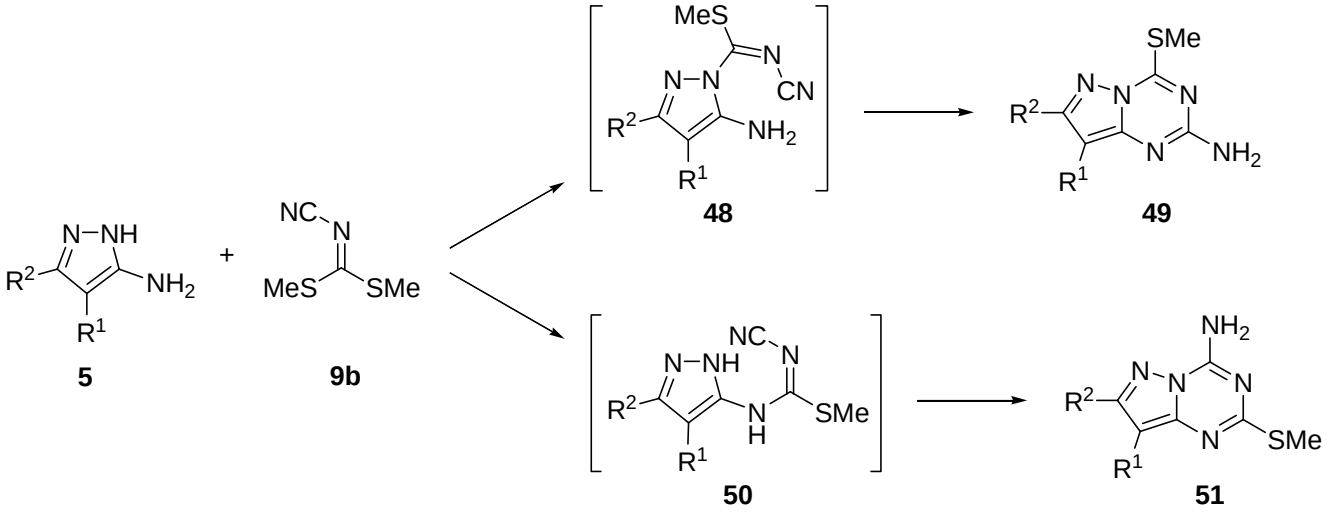
The synthesis of 2-amino-4-oxopyrazolo[1,5-*a*][1,3,5]triazine (5-aza-9-deazaguanine, **47**) was developed using the reaction of 3(5)-aminopyrazole (**5a**) with *N*-carbethoxy-*S*-methylisothiourea (**10d**) (Scheme 22).[28] This method was also successfully employed for the preparation of the corresponding *C*-nucleoside - guanosine isostere.



5a **10d** **47**

Scheme 22

Two synthetic pathways *via* intermediates **48** or **50** were proposed for the reaction of 3(5)-aminopyrazoles (**5**) with dimethyl *N*-cyanodithiocarbonimidate (**9b**) (Scheme 23).



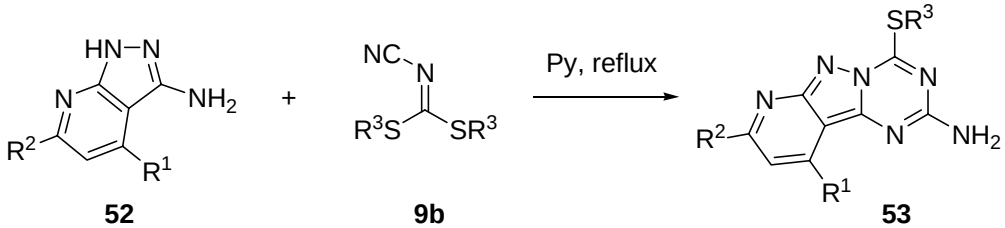
5 **9b** **48** **49** **50** **51**

Scheme 23

The reactions were reported to proceed under basic catalysis (potassium carbonate,[29] triethylamine,[30] diethylisopropylamine[31] or piperidine[32-35]) or high temperature (180 °C)[36] affording regioisomeric structures **49**[31-35] with 2-amino and 4-methylthio groups at 1,3,5-triazine nucleus or *vice versa* **51**.[29-31,36] Only one of the isomers (**49** or **51**) was isolated from the reactions and their mixture was never obtained.

However, no special study on the effects of substituents at pyrazole nucleus, reaction conditions or type of catalyst is currently available. Furthermore, no unequivocal evidence for the assigned structures **49** and **51** has been reported despite a large number of the compounds synthesized by different groups.[29-36] Obviously, further investigation of the reaction is necessary to clarify the regiochemistry of the heterocyclization.

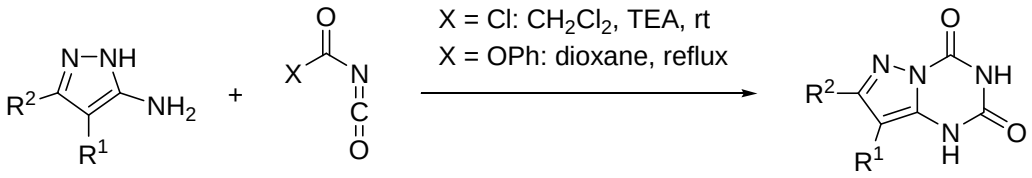
Similarly, the structure of tricyclic 1,3,5-triazines **53** assigned[37] to products from the reaction of 3-aminopyrazole[3,4-*b*]pyridines (**52**) with dialkyl *N*-dithiocarbonimidate (**9b**) (Scheme 24) also required more detailed investigation since the regioselectivity of the reaction is uncertain.



52 **9b** **53**

Scheme 24

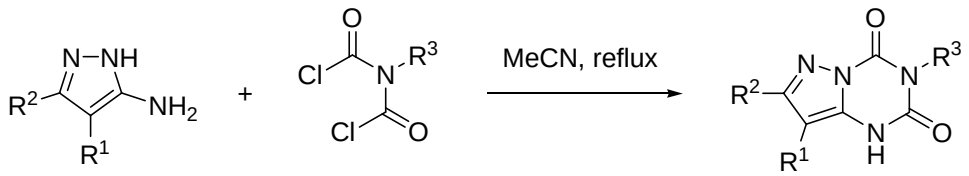
The annelation of 2,4-dioxo-1,3,5-triazine nucleus to 3(5)-aminopyrazoles (**5**) was achieved using chlorocarbonyl isocyanate (**54**, X = Cl)[38] or phenoxycarbonyl isocyanate (**54**, X = OPh)[39] as -C(=O)-NH-C(=O)- introducing reagents (Scheme 25). It was found that two equivalents of chlorosulfonyl isocyanate could also be used instead of **54** for the preparation of pyrazolo[1,5-*a*][1,3,5]triazines **55**.[38]



5 **54** **55**

Scheme 25

The 3-alkyl-2,4-dioxopyrazolo[1,5-*a*][1,3,5]triazines **57** were claimed[40] to be products of the cyclocondensation of 3(5)-aminopyrazoles (**5**) with *N*-alkyl bis(chloroformyl)amines (Scheme 26).



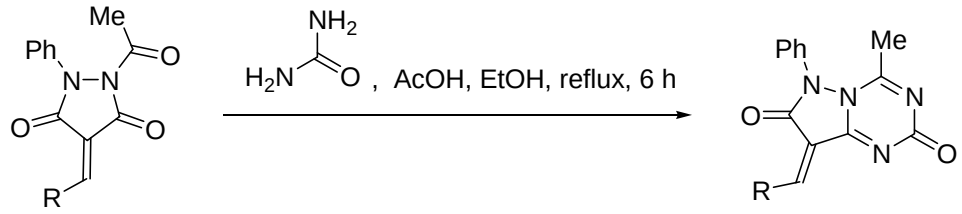
5 **56** **57**

R^1 = H, Me, CN, $CONH_2$, NHAc;
R^2 = H, Me, *i*-Pr;
R^3 = *i*-Pr, *s*-Bu, *i*-Bu, *c*-Pent, c-Hex

Scheme 26

2.4. Two-bond formation (3+3) through cyclization of 1-acylpyrazolidinediones with reagents introducing N-C-N fragment.

Heating of *N*-acetylpyrazolidinediones **58** with urea in ethanol in the presence of acetic acid was reported to afford the formation of pyrazolo[1,5-*a*][1,3,5]triazines **59** (Scheme 27).[41]



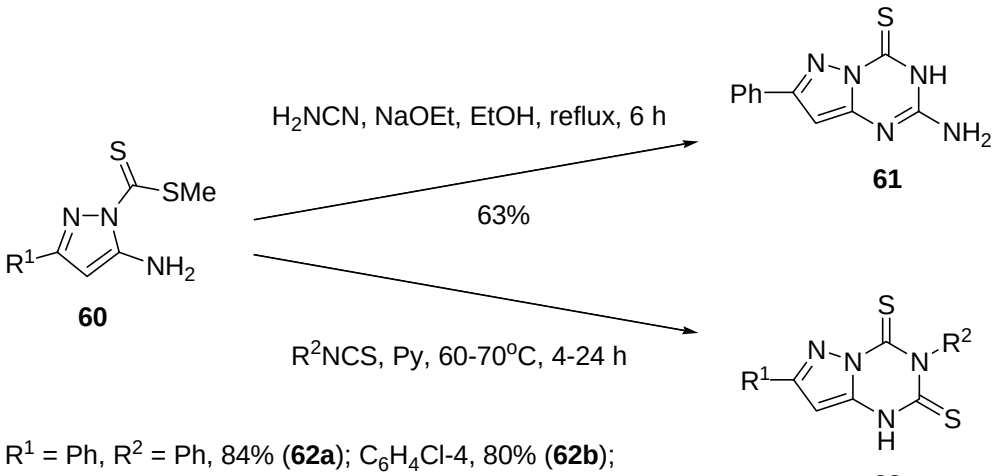
58 **59**

R = $C_6H_4(OMe)_2$-3,4, 49% (**59a**); 1-naphthyl, 53% (**59b**); 2-thienyl, 51% (**59c**)

Scheme 27

2.5. Two-bond formation (4+2) through cyclization of 5-aminopyrazoles having carbon atom at N1 with reagents introducing C-N fragment.

This type of hetrocyclization was observed when methyl 5-amino-3-arylpyrazole-1-carbodithioates (**60**) were reacted with cyanamide or isothiocyanates to afford 2-amino-4-thioxo- or 2,4-dithioxopyrazolo[1,5-*a*][1,3,5]triazines **61** or **62**, respectively (Scheme 28).[42,43]



60 **61** **62**

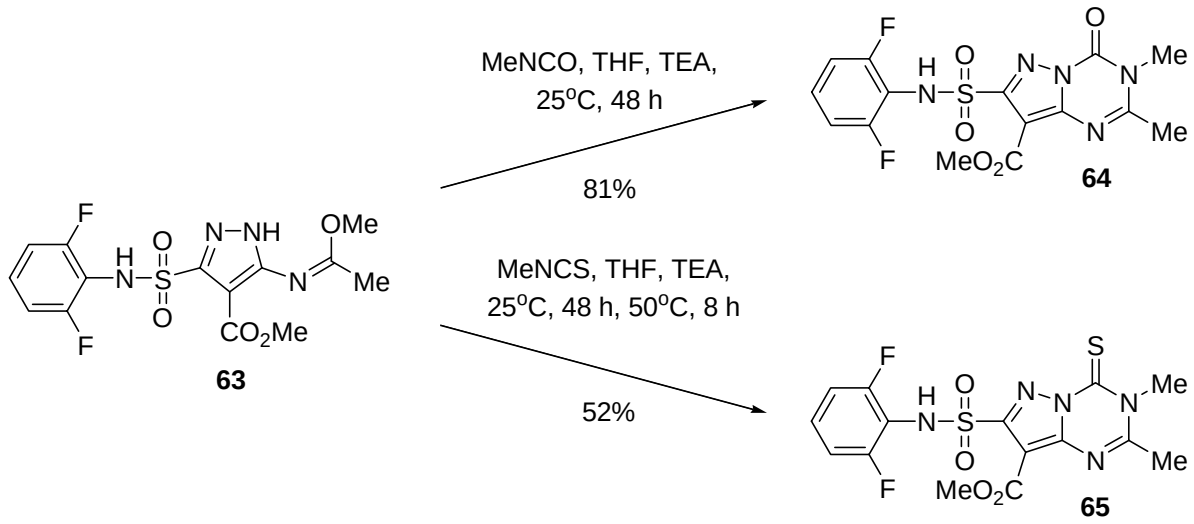
R^1 = Ph, R^2 = Ph, 84% (**62a**); C_6H_4Cl-4, 80% (**62b**);
R^1 = C_6H_4Cl-4, R^2 = Et, 40% (**62c**); Ph, 35% (**62d**)

Scheme 28

2.6. Two-bond formation (4+2) through cyclization of pyrazoles having N-C appendage at C3(5) with reagents introducing C-N fragment.

The reactions of 3(5)-aminopyrazole derivatives with isocyanates or isothiocyanates as diatomic synthons were used in this type of cyclization. For example, when imidate **63** was allowed to react with methyl isocyanate or methyl isothiocyanate, the corresponding 4-oxo- or 4-thioxopyrazolo[1,5-*a*][1,3,5]triazines **64** or **65** were formed (Scheme 29).[44] Compounds **64** and **65** and their analogues were claimed[44] as

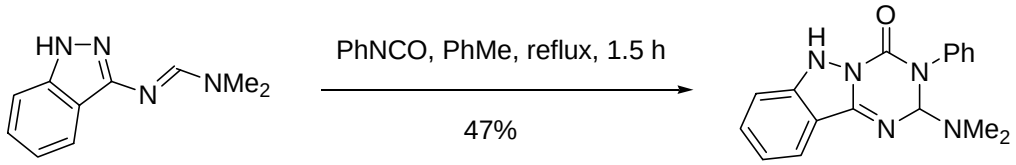
potential herbicides and plant growth regulators.



63 **64** **65**

Scheme 29

It was reported that 1,4-dipolar cycloaddition of phenyl isocyanate to 3-azomethine substituted indazole (**66**) resulted in the formation of tricyclic 1,3,5-triazine ring system **67** (Scheme 30).[20]



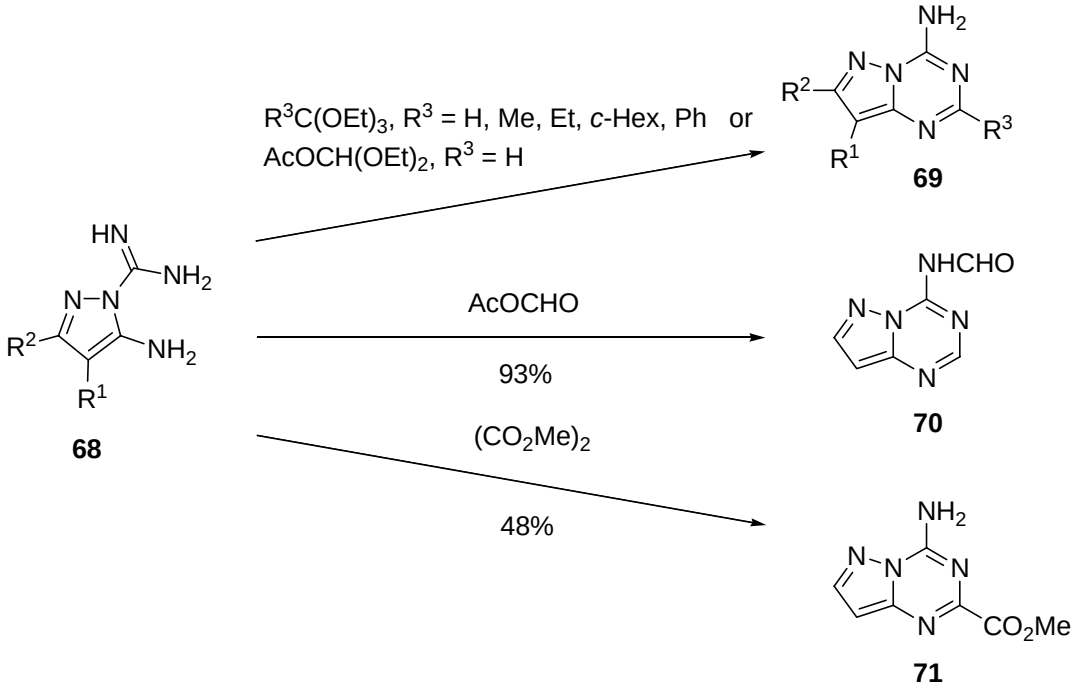
66 **67**

Scheme 30

2.7. Two-bond formation (5+1) through cyclization of 5-aminopyrazoles having C-N appendage at N1 with one carbon atom.

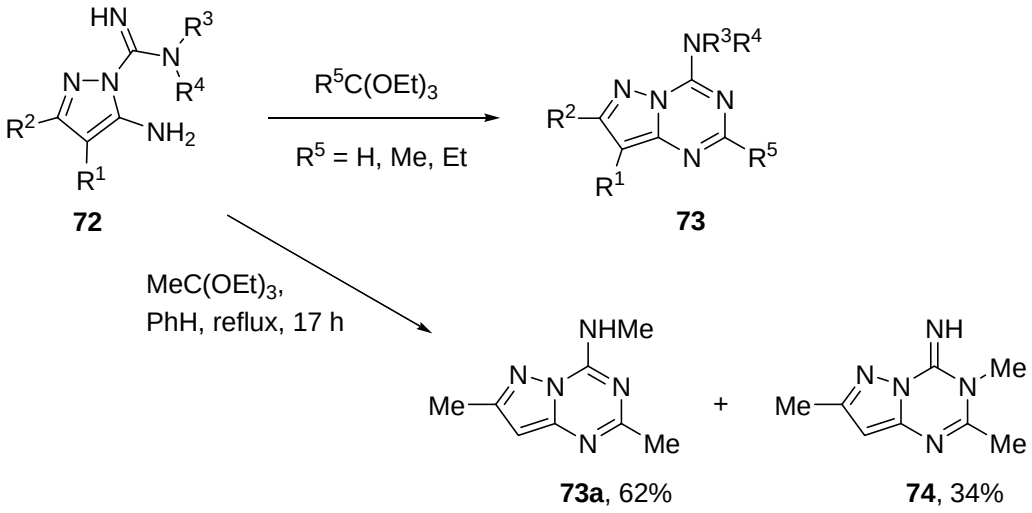
Diverse one-carbon inserting reagents open a prospect for introducing different substituents including alkyl, aryl, carbethoxy, amino, oxo and thioxo groups into position 2 of pyrazolo[1,5-*a*][1,3,5]triazine nucleus. The structure of the C-N appendage at N1 atom of starting aminopyrazoles determines type of other substituents at the triazine ring formed. Thus, 1-amidino-5-aminopyrazoles (**68**) were used for the preparation of various 4-aminopyrazolo[1,5-*a*][1,3,5]triazines (**69-71**) (Scheme 31).[42,45-50] Using of triethyl orthoformate[42,45-47] or diethoxymethyl acetate[48] as one-carbon inserting reagent provided the 4-aminopyrazolo[1,5-*a*][1,3,5]triazines (**69**, R^3 = H). The formylation of 4-amino group together with the cyclization was observed when acetic-formic mixed anhydride was employed for the analogous reaction.[47] The synthesis of 2-aklyl- and 2-aryl- substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazines (**69**) was achieved *via* ring closure with corresponding orthoesters.[47,49,50] The reaction of

1-amidino-5-aminopyrazole (**68**, R^1 = R^2 = H) and dimethyl oxalate was reported to result in the formation of methyl 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-2-carboxylate (**71**).[50]



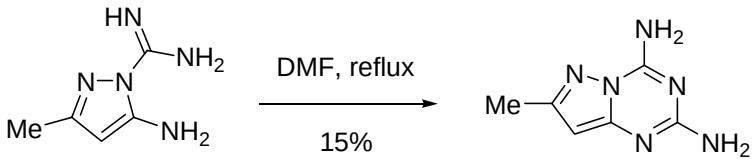
Scheme 31

The synthesis of pyrazolo[1,5-*a*][1,3,5]triazines (**73**) with mono- and disubstituted amino group was performed using corresponding pyrazole derivatives **72** and orthoesters (Scheme 32).[46,47] However, an analogous reaction of **72a** (R^1 = R^3 = H, R^2 = R^4 = Me) with triethyl orthoformate was reported[50] to give a mixture of products **73a** and **74** with methyl group at exo- and endocyclic nitrogens, respectively.



Scheme 32

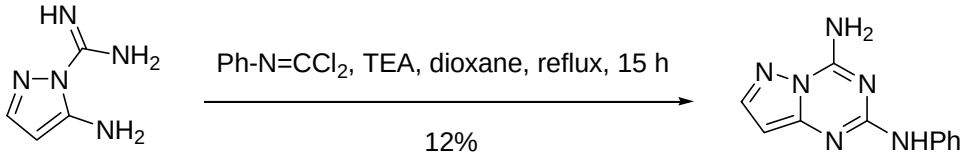
It was reported[24] that heating of 1-amidino-5-amino-3-methylpyrazole (**68a**) in DMF (Scheme 33) provided 2,4-diamino-7-methylpyrazolo[1,5-*a*][1,3,5]triazine (**39b**), which was prepared *via* an alternative procedure (*vide supra* Scheme 19).



68a **39b**

Scheme 33

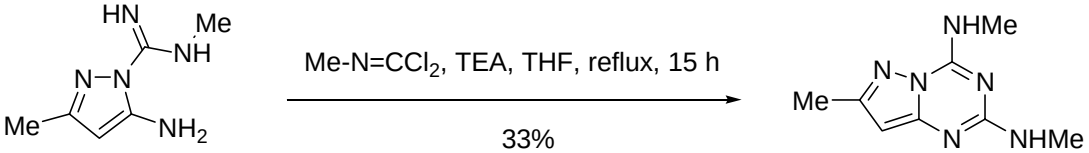
The ring closure reaction of 1-amidino-5-aminopyrazole (**68b**) with phenyl isocyanide dichloride was found to introduce phenylamino group into position 2 of the pyrazolo[1,5-*a*][1,3,5]triazine nucleus affording **75** (Scheme 34).[50]



68b **75**

Scheme 34

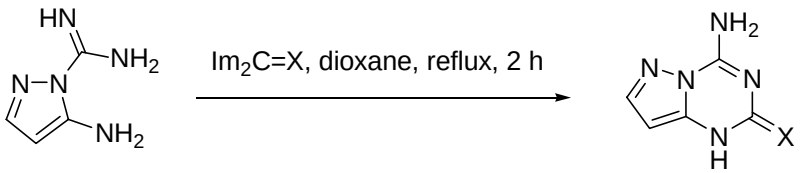
In an analogous manner, 2,4-bis(methylamino)-7-methylpyrazolo[1,5-*a*][1,3,5]triazine (**76**) was obtained by treatment of **72a** with methyl isocyanide dichloride (Scheme 35).[24]



72a **76**

Scheme 35

The ring closure carbonylation of 1-amidino-5-aminopyrazole (**68b**) with *N,N'*-carbonyldiimidazole was used for the preparation of **77a**, which is 5-aza-9-deaza isostere of isoguanine (Scheme 36).[50] Using *N,N'*-thiocarbonyldiimidazole under similar conditions, thio analogue **77b** was synthesized, but yield was lower.



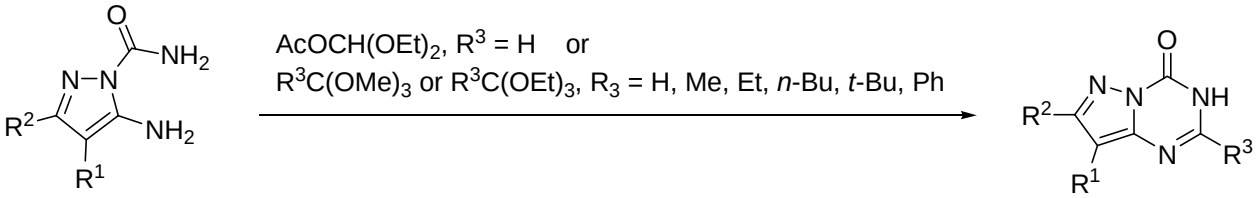
68b **77**

X = O, 89% (**77a**); S, 43% (**77b**)

Scheme 36

The ring closure reactions of 5-amino-1-carbamoylpyrazoles (**78**) with diethoxymethyl acetate or orthoesters as one-carbon inserting reagents were used for the preparation of 5-aza-9-deazahypoxanthine and a variety of other 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**79**) (Scheme 37).[42,48,49,51-62] This approach

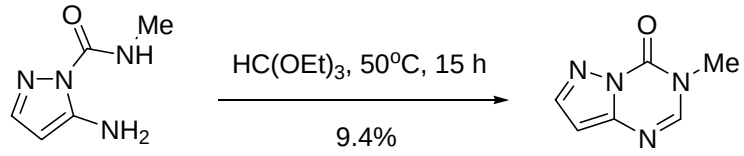
found a wide application for the synthesis of xanthine oxidase[55,56] and phosphodiesterase[57,58] inhibitors, antiandrogen agents[59] as well as important intermediates for other biologically active compounds (*vide infra* Section 6).[60-62]



78 **79**

Scheme 37

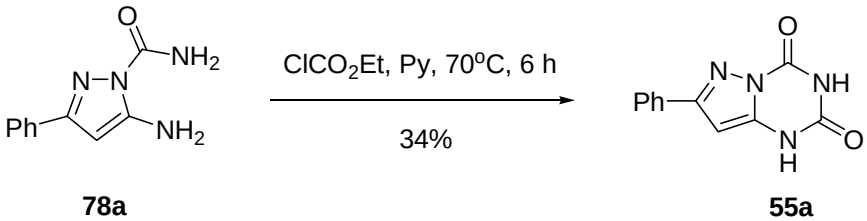
In a similar way, heating of 5-amino-1-methylcarbamoylpyrazole (**80**) with triethyl orthoformate resulted in the formation of 3-methyl-4-oxopyrazolo[1,5-*a*][1,3,5]triazine (**81**) (Scheme 38).[63]



80 **81**

Scheme 38

The synthesis of 2,4-dioxo-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**55a**) by heating of 5-amino-1-carbamoyl-3-phenylpyrazole (**78a**) with ethyl chloroformate in pyridine (Scheme 39) was developed.[42] This reaction can be considered as an alternative for the (3+3) cyclization of 3(5)-aminopyrazoles[38] (*vide supra* Scheme 25).

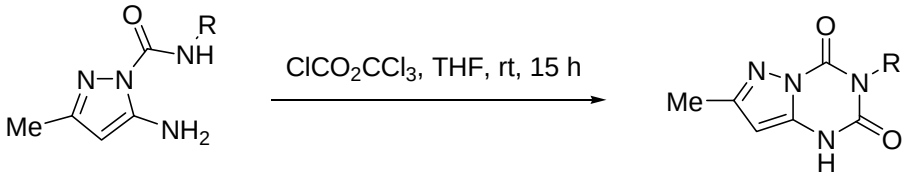


78a **55a**

Scheme 39

Similarly, 3-substituted 2,4-dioxo-7-methylpyrazolo[1,5-*a*][1,3,5]triazines (**83**) were synthesized from the 5-aminopyrazole **82** by treatment with diphosgene (Scheme 40).[64] The antialgal[64] and antifungal[65] activities of compounds **83** were investigated.

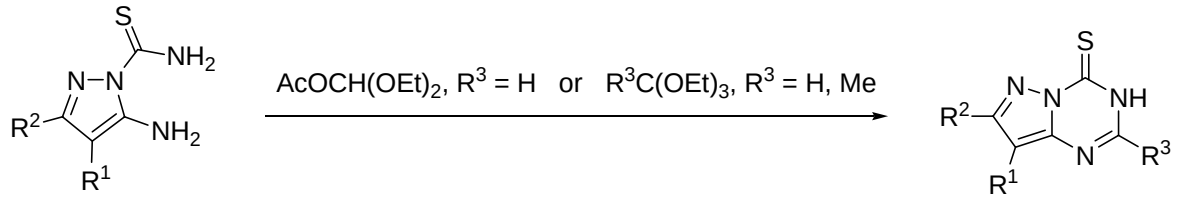
The synthesis of 4-thioxopyrazolo[1,5-*a*][1,3,5]triazines (**85**) was successfully achieved *via* ring closure reactions of 5-amino-1-thiocarbamoylpyrazoles (**84**) with diethoxymethyl acetate[48] or triethyl orthoformate[19,42,66-69] and triethyl orthoacetate[49,57,70,71] (Scheme 41).



82 **83**

R = Et, 70% (**83a**); Bu, 97% (**83b**); *s*-Bu, 75% (**83c**);
c-Hex, 75% (**83d**); Bn, 70% (**83e**); Ph, 46% (**83f**)

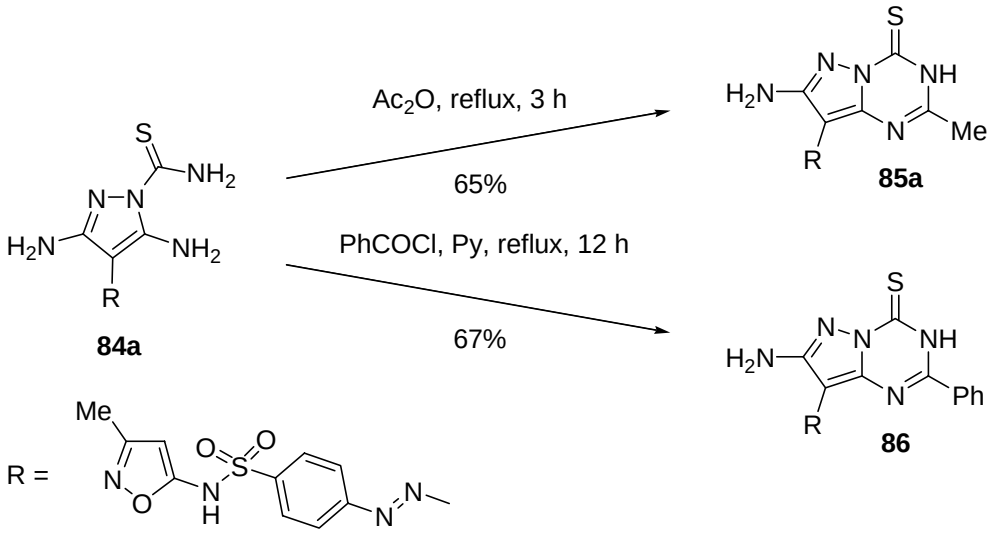
Scheme 40



84 **85**

Scheme 41

Similar reactions were also performed for the preparation of 4-thioxopyrazolo[1,5-*a*][1,3,5]triazines **85a** and **86** using acetic anhydride or benzoyl chloride as one-carbon inserting reagents, respectively (Scheme 42).[69]

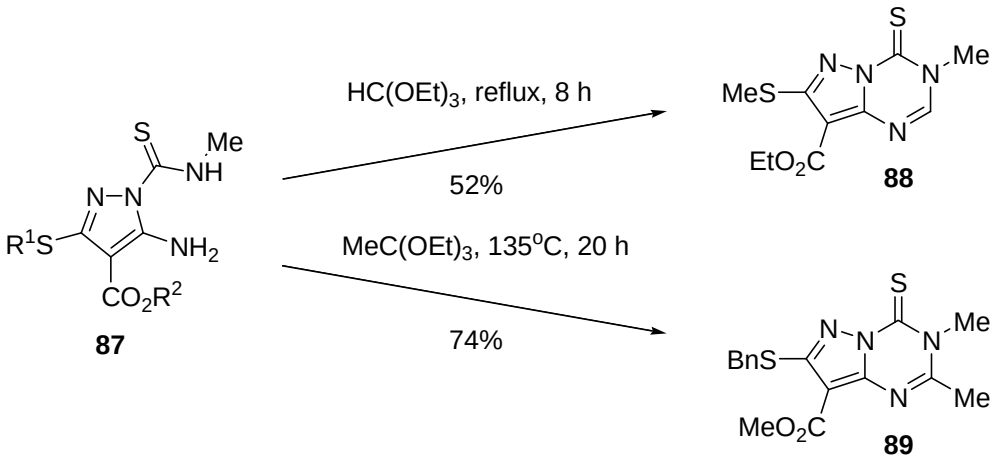


84a **85a** **86**

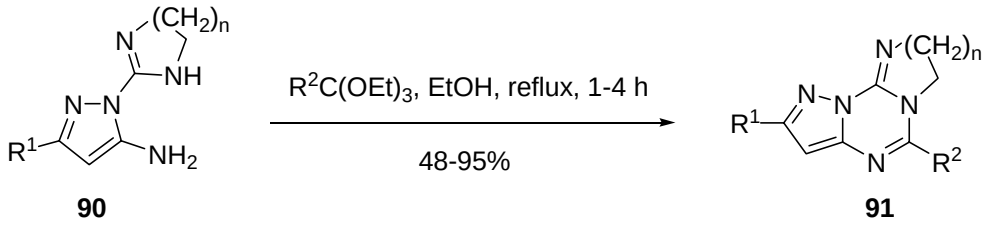
Scheme 42

It was reported that 5-amino-1-methylthiocarbamoylpyrazoles (**87**) reacted with triethyl orthoformate[66] and triethyl orthoacetate[44] to afford corresponding 3-methyl-4-thioxopyrazolo[1,5-*a*][1,3,5]triazines **88** and **89**, respectively, as exemplified in Scheme 43.

This type of 1,3,5-triazine ring construction using orthoesters was applied for the syntheses of some polyfused systems comprising pyrazolo[1,5-*a*][1,3,5]triazine nucleus. Thus, tricyclic compounds **91** were prepared from **90** *via* heterocyclization with triethyl orthoesters (Scheme 44).[72]



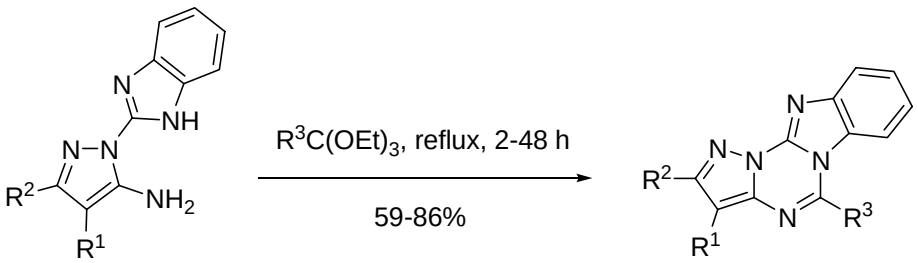
Scheme 43



n = 1-3; R^1 = Me, Ph, C_6H_4Me-4; R^2 = H, Me, Et, Ph

Scheme 44

Analogously, heating of substituted 5-amino-1-(benzimidazol-2-yl)pyrazoles **92** with triethyl orthoformate or triethyl orthoacetate was reported to afford tetracyclic compounds **93** (Scheme 45).[73]



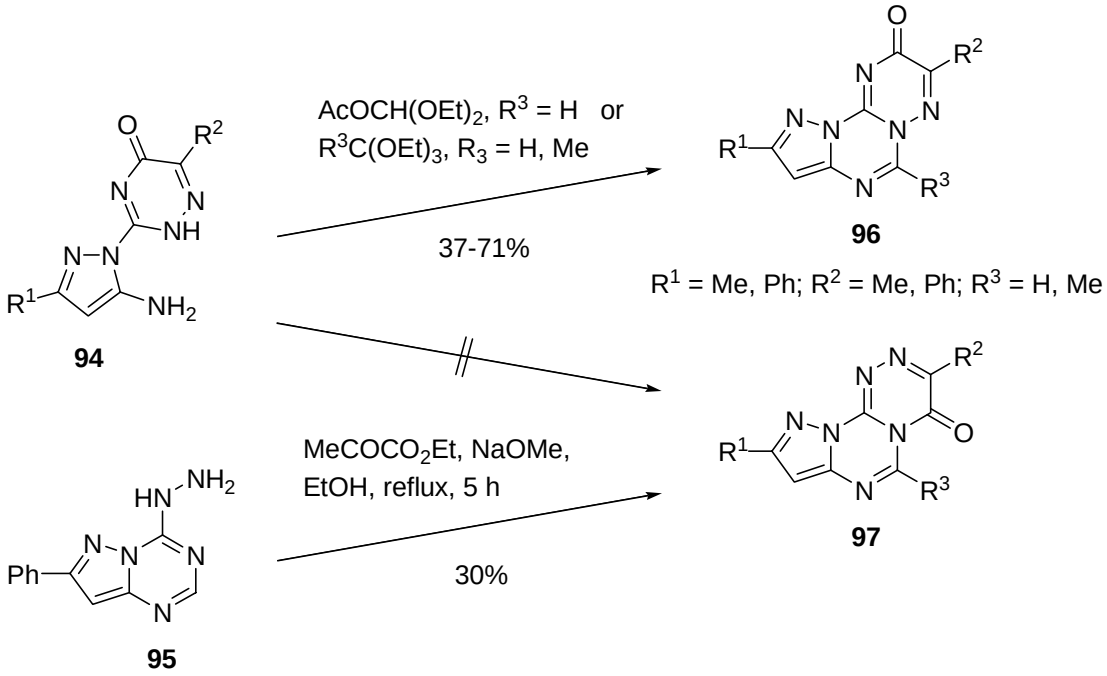
R^1 = H, Ph, COOEt, CN; R^2 = H, Ph; R^3 = H, Me

Scheme 45

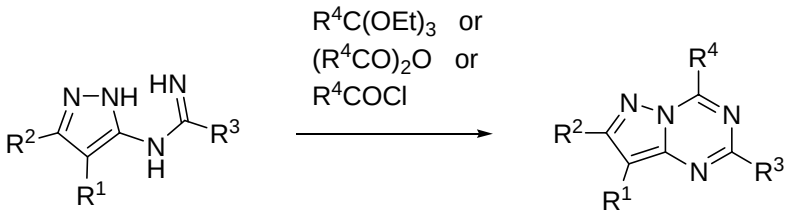
The synthesis of pyrazolo[1',5':3,4][1,3,5]triazino[1,2-*b*][1,2,4]triazines (**96**) from **94** was reported (Scheme 46).[74] The structure of products **96** was confirmed by independent synthesis of the isomeric pyrazolo[1',5':3,4][1,3,5]triazino[2,1-*c*][1,2,4]triazine **97a** (R^1 = Ph, R^2 = Me, R^3 = H) from 4-hydrazino-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**95**) and ethyl pyruvate.

2.8. Two-bond formation (5+1) through cyclization of pyrazoles having N-C-N appendage at C3(5) with one carbon atom.

The most explored within this synthetic approach are heterocyclization of 3(5)-pyrazolylamidines **98** using different one-carbon inserting reagents. Since the first report[75] on the synthesis of 2,4-dimethylpyrazolo[1,5-*a*][1,3,5]triazine (**99a**) with quantitative yield by heating of acetic acid salt of **98a** (R^1 = R^2 = H, R^3 = Me) in triethyl orthoacetate, this reaction was successfully adopted for the synthesis of various pyrazolo[1,5-*a*][1,3,5]triazines **99** from amidines **98** and orthoesters (Scheme 47).[49,57,76-79] The heterocyclization of 3(5)-pyrazolylamidines (**98**) with formation of **99** was also successfully achieved employing acid anhydrides[57,77] or acid chlorides[10] as one-carbon inserting reagents.

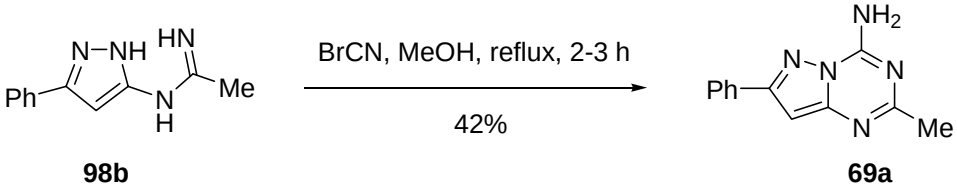


Scheme 46



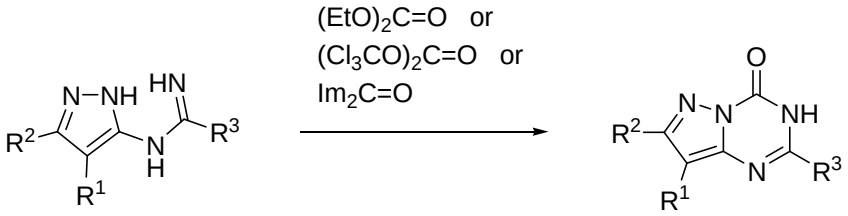
Scheme 47

The reaction of acetamidine **98b** with cyanogen bromide was found to give 4-amino-2-methyl-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**69a**) (Scheme 48).[49]



Scheme 48

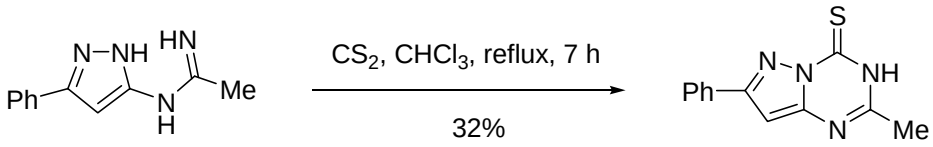
Several methods for the ring closure carbonylation of the amidines **98** were considered as an alternative way (*cf.* Scheme 37) for the preparation of the 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**79**) (Scheme 49). Diethyl carbonate,[49,55,57,61,79-87] *N,N'*-carbonyldiimidazole[86-88] and triphosgene[89] were used as carbonylating reagents in the syntheses of **79**. This approach found an application for the preparation of compounds with valuable biological properties (*vide infra* Section 6).



98 **79**

Scheme 49

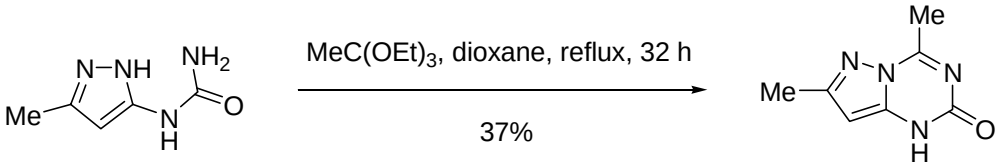
The synthesis of 2-methyl-7-phenyl-4-thioxopyrazolo[1,5-*a*][1,3,5]triazine (**85b**) was achieved *via* ring closure thiocarbonylation of acetamidine **98b** with carbon disulfide (Scheme 50).[49]



98b **85b**

Scheme 50

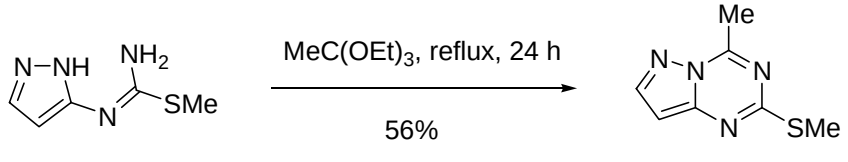
The reaction of pyrazolylurea **100** with triethyl orthoacetate was found to provide 4,7-dimethyl-2-oxopyrazolo[1,5-*a*][1,3,5]triazine (**101**) (Scheme 51).[50]



100 **101**

Scheme 51

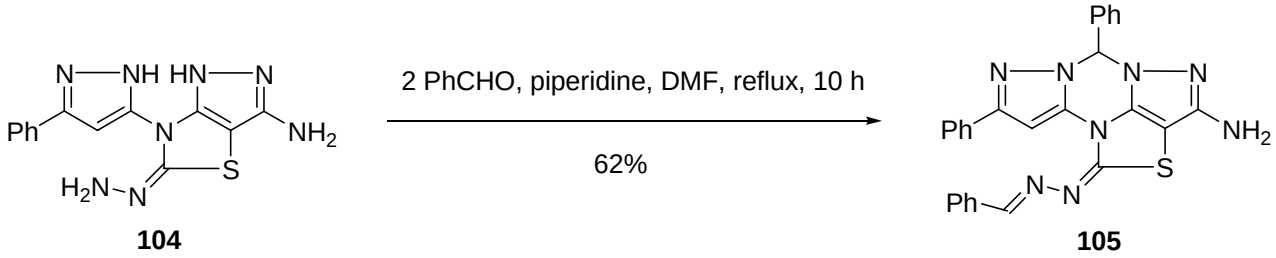
Analogously, triethyl orthoacetate was used for the cyclization of *S*-methyl-*N*-(pyrazol-3(5)-yl)isothiourea (**102**) yielding 4-methyl-2-methylthiopyrazolo[1,5-*a*][1,3,5]triazine (**103**) (Scheme 52).[90,91]



102 **103**

Scheme 52

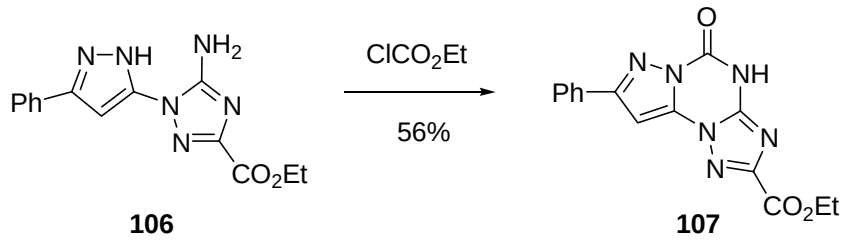
The piperidine catalyzed ring closure of **104** with benzaldehyde under heating in DMF was reported to give tetracyclic compound **105** (Scheme 53).[92]



104 **105**

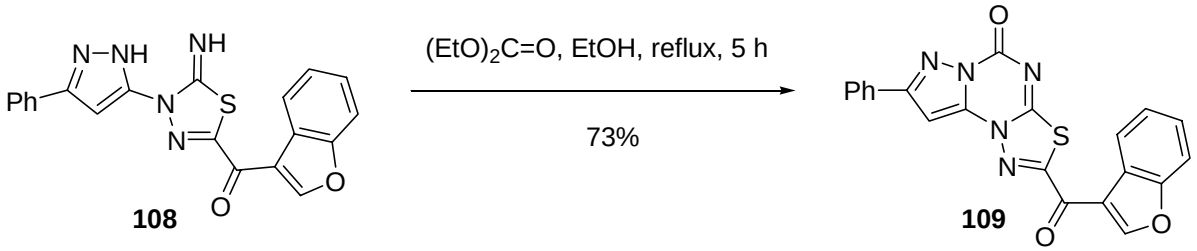
Scheme 53

Two similar tricyclic compounds **107** and **109** were prepared *via* ring closure carbonylation of 5(3)-hetaryl-3(5)-phenylpyrazoles **106** and **108** using ethyl chloroformate[93] or diethyl carbonate,[94] respectively (Schemes 54 and 55).



106 **107**

Scheme 54



108 **109**

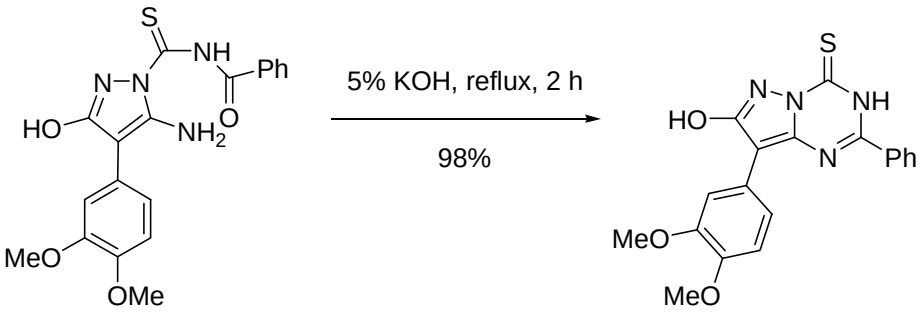
Scheme 55

2.9. One bond formation through intramolecular cyclization of 5-aminopyrazoles having C-N-C appendage at N1.

It was found that the pyrazole **110** underwent intramolecular heterocyclization undre alkaline condition affording the pyrazolo[1,5-*a*][1,3,5]triazine ring system (Scheme 56).[95] The product **111** was found to possess low toxicity and anti-inflammatory activity without showing ulcerogenic effect.

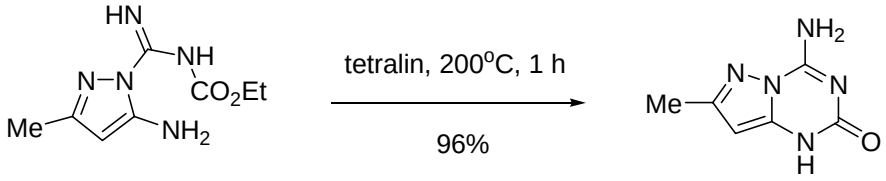
The thermal intramolecular ring closure reaction of the pyrazole **112** was successfully implemented for the preparation of 4-amino-7-methyl-2-oxopyrazolo[1,5-*a*][1,3,5]triazine (**113**) (Scheme 57).[47,50]

The heterocyclization of substituted 5-aminopyrazole **114** in the presence of DBU was found to result in the formation of 8-cyano-4-methylthio-2-oxopyrazolo[1,5-*a*][1,3,5]triazine (**115**), which was used as an intermediate for the synthesis of the protein kinase inhibitors (Scheme 58).[96]



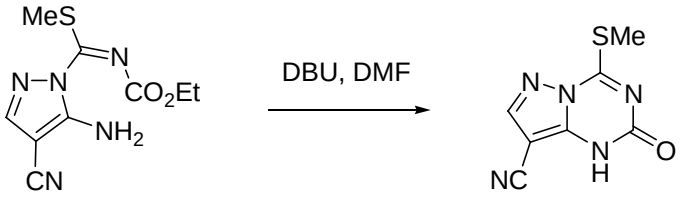
110 **111**

Scheme 56



112 **113**

Scheme 57



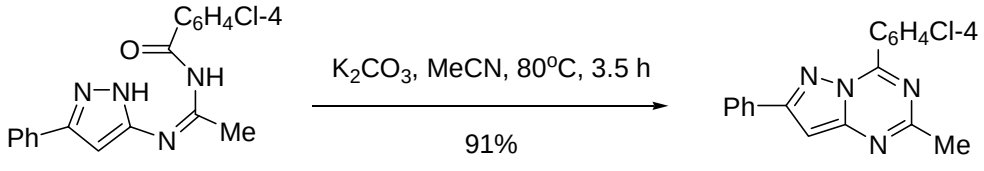
114 **115**

Scheme 58

2.10. One bond formation through intramolecular cyclization of pyrazoles having N-C-N-C appendage at C3(5).

This synthetic approach implicates the heterocyclizations of the pyrazole derivatives, *i.e. N*-acyl and *N*-carbethoxy substituted amidines, guanidines, ureas and thioureas. High temperature and/or basic conditions were applied to promote the reactions.

The cyclization of acetamidine **116** required heating in the presence of potassium carbonate to give pyrazolo[1,5-*a*][1,3,5]triazine **117** (Scheme 59).[11]

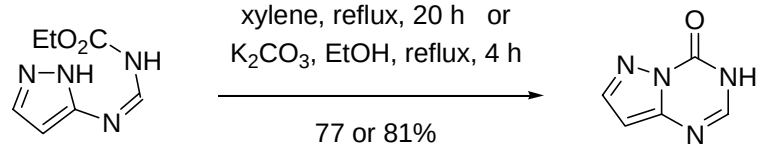


116 **117**

Scheme 59

It was demonstrated that on heating in xylene or upon treatment with a base, *N*-carbethoxy-*N′*-(3(5)-pyrazolyl)formamidine (**118**) cyclized to produce 5-aza-9-deazahypoxanthine

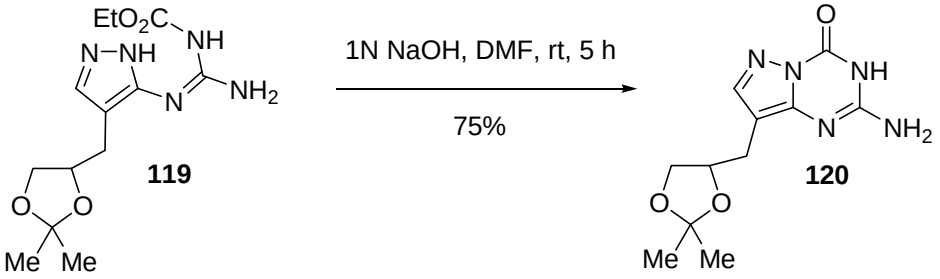
(**79a**) (Scheme 60).[15] The potassium carbonate promoted cyclization was used for the preparation of the *C*-nucleosides *viz.* an isostere of inosine and its α-anomer.[15]



118 **79a**

Scheme 60

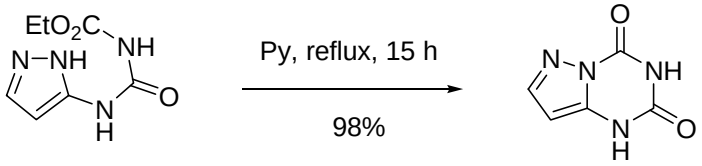
The intramolecular cyclization of carbethoxyguanidine **119** under treatment with sodium hydroxide afforded the formation of 2-amino-4-oxopyrazolo[1,5-*a*][1,3,5]triazine **120** (Scheme 61).[19] This method was also successfully applied for the synthesis of 5-aza-9-deazaguanosine.[28]



119 **120**

Scheme 61

Capuano and Schrepfer reported the synthesis of 5-aza-9-deazaxanthine (**122**) *via* ring closure reaction of *N*-carbethoxy-*N*′-(3(5)-pyrazolyl)urea (**121**) (Scheme 62). [97]



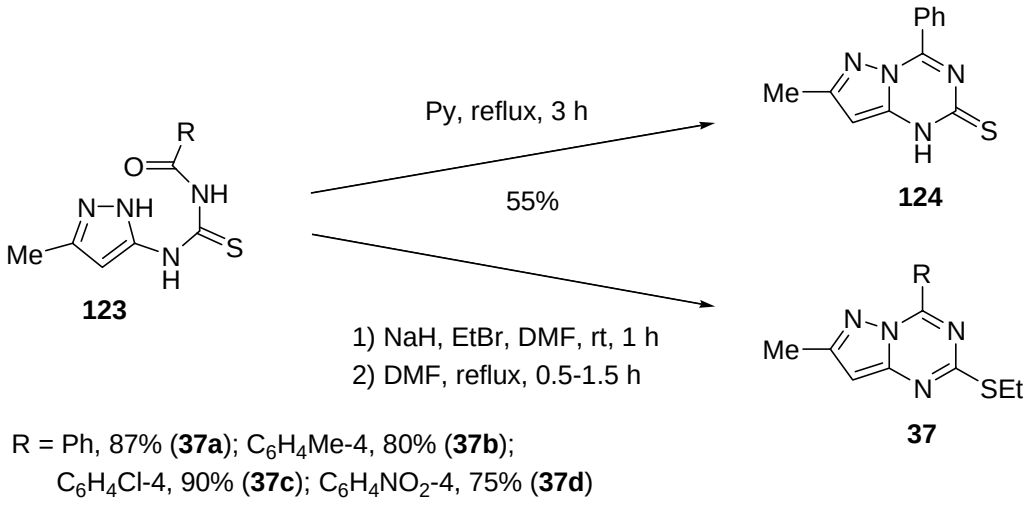
121 **122**

Scheme 62

The most significant group of the synthons used in this subcategory of herecocyclization was represented by the thiourea derivatives of pyrazoles, in particular the *N*-aroyl- and *N*-carbethoxythioureas. Thus, *N*-benzoylthiourea **123** (R = Ph) was found to cyclize upon heating in pyridine providing 7-methyl-4-phenyl-2-thioxopyrazolo[1,5-*a*][1,3,5]triazine (**124**) (Scheme 63).[98] The subsequent *S*-alkylation and thermal ring closure reaction allowed to convert **123** into 4-aryl-2-ethylthio-7-methylpyrazolo[1,5-*a*][1,3,5]triazines (**37**).[22]

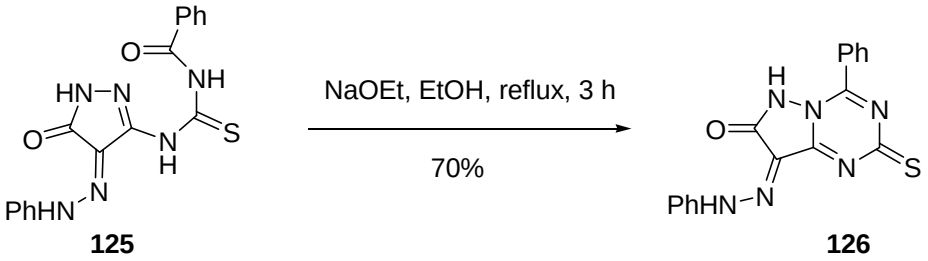
The synthesis of pyrazolo[1,5-*a*][1,3,5]triazine **126** was achieved *via* the cyclization of *N*-benzoylthiourea **125** in the presence of sodium ethoxide (Scheme 64).[99]

Similarly, tricyclic system **128** incorporating pyrazolo[1,5-*a*][1,3,5]triazine nucleus was prepared from *N*-benzoylthiourea **127** under similar reaction conditions (Scheme 65).[100]

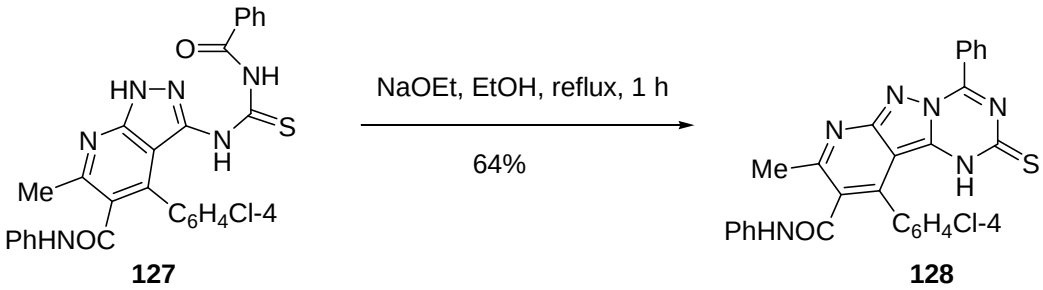


R = Ph, 87% (**37a**); C_6H_4Me-4, 80% (**37b**);
C_6H_4Cl-4, 90% (**37c**); $C_6H_4NO_2$-4, 75% (**37d**)

Scheme 63

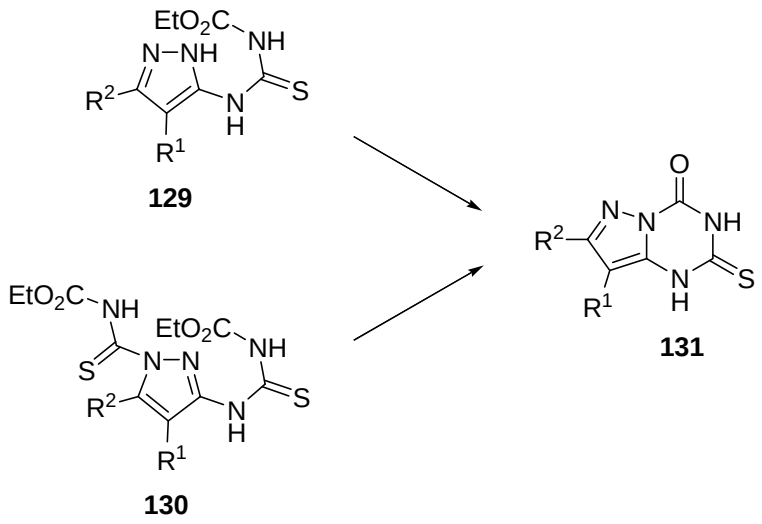


Scheme 64



Scheme 65

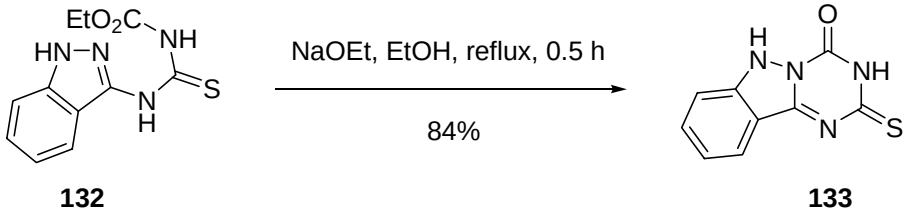
The synthesis of 4-oxo-2-thioxopyrazolo[1,5-*a*][1,3,5]triazines (**131**) was realized *via* intramolecular cyclization of *N*-carbethoxythioureas **129** or **130** as well as from the crude mixture of **129**+**130** (Scheme 66), which was formed from the reaction of 3(5)-aminopyrazoles with ethoxycarbonylsothiocyanate. The reaction was found to proceed readily under different conditions (usually in the presence of base). Thus, thermally induced cyclization at 180 °C,[91] heating in pyridine or triethylamine,[97] treatment with ammonium hydroxide,[96,101] sodium hydroxide,[55,63,90,91,102] sodium methoxyde,[31] sodium ethoxide[19,61,103] or potassium carbonate[104] were used for the ring closure. The method was also successfully applied for the preparation of *C*-nucleosides. This synthetic approach found an application for the synthesis of biologically active compounds and their intermediates, *e.g.* preparation of inhibitors of DNA gyrase,[31] xanthine oxidase,[55] phosphodiesterases[91] and protein kinases[96] (*vide infra* Section 6) as well as stimulants of neurotrophic factor production.[61]



Scheme 66

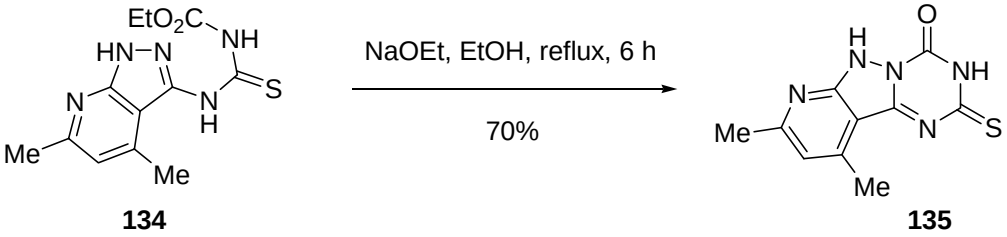
It was shown that synthesized 4-oxo-4-thioxopyrazolo[1,5-*a*][1,3,5]triazines (**131**) could be easily attached onto Merrified resin that was effectively implemented for the solid-phase combinatorial syntheses of pyrazolo[1,5-*a*][1,3,5]triazines.[103]

It was reported that *N*-carbethoxy-*N*′-indazolylthiourea (**132**) upon treatment with sodium ethoxide underwent intramolecular cyclization affording benzofused 4-oxo-2-thioxopyrazolo[1,5-*a*][1,3,5]triazine (**133**) (Scheme 67).[20]



Scheme 67

Analogously, tricyclic system **135** comprising pyrazolo[1,5-*a*][1,3,5]triazine and pyridine nuclei was prepared *via* ring closure of *N*-carbethoxythiourea **134** (Scheme 68).[105]

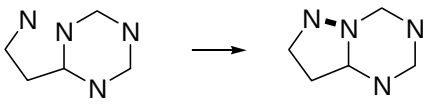


Scheme 68

3. SYNTHESIS BY ANNELATION OF THE PYRAZOLE RING ONTO A 1,3,5-TRIAZINE SCAFFOLD

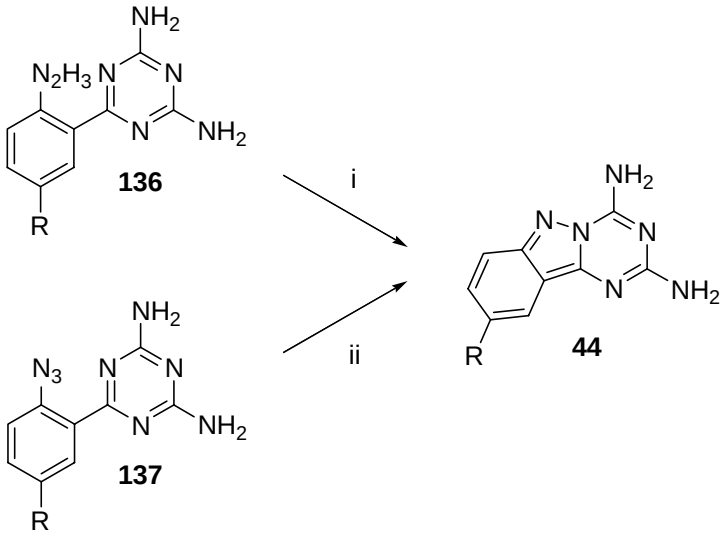
In the chemistry of pyrazolo[1,5-*a*][1,3,5]triazines, methods for the construction of the pyrazole ring on a 1,3,5-triazine skeleton are limited. Only one type of cyclization was reported *viz.* one-bond formation *via*

intramolecular cyclization of 1,3,5-triazines having C-C-N fragment (Scheme 69).[106-108]



Scheme 69

This synthetic approach involved decomposition of hydrazines **136** or azides **137** which resulted in pyrazole ring closure with the formation of the 2,4-diamino-1,3,5-triazino[1,2-*b*]indazoles (**44**) and evolution of ammonia or nitrogen, respectively (Scheme 70). The reactions were found to proceed smoothly under pyrolysis conditions,[106] heating in acetic acid[107] or photolysis.[108]



i: 250-270°C, 1 h, sublimation 300°C, 5 mmHg; R = H (**44a**); Me, 80% (**44b**); Br, 50% (**44c**);
ii: 200°C, 1 h, sublimation 300°C, 5 mmHg; R = H, 70% (**44a**); Br (**44c**);
AcOH, reflux, 1 h; R = H, 85% (**44a**); Me, 80% (**44b**); Br, 90% (**44c**);
acetone, hν, 100 W, 30 h; R = H, 75% (**44a**)

Scheme 70

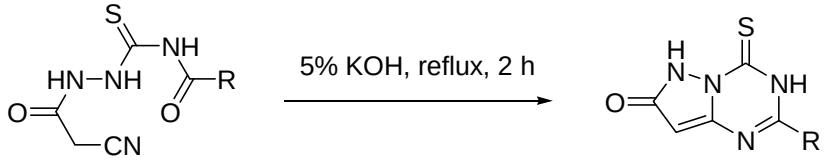
4. SYNTHESIS BY CONCURRENT FORMATION OF BOTH THE 1,3,5-TRIAZINE AND PYRAZOLE RINGS

This synthetic strategy for the preparation of pyrazolo[1,5-*a*][1,3,5]triazines represented by only one type of cyclization *viz.* double ring closure comprising two-bound formation by intramolecular cyclization of open-chain structures consisting of five carbon and four nitrogen atoms (C_5N_4) (Scheme 71).

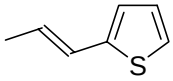
Scheme 71

It was shown that upon heating in potassium hydroxide solution, *N*-acyl-2-cyanoacetylthiosemicarbaside (**138**) underwent intramolecular cyclization giving the formation of 7-oxo-4-thioxopyrazolo[1,5-*a*][1,3,5]triazines (**139**) with methyl,[109] phenyl[110] or 2-(2-thienyl)vinyl[111,112]

substituent at position 2 (Scheme 72).



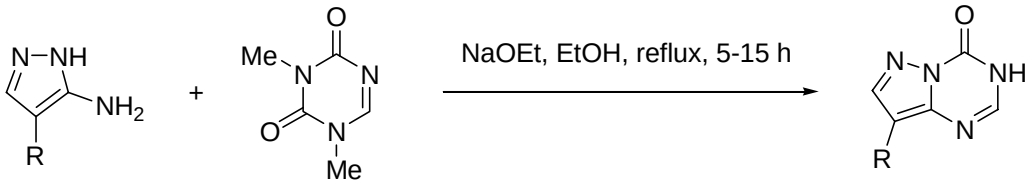
138 **139**

R = Me, 60% (**139a**); Ph, 92% (**139b**);  , 55% (**139c**)

Scheme 72

5. SYNTHESIS *VIA* RING TRANSFORMATION REACTIONS

In this synthetic category, three types of reactions were identified. First reaction can be also formally classified as a 1,3,5-triazine ring annelation *via* cyclization of 3(5)-aminopyrazoles (**5**). However, since 1,3,5-triazine ring is already present in the structure of another reagent (**140**), we describe this reaction in the ring transformation section. It was found that under treatment with 3(5)-aminopyrazoles (**5**), 1,3-dimethyl-5-azauracil (**140**) underwent ring transformation providing 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**141**) (Scheme 73).[113,114] The utility of this reaction was also demonstrated for the synthesis of *C*-nucleosides.[114]

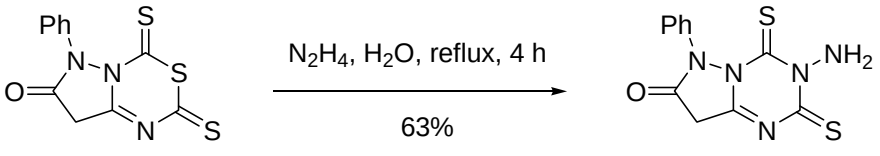


5 **140** **141**

R = Me, 64% (**141a**); Et (**141b**); CO_2Et, 43% (**141c**)

Scheme 73

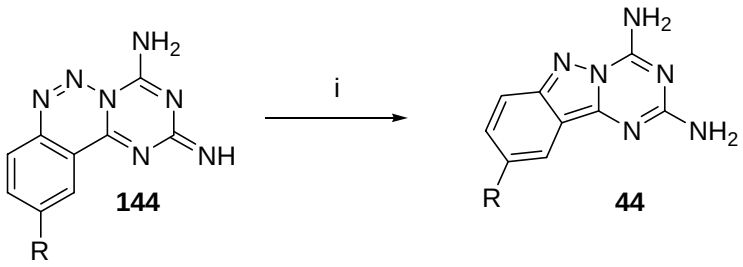
The transformation of 1,3,5-thiadiazine ring of **142** into 1,3,5-triazine nucleus upon treatment with hydrazine resulted in the formation of pyrazolo[1,5-*a*][1,3,5]triazine **143** (Scheme 74).[115]



142 **143**

Scheme 74

The 1,2,3-triazine to pyrazole (**144** to **44**) ring transformation was also reported (Scheme 75).[106,107] In these reactions, the hydrazines **136** or azides **137** were proposed to be intermediates (*cf.* Scheme 70).



i: 1) $SnCl_2$, EtOH, reflux, 1.5 h; 2) 2N NaOH, pH 11; 3) sublimation 300°C, 5 mmHg;
R = H, 70% (**44a**); Me, (**44b**); Br (**44c**) (*ref. 106*);
NaN_3, AcOH, reflux, 1 h; R = H, 70% (**44a**); Me, 70% (**44b**); Br, 78% (**44c**) (*ref. 107*)

Scheme 75

6. BIOLOGICAL ACTIVITY OF PYRAZOLO[1,5-*a*][1,3,5]TRIAZINE DERIVATIVES

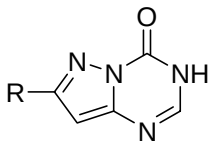
The close structural similarity between pyrazolo[1,5-*a*][1,3,5]triazine and purine systems provides a rational to design pyrazolo[1,5-*a*][1,3,5]triazines, which may potentially affect the targets (*e.g.* enzymes and receptors) of biogenic purines such as xanthine, adenosine and guanosine.

6.1. Enzyme inhibitors

The last steps of purine catabolism involve the enzyme xanthine oxidase (XO), which oxidizes hypoxanthine to xanthine and eventually to uric acid. Therefore, this enzyme is a good target to control hyperuricemia, particularly in the treatment of gout. In the search of new inhibitors of XO, Robins *et al.*[55] identified 8-phenyl-5-aza-9-deazahypoxanthine (**79b**, Figure 3) as one of the leads in the study. This compound had more than three order activity as compared to unsubstituted 5-aza-9-deazahypoxanthine (**79a**).

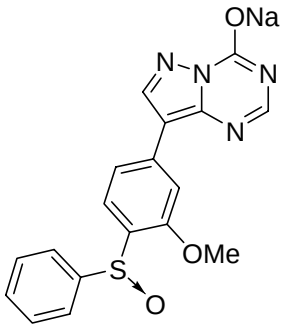
Japanese research group[56,116,117] developed a very potent XO inhibitor BOF 4272 (**145**) (Figure 3), which showed promising results in *in vitro* and *in vivo* studies[118-120] including experimental data on healthy human volunteers.[121] The BOF 4272 targets the main organs of uric acid production in human *viz.* liver and small intestine, thus significantly decreasing XO activity. It was found that BOF 4272 could also prevent cell necrosis by reducing the concentration of free radicals generated by xanthine oxidase.[122]

The mechanism of XO inhibition by BOF 4272 was studied in detail[118,119] and stereochemistry was found to play an important role in the activity of BOF 4272. The *in vitro* studies showed that both of the enantiomers were mixed type inhibitors, wherein (*S*)-(-)-enantiomer was much more potent than (*R*)-(+)-enantiomer (Figure 3).[118,119] The stereoselectivity was also observed for the pharmacokinetic parameters and biotransformation of BOF 4272.[123-127] Considering these facts, the asymmetric syntheses of BOF 4272 were developed.[128-130]



79

R = H (**79a**): IC_{50} (XO) = 84,000 nM
R = Ph (**79b**): IC_{50} (XO) = 47 nM

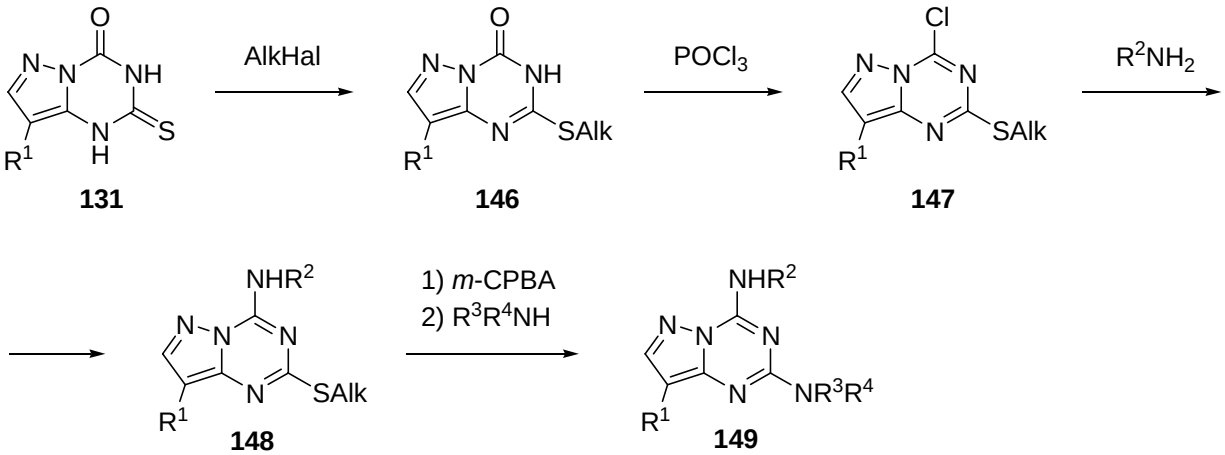


145, BOF 4272

(*S*)-(-)-isomer K_i (XO) = 1.2 nM
(*R*)-(+)-isomer K_i (XO) = 300 nM

Figure 3

It was reported that substituted 2,4-diaminopyrazolo[1,5-*a*][1,3,5]triazines were able to inhibit type 2 cyclin-dependent kinase (CDK2), which are involved in the regulation of the cell cycle. [96,104,131] Therefore, antiproliferative activity of the identified inhibitors was also evaluated using a panel of cancer cell lines.[96,131] The synthesis of CDK2 inhibitors with pyrazolo[1,5-*a*][1,3,5]triazine nucleus was performed from 4-oxo-2-thioxopyrazolo[1,5-*a*][1,3,5]triazines (**131**) (Scheme 66). The reaction of **131** with alkyl halides (methyl iodide or benzyl bromide) afforded alkylated product **146**, which was heated with phosphorus oxychloride to give 2-alkylthio-4-chloropyrazolo[1,5-*a*][1,3,5]triazines (**147**) (Scheme 76). Compound **147** was converted into the active 2,4-diaminopyrazolo[1,5-*a*][1,3,5]triazines **149** *via* **148**.

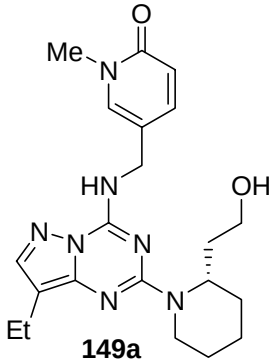


Scheme 76

The pyrazolo[1,5-*a*][1,3,5]triazines **149** with CDK2 inhibitory activity possess a wide range of substituents (R^2-R^4), but they have some common restrictions for substitution at pyrazole ring (unsubstituted position 7) *e.g.* **149a**[104] and **149b**[96] (Figure 4). The antiproliferative activity study showed that **149b** was also active against human colon cancer cells.[96]

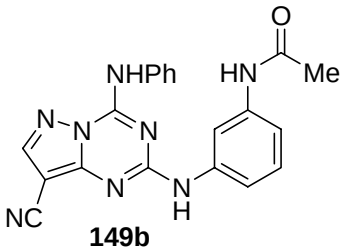
The significant improvement of anticancer activity of pyrazolo[1,5-*a*][1,3,5]triazines **149** was successfully achieved by further transformation of **149c** to the macrocyclic derivatives (*e.g.* **152**) as shown in Scheme 77.[101] The saponification of ester **150**, prepared from **149c**, resulted in the formation of

acid **151**, which was subsequently cyclyzed under treatment with coupling reagent HATU and then converted to the amide (*e.g.* **152**) using a variety of amines. The macrocyclic pyrazolo[1,5-*a*][1,3,5]triazines inhibited CDK2 and were active against human prostate and colon cancer cell lines in *in vitro* experiments.



149a

K_i (CDK2) = 0.48 nM

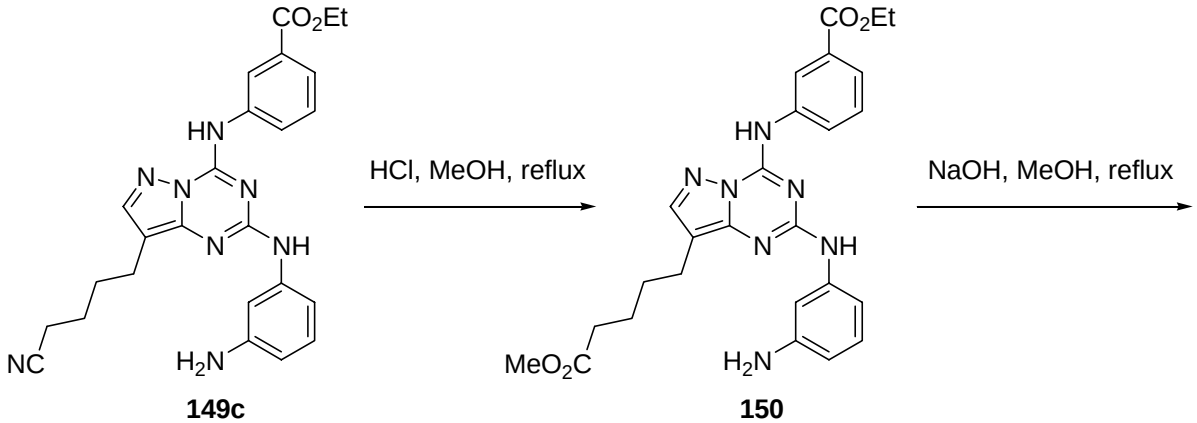


149b

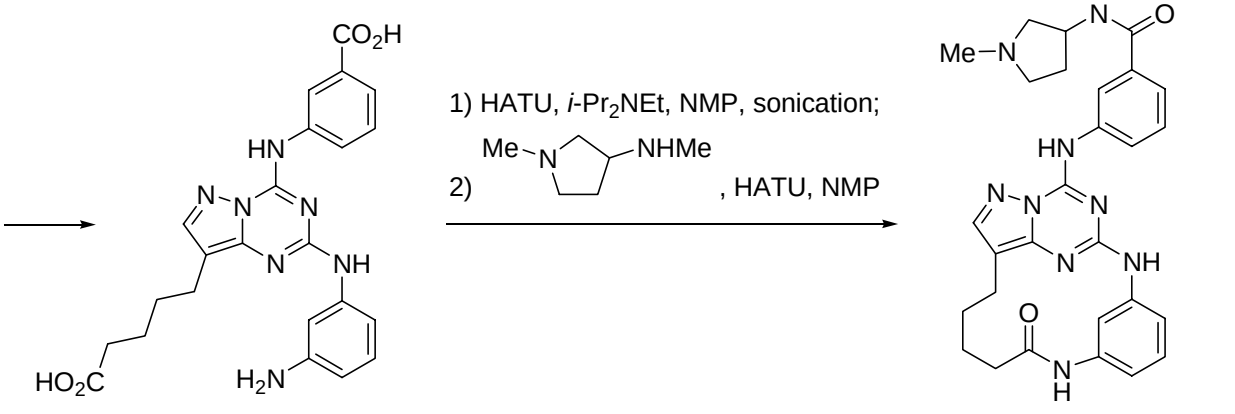
K_i (CDK2) = 0.35 nM

IC_{50} (HCT116) = 990 nM

Figure 4



149c **150**



151 **152**

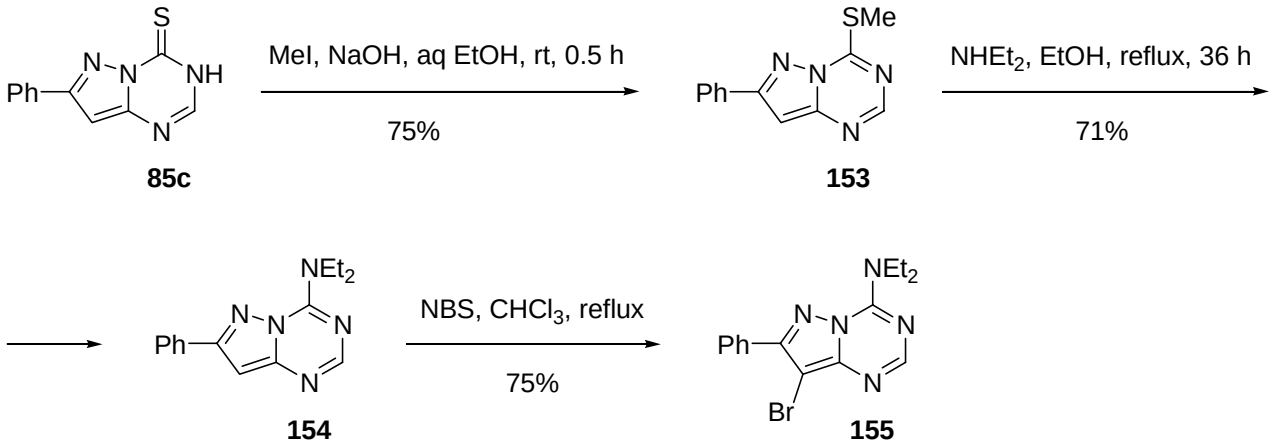
K_i (CDK2) = 2.0 nM

IC_{50} (HCT116) = 83 nM

IC_{50} (PC3) = 120 nM

Scheme 77

The cyclic nucleotide phosphodiesterases (PDE) represent another group of enzymes consisting of at least 11 families, which can be potential targets for pyrazolo[1,5-*a*][1,3,5]triazines. These enzymes hydrolyze (with different selectivity) cAMP and cGMP, which are second messengers involved in cellular responses to extracellular stimuli (*e.g.* neurotransmitters or hormones). The specific PDE are distributed unequally in different tissues and cells types. Therefore, in the search of new PDE inhibitors, one of the main focuses is selectivity in the inhibition of enzyme isoforms. The potent and rather selective inhibitors of cAMP PDE from brain and lung (compounds **154** and **155**) were synthesized according to Scheme 78 (the activity of the compounds was expressed in relation to the inhibitory activity of reference drug theophylline, $\alpha = IC_{50}$[theophylline] / IC_{50}[compound]).[58,77,132] The *S*-methylation of thione **85c** (Scheme 41) followed by nucleophilic substitution of metylthio group of **153** with diethylamine resulted in the formation of 4-(*N*,*N*-diethylamino)-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**154**) (Scheme 78). The bromination in **154** with *N*-bromosuccinimide provided **155** with improved PDE inhibitory activity and selectivity.



85c **153** **154** **155**

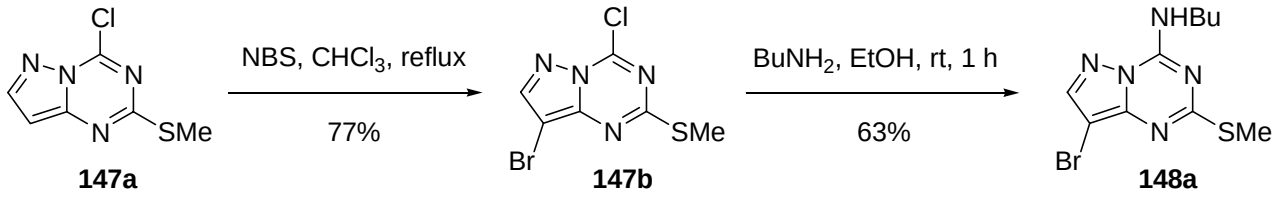
PDE: $\alpha_{brain} = 146$; $\alpha_{lung} = 143$; $\alpha_{heart} = 57$ PDE: $\alpha_{brain} = 250$; $\alpha_{lung} = 185$; $\alpha_{heart} = 40$

Scheme 78

The bromination of 4-chloro-2-methylthiopyrazolo[1,5-*a*][1,3,5]triazine (**147a**, R^1 = H, Alk = Me) (Scheme 76) followed by treatment of compound **147b** (R^1 = Br, Alk = Me) with *n*-butylamine provided the selective inhibitor of cAMP PDE from lung, compound **148a** (Scheme 79).[77,91]

The high level of selectivity towards cAMP PDE from brain was observed for 2-ethyl-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**99a**) (Figure 5), which was synthesized according to general Scheme 47 by heating of **98** (R^1 = H, R^2 = Ph, R^3 = Et) with triethyl orthoformate (54% yield).[57,77,132]

In another study,[133] 4-azido-7-phenylpyrazolo[1,5-*a*][1,3,5]triazine (**156**) (Figure 5) was found to be a potent irreversible inhibitor of calmodulin-dependent PDE (PDE1), but there was no investigation on selectivity. However, in the earlier report,[58] **156** was found to possess $\alpha_{heart} = 1.0$ and $\alpha_{lung} = 0$ that may suggest some selectivity for PDE1 inhibition.



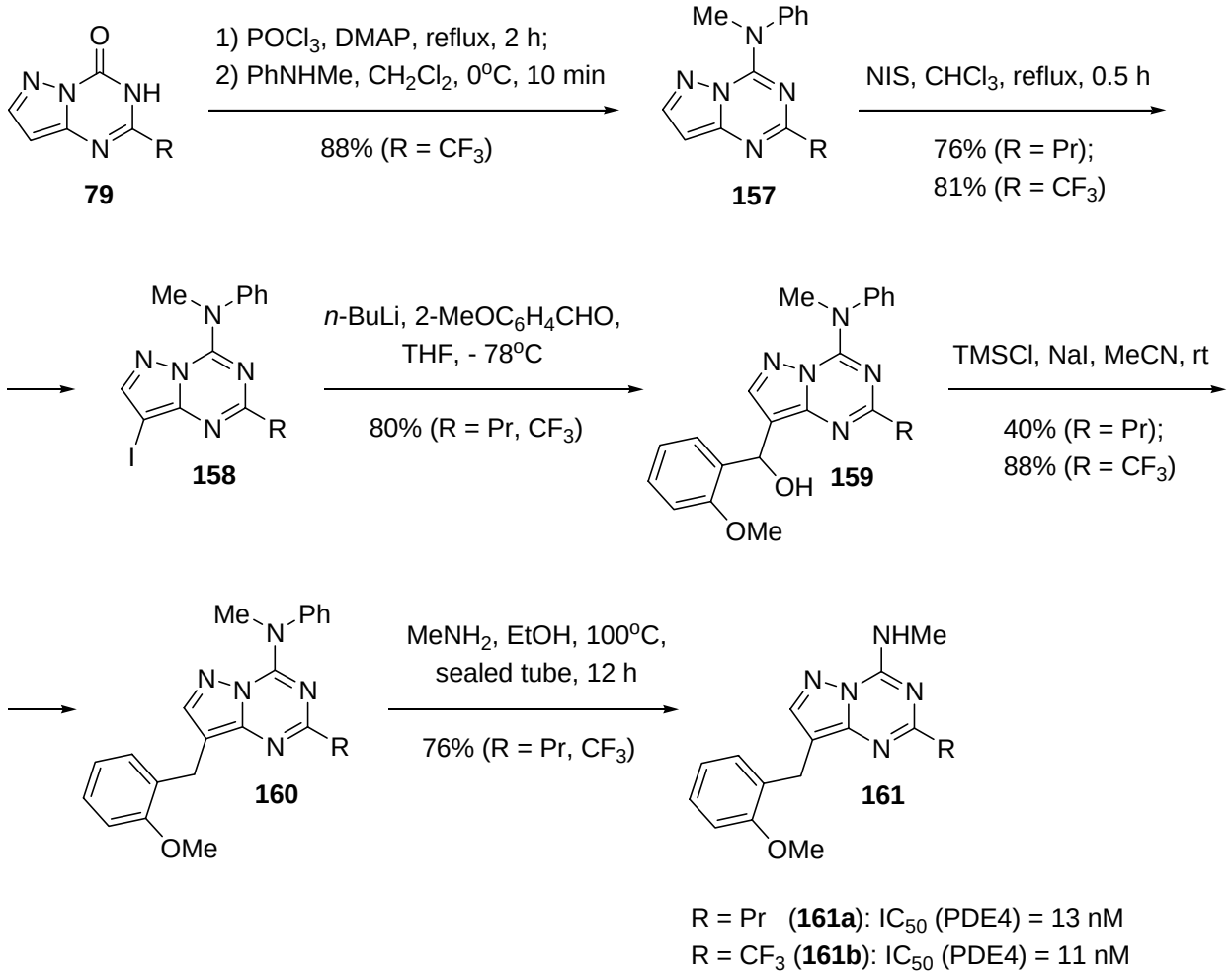
PDE: α_{brain} = 18; α_{lung} = 160; α_{heart} = 12.5

Scheme 79

PDE: α_{brain} = 97; α_{lung} = 14; α_{heart} = 0.5

Figure 5

In the search of new potential PDE4 inhibitors for treatment of autoimmune and inflammatory diseases, two very potent compounds **161a,b** were identified.[85] Both compounds were prepared *via* identical synthetic rout (Scheme 80) and possess similar substitution pattern.

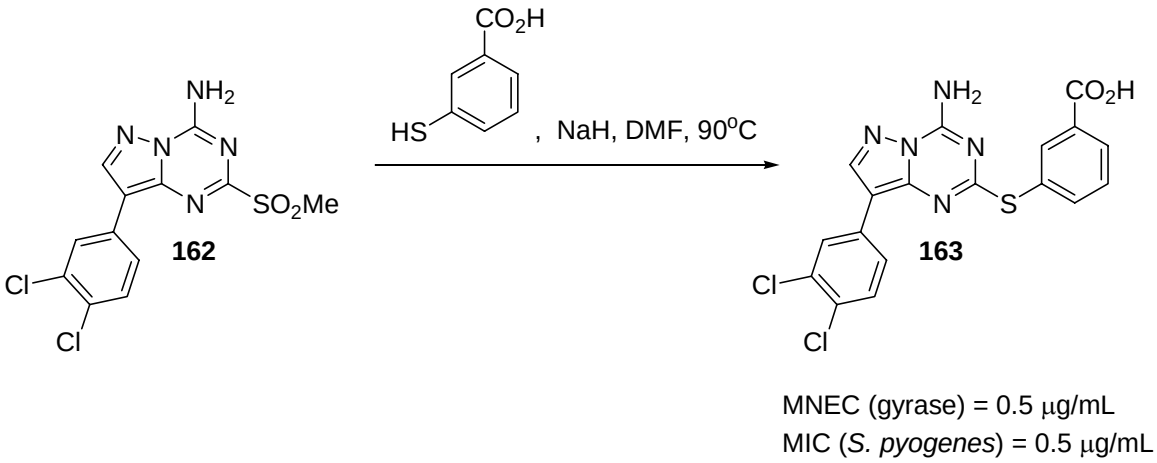


R = Pr (**161a**): IC_{50} (PDE4) = 13 nM
R = CF_3 (**161b**): IC_{50} (PDE4) = 11 nM

Scheme 80

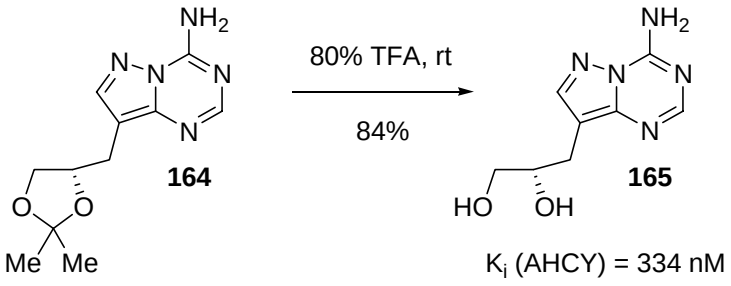
The starting 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**79**) were converted to 4-(*N*-methyl-*N*-phenylamino) derivatives **157** and then to **158** (Scheme 80). The iodinated compounds **158** were transformed into compounds **159** and then to **160**, which were converted into the target compounds **161** upon heating with methylamine in sealed tube. The selectivity aspect of PDE4 inhibition by **161** was investigated using PDE1, PDE2, PDE3 and PDE5 isoforms showing that both **161a** and **161b** inhibited PDE4 with high level of selectivity.

It was found that some pyrazolo[1,5-*a*][1,3,5]triazines, *e.g.* **163**, were able to inhibit bacterial enzyme DNA gyrase,[31] which is not present in human and therefore represents a good target for antibacterial therapy. The synthesis of **163** was performed from **162** according to general Scheme 81. Compound **163** showed similar values of maximal non-effective concentration (MNEC) towards DNA gyrase and minimal inhibitory concentration (MIC) against *Staphylococcus pyogenes*.



Scheme 81

The deprotection of **164** was reported to afford the *S*-adenosylhomocysteinase inhibitor **165** (Scheme 82).[19]



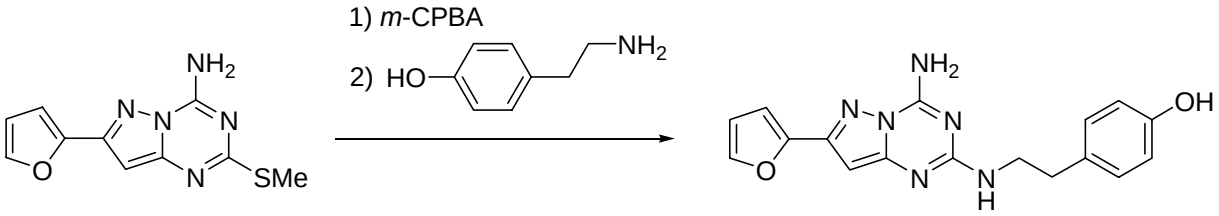
Scheme 82

6.2. Receptor ligands

A number of G-protein coupled receptors have been identified as potential targets for pyrazolo[1,5-*a*][1,3,5]triazines with various structures. Those include: adenosine, $P2Y_1$, cotricotropin-releasing factor, neuropeptide Y, 5-hydroxytryptamine (5-HT), cannabinoid and angiotensin

receptors.

The pyrazolo[1,5-*a*][1,3,5]triazine nucleus was claimed[36,134,135] to be a suitable scaffold for the preparation of adenosine receptor antagonists. This can be exemplified by the synthesis of LUF 5441 (**166**) (Scheme 83), which is a deaza-analogue of very potent A_{2A} adenosine receptor inhibitor ZM 241385.[134]

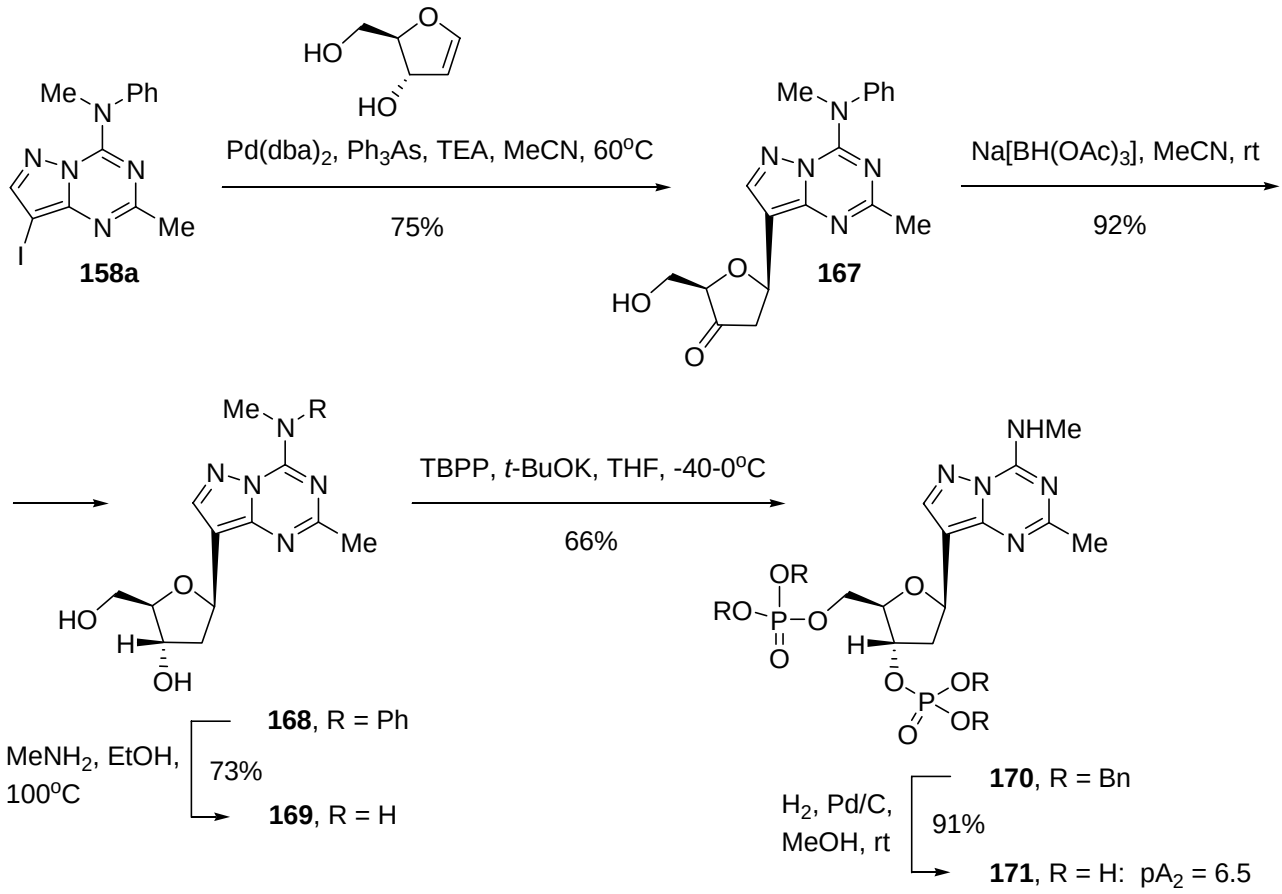


K_i (A_1) = 56.4 μM K_i (A_{2B}) = 31 μM
K_i (A_{2A}) = 9.3 μM K_i (A_3) = 464 μM

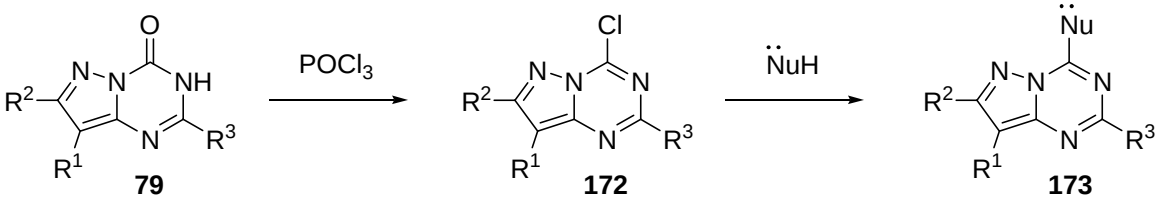
Scheme 83

The $P2Y_1$-receptors are known to be involved in purinergic signaling, and they can be activated mainly by ADP and related diphosphate analogues. The synthesis of potential $P2Y_1$-receptor antagonist **171**, diphosphate with pyrazolo[1,5-*a*][1,3,5]triazine skeleton, was developed.[136] The palladium-mediated cross-coupling reaction of **158a** with 1,4-anhydro-2-deoxy-*D*-*erythro*-pent-1-enitol was found to proceed regio- and stereoselectively giving the *C*-furanosyl-4-one **167** (Scheme 84). The stereoselective reduction of the ketone group of **167** followed by the subsequent replacement of the *N*-methyl-*N*-phenylamino group of **168** using methylamine provided *C*-nucleoside **169**, which was converted into phosphate **170**. The catalytic hydrogenolysis of **170** aforded active compound **171**. No direct data on the affinity of **171** towards $P2Y_1$-receptors were reported, but it was found to be active in the functional assays exhibiting strong inhibition of ADP-induced platelet aggregation *in vitro* (pA_2 = 6.5) and *in vivo*.

Cotricotropin-releasing factor (CRF) is a hormone and neurotransmitter, which is released in the brain in response to stress and coordinates endocrine, immune, autonomic and behavioral reactions. The CRF receptor antagonists particularly selective towards CRF_1 are believed to be potential agents for therapy of anxiety and mood disorders. Two groups of potent CRF receptor antagonists with pyrazolo[1,5-*a*][1,3,5]triazine nucleus were reported. The synthesis of one group of pyrazolo[1,5-*a*][1,3,5]triazines (**173**) was performed as shown in Scheme 85. The treatment of 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**79**) (Scheme 49) with phosphorus oxychloride followed by the reaction with various nucleophilic reagents provided **173**.[62,79,80,83,84,137-140] At the last step, instead of the nucleophilic substitution of chlorine atom of **172**, substitution of methylthio group of similar compounds was also applied.[71] The examples of biologically active **173** are presented in Figure 6.



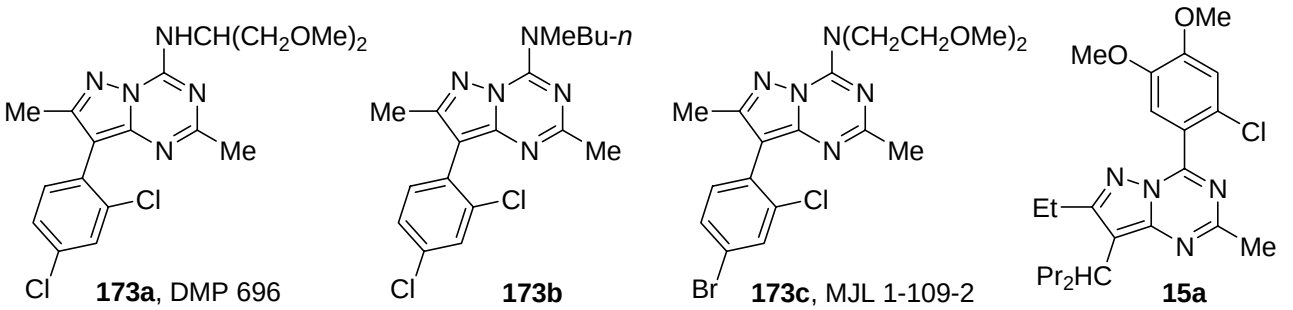
Scheme 84



Scheme 85

The DMP 696 (**173a**, Figure 6) was shown to be a noncompetitive antagonist with high affinity and selectivity for CRF_1 receptors. This compound (**173a**) exhibited high anxiolytic and antidepressant activities as well as good oral bioavailability and desirable pharmacokinetic properties. The DMP 696 (**173a**) is widely used as a reference compound and as an effective tool for the investigation of the role of CRF and its receptors in the behavior. The details on the mechanisms of action, side effects, pharmacokinetics and advantages of DMP 696 (**173a**) in comparison with other CRF_1 blocking agents can be found in the special reviews.[141,142] The systemic effects of MJL 1-109-2 (**173c**, Figure 6) were investigated in detail using a battery of behavioral tests.[143] The radiolabeled [^{76}Br] MJL 1-109-2 was also synthesized and used for the autoradiographic visualization of CRF_1 receptors.[84]

The preparation of the structurally different group of pyrazolo[1,5-*a*][1,3,5]triazines (*e.g.* **15a**, Figure 6) possessing high affinity to CRF receptor was carried out as outlined in Schemes 7 and 47.[10]



173a, DMP 696 K_i (CRF_1) = 1.7 nM

173b K_i (CRF_1) = 0.4 nM

173c, MJL 1-109-2 K_i (CRF_1) = 1.9 nM

15a K_i (CRF) = 0.7 nM

Figure 6

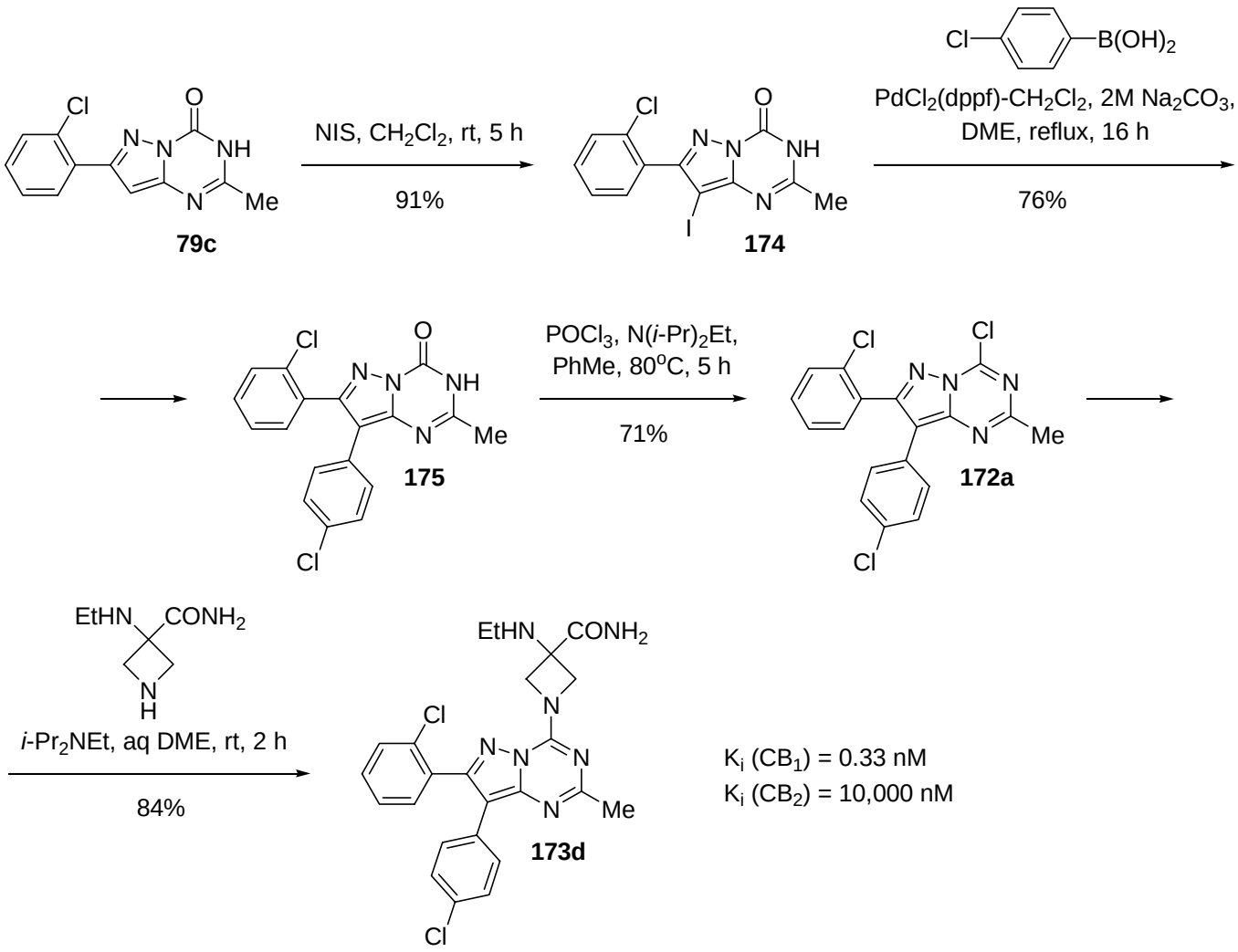
Differently substituted 4-amino-8-aryl-2,7-dimethylpyrazolo[1,5-*a*][1,3,5]triazines (**173**, R^1 = Ar; R^2 = R^3 = Me; Nu = NHR^4) were also claimed[81,82] to be modulators of neuropeptide Y_1 receptors. The synthesis of these compounds involved the reaction sequences presented in Scheme 49 (formation of pyrazolo[1,5-*a*][1,3,5]triazine nucleus) and Scheme 85 (amination).

Analogous amination of **34** was found to afford corresponding **173** (R^1 = SO_2Ph; R^2 = SMe; R^3 = Me; Nu = NR^4R^5), which were claimed[21] to be effective ligands of 5-HT_6 receptors.

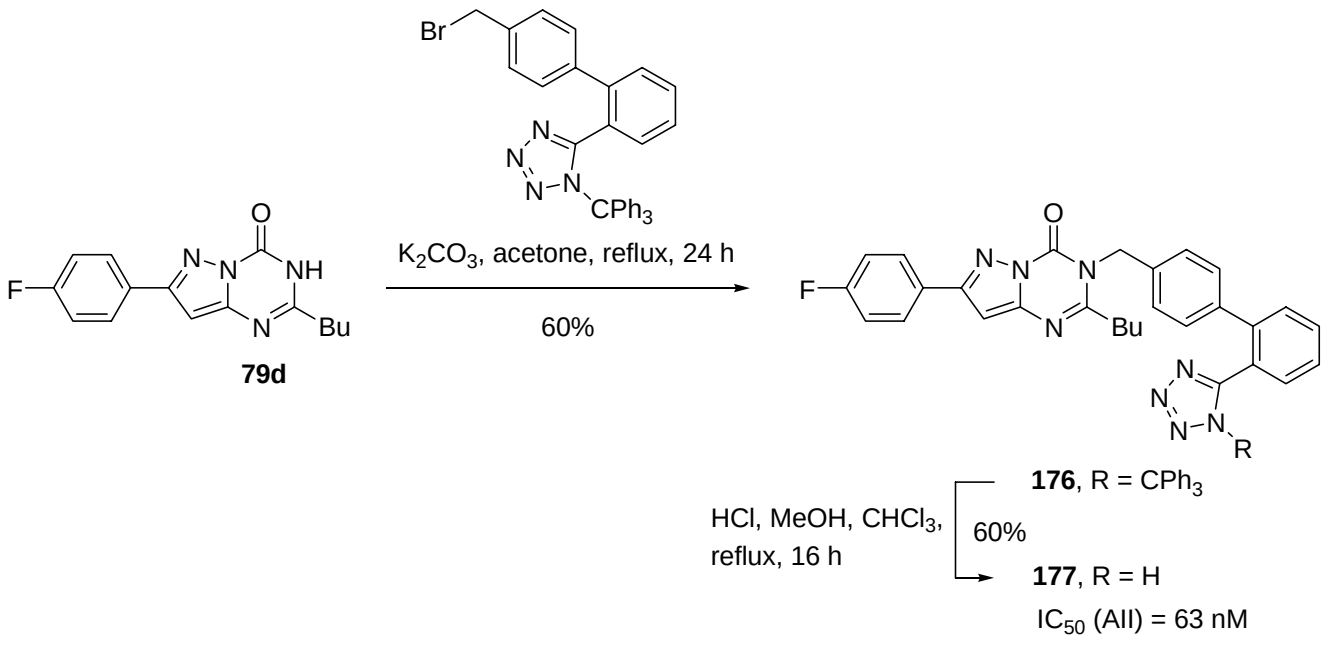
Cannabinoid (CB) receptors are known to be involved in regulation of several processes in central nervous system (CNS). The synthesis of CB receptor antagonists of general structures **79** and **173** was reported[86-88] and these compounds were claimed to be potential therapeutic agents for treatment of CNS disorders. The heterocyclization according to general Scheme 49 was used for the preparation of both types of structures. The iodination of **79c** with *N*-iodosuccinimide gave intermediate **174**, which was converted into **175** using Suzuki coupling (Scheme 86). The subsequent treatment of **175** with phosphorus oxychloride and then with 3-ethylaminoazetidine-3-carboxamide provided **173d**. It was found that **173d** (used as benzenesulfonate salt) bound CB_1 receptors with high affinity and selectivity.[144] The systemic administration of **173d** was reported to enhance antiparkinsonian action of L-DOPA in the rhesus monkeys with parkinsonism model. The observations suggested that CB_1 antagonists such as **173d** can be used in combination with dopaminomimetics for the therapy of Parkinson's disease.

The pyrazolo[1,5-*a*][1,3,5]triazine **79d** was converted into **176** by alkylation (Scheme 87).[60] The deprotection of the trityl group in **176** afforded 3-substituted 4-oxopyrazolo[1,5-*a*][1,3,5]triazines (**177**), which where identified as potent antagonists of angiotensine II (AII) receptors. These compounds demonstrated high affinity to the receptors in *in vitro* experiments as well as significant reduction of the AII hypertensive response *in vivo*.

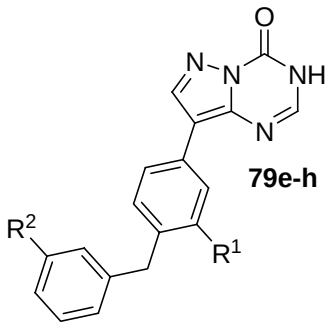
The modulation of nuclear hormone receptors particularly androgen receptors (AR) by pyrazolo[1,5-*a*][1,3,5]triazines also provided a potential for using them in medicine. It was reported[59] that 8-aryl-4-oxopyrazolo[1,5-*a*][1,3,5]triazines (*e.g.* **79e-h**, Figure 7) were able to inhibit effectively binding of ^{3}H-mibolerone to AR. The synthesis of these compounds was carried out according to Scheme 37.



Scheme 86



Scheme 87



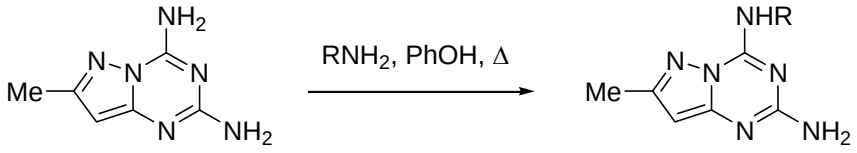
79e-h

79	R^1	R^2	IC_{50} (AR), nM
e	Me	Me	20
f	Me	OMe	12
g	OMe	Me	18
h	OMe	OMe	23

Figure 7

6.3. Miscellaneous biological activities

Among other biologically active pyrazolo[1,5-*a*][1,3,5]triazines, 2,4-diamino-7-methyl-pyrazolo[1,5-*a*][1,3,5]triazine (LA 2851, Dametralast, **39b**) showed combination of two principal effects that are useful in asthma therapy, namely bronchodilator[145,146] and antiallergic[145-147] activities, as well as low toxicity. Anti-inflammatory properties (not attributed to cyclooxygenase inhibition or mediator release) were also identified for LA 2851.[148] It was found that LA 2851 inhibited to some extent PDE, but this enzyme was not its primary target. The investigations on the mechanism of action of LA 2851 proposed that the lipoxygenase pathway was affected. The analogues (**39** and **76**) as well as derivatives (**46**) of LA 2851 and itself (**39b**) were prepared (Schemes 19, 21, 33, 35 and 88) and investigated as antiasthmatic agents using a variety of animal models and were also clinically tested in human.[24] There is no detailed information on the mechanism involved into the realization of biological activities of the compounds available. However, structural similarity and the observed pharmacological profile, particularly effects on CNS and cardiovascular system, may suggest that these compounds work as adenosine receptor antagonists.



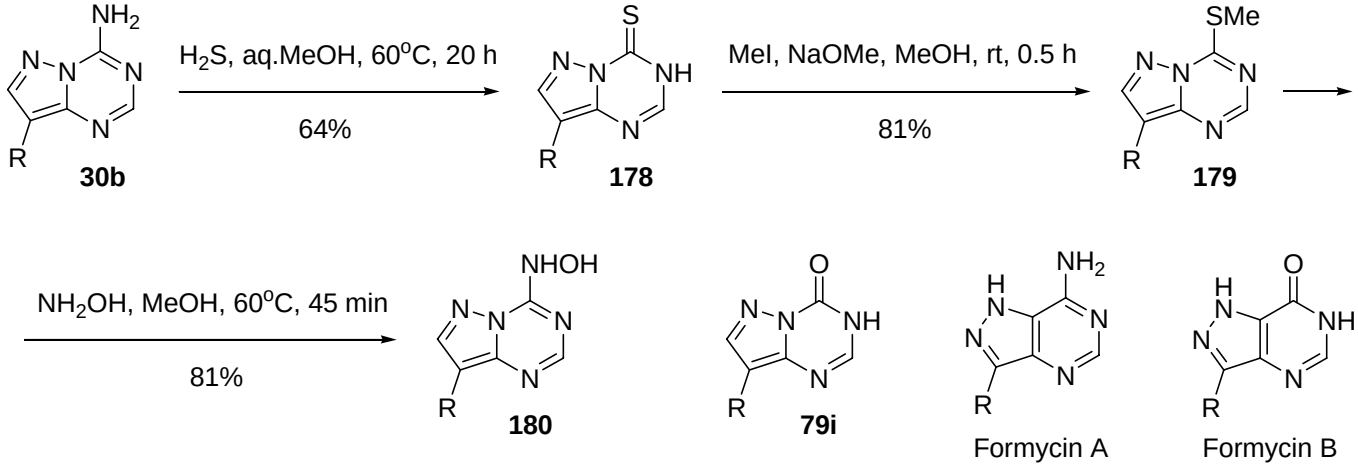
39b, LA 2851, Dametralast

46

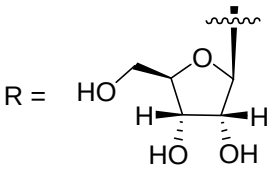
Scheme 88

It is also of interest to review some transformations of functional groups at C-4 of pyrazolo[1,5-*a*][1,3,5]triazine *C*-nucleosides with antileukemic properties.[28] The isostere of adenosine and formycin A, nucleoside **30b**, was prepared according to Scheme 13. The treatment of **30b** with hydrogen sulfide allowed to synthesize an isostere of 6-thioinosine, *C*-nucleoside **178**, which was further methylated to give **179** (Scheme 89). The nucleophilic substitution of methylthio group of **179** with hydroxylamine provided **180**. The isostere of inosine and formycin B, nucleoside **79i**, was prepared as outlined in the Scheme 60. The antileukemic activity of the compounds was evaluated in comparison with

formycin A and B using two cell lines. The nucleosides **30b** and **79i** were found to be more active than their formycin type counterparts. The most active compound in the series was 4-methylthio-8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*][1,3,5]triazine (**179**).



Compound	IC_{50}, μg/mL	
	L1210	P815
30b	0.1	0.2
79i	0.5	0.4
178	0.7	1.0
179	0.09	0.07
180	>10.0	0.3
Formycin A	2.6	2.4
Formycin B	5.5	>10.0



Scheme 89

7. CONCLUSION

A variety of effective methods for the preparation of pyrazolo[1,5-*a*][1,3,5]triazines has been reported. Mainly, the construction of the 1,3,5-triazine ring onto a pyrazole skeleton has found practical significance. The pyrazolo[1,5-*a*][1,3,5]triazine nucleus has been utilized as suitable scaffold for the design of biologically active compounds targeting different enzymes and receptors. Some of the identified agents possess high level of selectivity towards specific targets and good therapeutical potential. At the same time, it may be also of interest to develop multitarget agents with pyrazolo[1,5-*a*][1,3,5]triazine nucleus, since the combination of some particular properties may be useful for the treatment of certain pathological conditions, such as inflammation (*e.g.* PDE4 inhibitors and adenosine A_{2B} receptor antagonists) and CNS disorders (*e.g.* adenosine A_{2B}, 5-HT_6 and CB_1 receptor antagonists for the parkinsonism therapy).

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