New Trends in the Chemistry of 5-Aminopyrazoles

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I. INTRODUCTION.

The biological and medicinal activities of 5-aminopyrazoles have prompted enormous research aimed at developing synthetic routes to these ring systems [1-4]. A search of the literature revealed large number of 5-aminopyrazole ring systems that fit this criteria. Such a fact may not be surprising for those who are interested in the chemistry of this class of compounds as, of course, there are theoretical and practical reasons for this interest.

5-Aminopyrazoles (**1**) became of recent importance due to the reported anti-inflammatory and antipyretic properties of many of these derivatives [1-4]. Moreover, in recent years, these derivatives have been extensively utilized as intermediates for synthesis of fused pyrazoles of potential biological activity [1-4].

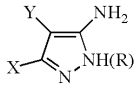
The chemistry of 5-aminopyrazoles have been reviewed in two books which were published in 1964 [5] and in 1967 [6]. The extensive literature that has been published since both books appeared made it mandatory to update knowledge in this area. It should be however, stated clearly here that some reports were not involved because it seemed mere repetition of the established and reviewed chemistry of these compounds.

On the other hand, some of the old literature is surveyed here because it seemed of vital importance in understanding the chemistry of this class of compounds.

II. METHODS OF PREPARATION

1- Reactions of α– or β-Functional Nitriles with Hydrazines.

5-Aminopyrazoles (**1**) have been extensively synthesized *via* the reaction of α–, β-functional nitriles with hydrazines [7-9]. A variety of α–, β-functional nitriles have been utilized for the synthesis of **1**.



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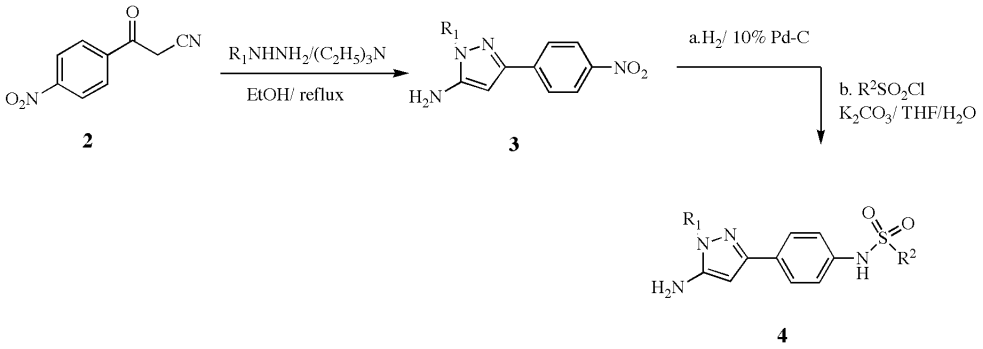
This review focuses on recently published methods of preparation of 5-aminpyrazoles. For example, cyano-4'-nitroacetophenone (**2**) undergoes cyclization upon treatment with arylhydrazines in the presence of triethylamine in refluxing ethanol to yield pyrazole **3**. The nitro group was then reduced to an amine under hydrogenation conditions and the amine was condensed to an aryl sulfonyl chloride to afford aminopyrazoles **4** in excellent yields [10] (Scheme 1).

Scheme 1

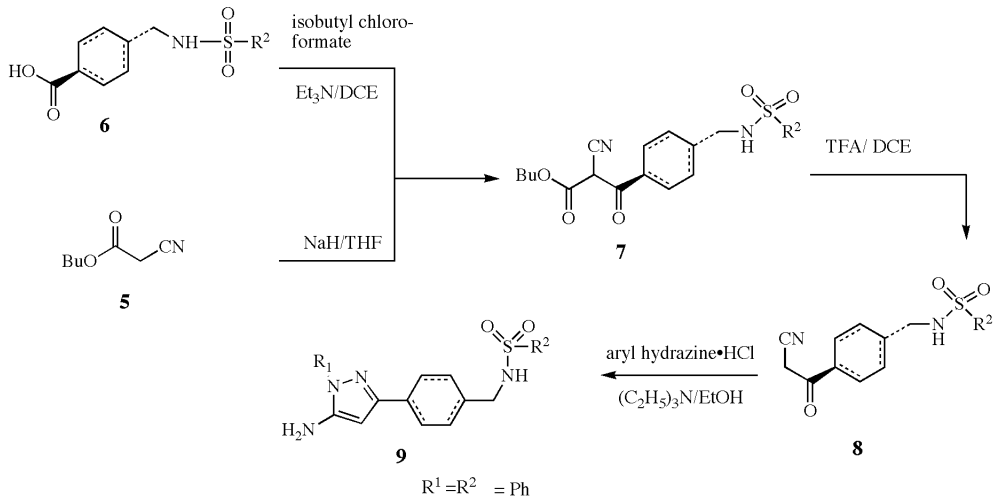


2 **3** **4**

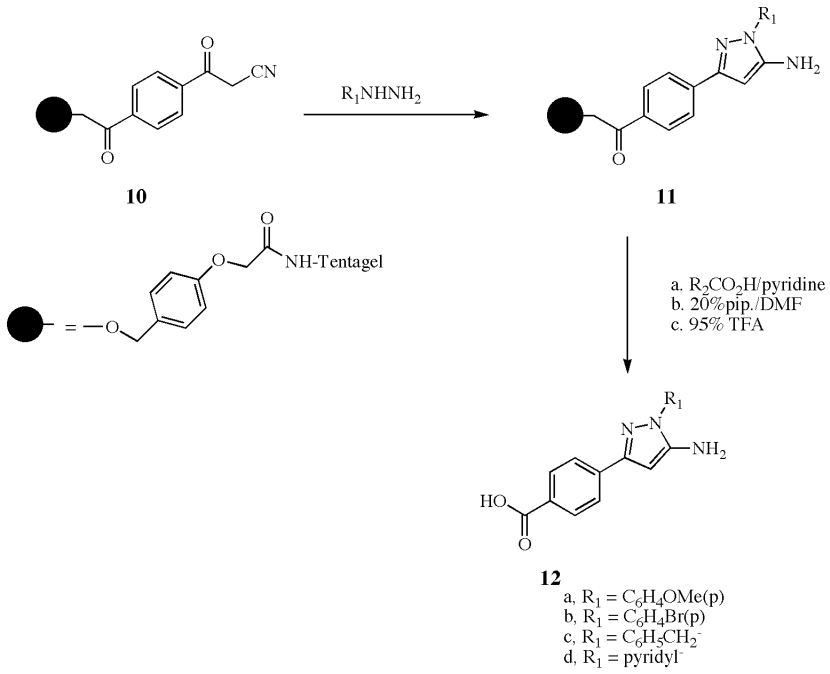
Alternatively, aminopyrazoles that contained a cyclohexylmethyl- or phenylmethyl- sulfonamido group were prepared as illustrated in (Scheme 2) [10]. These compounds were designed because the cyclohexylmethylsulfonamido group had previously been shown to be present in high-affinity ligands of the human nuropeptide y y^5 receptor [11].

On the other hand, Watson *et al.* [12] reported a novel solid phase syntheses of some 5-aminopyrazoles and their *N*-acyl and *N*-sulfonyl derivatives have developed utilizing the β-keto nitrile **10** as shown in (Scheme 3). The syntheses

Scheme 2



Scheme 3

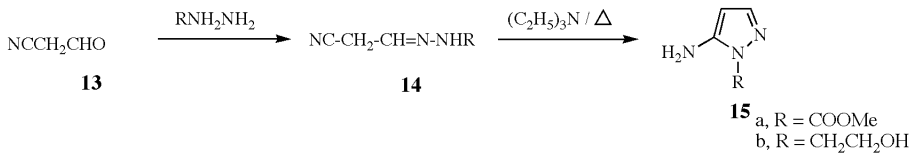


are versatile, affording compounds based around a known pharmacophoric template and are ideally suited for combinatorial library generation.

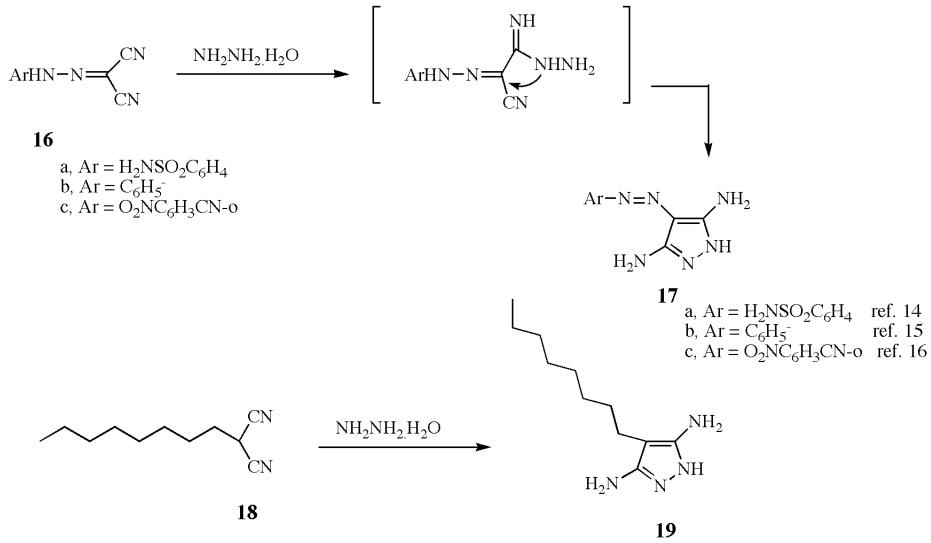
Jachak *et al*. [13] have recently reported a novel synthesis of 5-aminopyrazoles **15** *via* reaction of cyanoacetaldehyde (**13**) with hydrazines to give the hydrazones **14** which readily cyclized under basic conditions to give **15**.

Substituted malononitrile derivatives have been shown to react smoothly with hydrazine to yield 3,5-diaminopyrazoles with an expected wide spectrum of biological activity. Thus, it has been shown that [14-16] arylhydrazonomesoxalonitriles **16** react with hydrazines to yield 3,5-diamino-4-arylazopyrazoles **17** (Scheme 4).

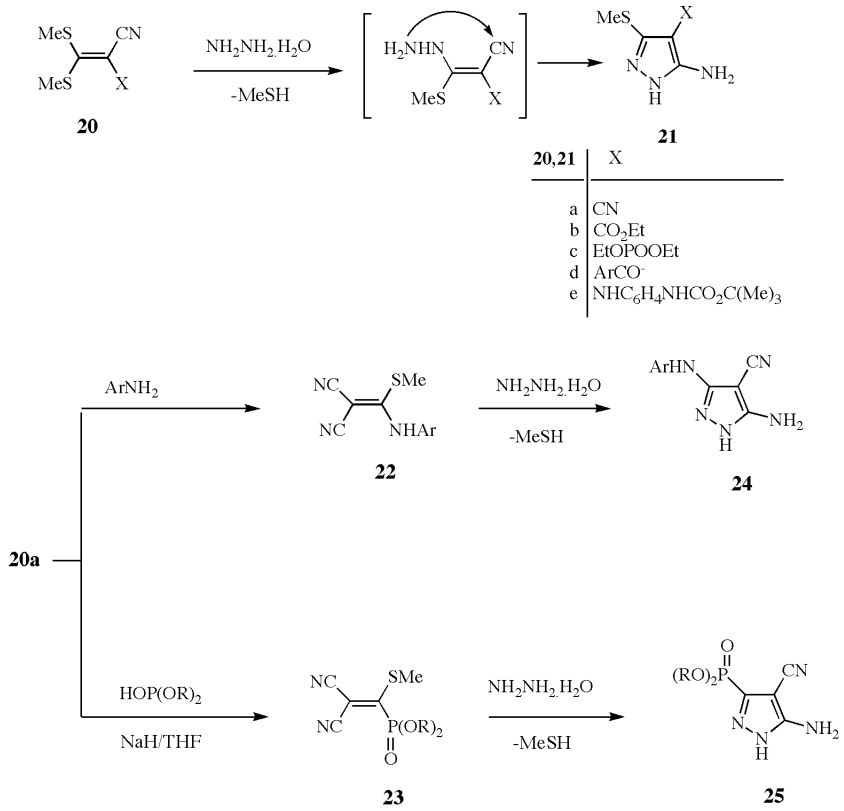
Similarly, Echevarria *et al*. [17] have reported that octyl-



Scheme 4



Scheme 5



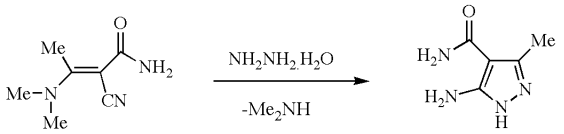
malononitrile (**18**) afforded 3,5-diamino-4-octylpyrazole (**19**) when heated with hydrazine hydrate in ethanol for 24 hs (Scheme 4).

2- Reactions of α,β-Unsaturated Nitriles with Hydrazines.

An efficient route for the synthesis of 5-aminopyrazoles is the reaction of α,β-unsaturated nitriles with hydrazines [18-25]. Thus, the ketene dithioacetals (**20**) cyclocondensed with hydrazine hydrate (70%) in refluxing methanol to give 5-aminopyrazoles (**21**) in good yield.

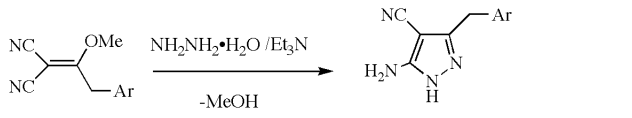
Also, compound **20a** underwent smooth conjugate addition with aryl amines and with diethyl phosphite to afford α,β-unsaturated nitriles **22** and **23**, respectively. Finally, cyclization reaction of **22** with hydrazine hydrate in refluxing ethanol affords 5-amino-3-arylaminopyrazole-4-carbonitrile derivative **24** [26]. While cyclization of **23** with hydrazine hydrate to construct 5-amino-4-cyano(ethoxycarbonyl)-3-phosphonylpyrazole (**25**) [27] was achieved under carefully controlled reaction temperature –5~0 °C in essentially quantitative yield (Scheme **5**).

Also, Nilov *et al*. [28] have reported the synthesis of 5-aminopyrazole-4-carboxamide (**27**) from reaction of α-cyano-β-dimethylaminocrotonamide (**26**) with hydrazine hydrate.



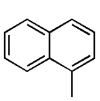
26 **27**

Recently, it has been reported [29,30] that 1,1-dicyano-2-methoxy-3-arylpropene **28** undergo cyclization when treated with hydrazine hydrate in ethanolic triethylamine to yield 5-aminopyrazole derivatives **29**.



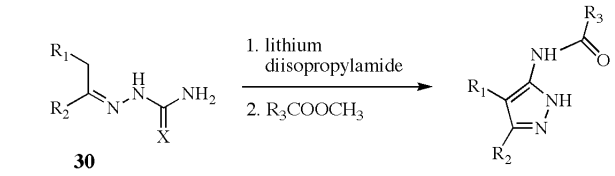
28 **29**

a, Ar = 

b, Ar = 

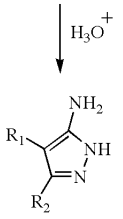
3-Other Syntheses.

Beam *et al*. [31] have reported a novel synthesis of 5-aminopyrazoles from polylithiated *C*(α),*N*-thiosemicabazones or *C*(α),*N*-semicarbazones. The polylithiated intermediates, prepared in an excess of lithium diisopropylamide, underwent cyclization and subsequent hydrolysis to give aminopyrazole derivative **32**.



30 **31**

a, X = O or S, R_3, R_2 = Ph, R_1 = H
b, X = O or S, R_3 = 2-OHC_6H_4, R_1,R_2 = -$(CH_2)_{10}$-



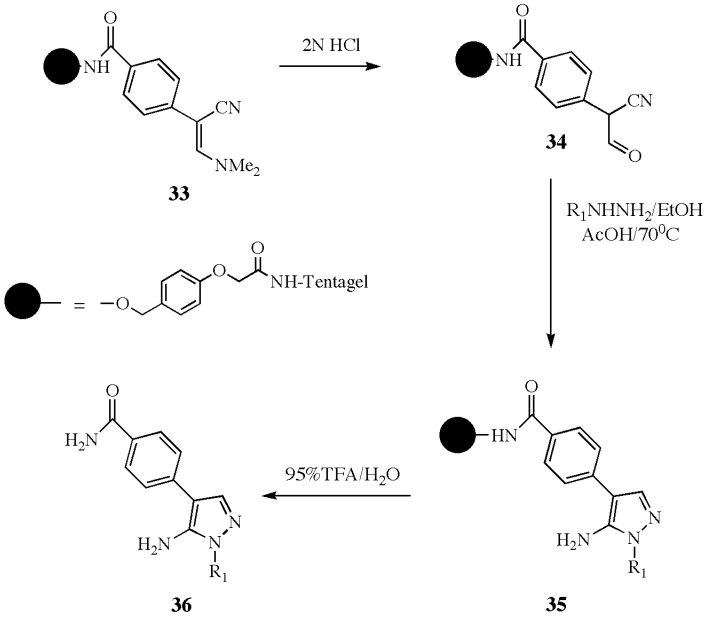
32

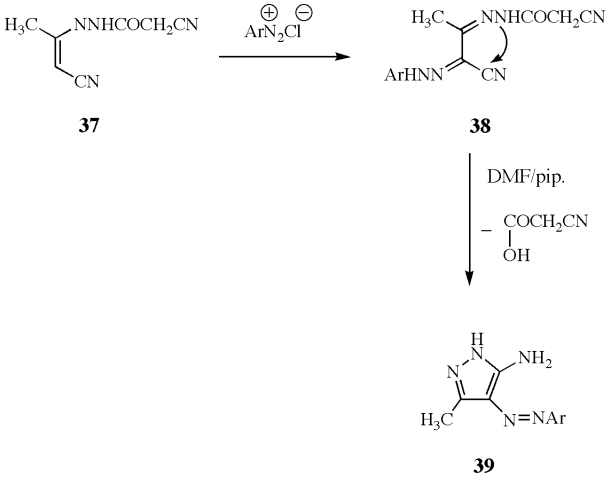
A second solid phase synthesis of 5-aminopyrazoles has been achieved [32] utilizing the enamine nitrile **33** [33] as starting material. In this reaction compound **33** was readily hydrolysed to afford the 4-(1-cyano-2-oxoethyl)benzamide derivative **34** which react efficiently with hydrazines to give the corresponding 5-aminopyrazoles **35**. Subsequent acylation and cleavage from the resin affords *N*-acyl-5-aminopyrazoles **36** (Scheme 6). This new 5-aminopyrazole synthesis is more versatile than its predecessor [12], in that it avoids the use of troublesome β-keto nitrile functionality. This new route is ideally suited for the synthesis of combinatorial libraries for screening against drug targets.

The enamine nitrile [34] **37** readily coupled with aryl diazonium chlorides to yield coupling products **38** that were converted to the aminopyrazole derivatives **39** by refluxing in DMF/piperidine [34].

Hutaud *et al*. [35] have reported a rare method for the preparation of 3,5-diaminopyrazoles **42** in good yields upon treatment of the alkenes **40** with trifluoroacetic acid. The Boc deprotection is spontaneously followed by a nucleophilic attack of the cyano group by the *N*-terminal nitrogen of the hydrazino substituent (Scheme 7).

Scheme 6



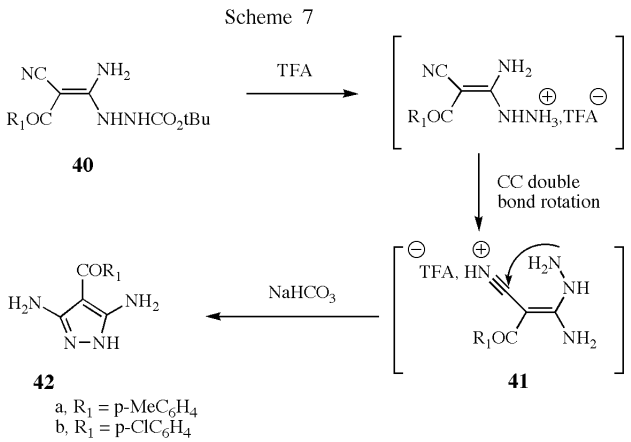


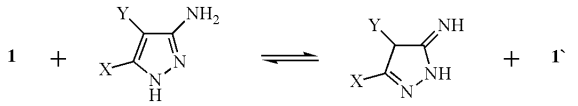
Other interesting syntheses that afford 5-aminopyrazole derivatives are also reported [18,33] in (Scheme 8).

III. STRUCTURE OF 5-AMINOPYRAZOLES.

(3)5-Aminopyrazoles (**1**) are tautomeric with its imino form (**1'**). It is difficult to make a clear cut distinction between the two structures. It is usually necessary to consider both structures, as well as their resonance stabilized ionic hybrid structures, to rationalize for the chemical behavior of these compounds [6]. However it has been stated that in a superficial way it is more or less apparent that 5-aminopyrazoles behave primarily as 5-imines [6]. Such a statement seems to be over simplified and it might even be wrong as the ultraviolet absorption studies have indicated that 5-iminopyrazoles exist as such under the conditions of measurements [36,37].

Scheme 7

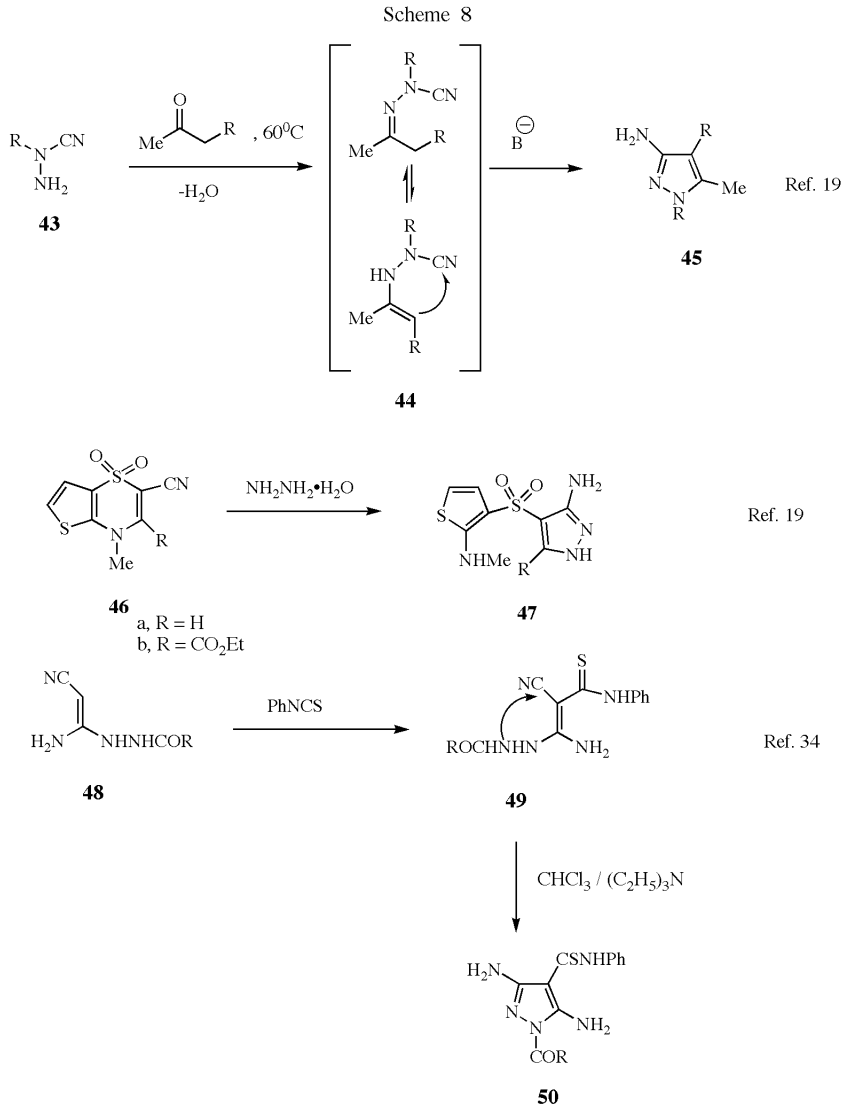




IV. CHEMICAL PROPERTIES.

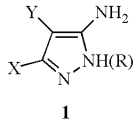
Generally, the chemical properties of 5-aminopyrazoles (Figure 1) resemble those of the corresponding 5-hydroxy analoges (5-pyrazolones) except in the reactions taking place mainly with the amino group. Electrophilic substitution usually takes place at the 4-position. Coupling with diazonium salts, nitrosation,

Scheme 8



halogenation and nitration takes place at this position. Acylation, sulphonation, hydrolysis have also been reported [5,6]. These reactions were previously surveyed efficiently in reference 5 and 6 and are summarized here in (Scheme 9).

It has been reported that the behaviour of 5-aminopyrazoles toward condensation with aldehydes and ketones resembles that of 2-aminoindole [38,39] since 5-aminopyrazoles behave primarily as 5-imines [36]. Swett *et al.* [40], have suggested a structure of type **58** as the most likely for this reaction. Since they were unable to either purify or characterize these products, they could not rule out the possibility of the formation of Schiff bases of type **57** which could rearrange to **58** (Scheme 10).



1

1	X	Y
a	Ph	H
b	phenazonyl-	H
c	Ph	Br
d	Me	H
e	Me	Br
f	NH_2	NO_2
g	NH_2	-N=NAr
h	-NHAr	CN
i	Ar	CN
j	Et	$-CONH_2$
k	isopropyl-	CN
l	$(C_6H_5)_2CH_2$-	CN
m		CN
n	Me	-COMe

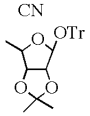
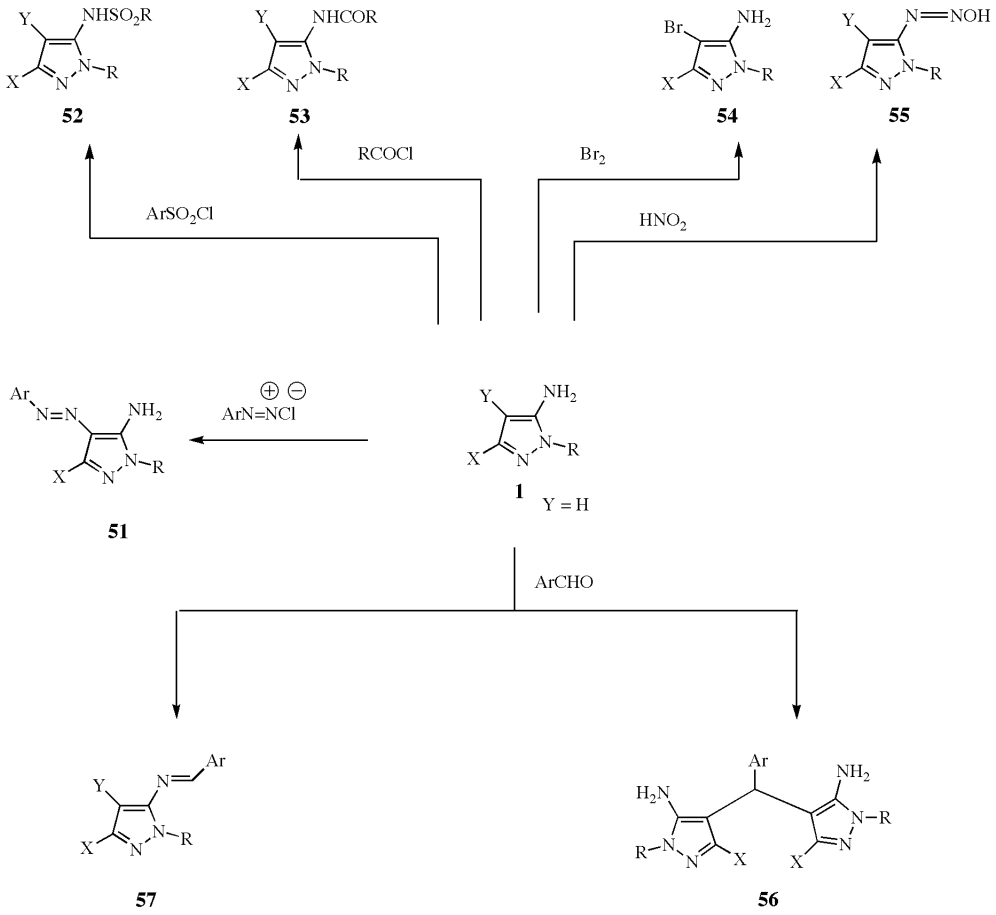
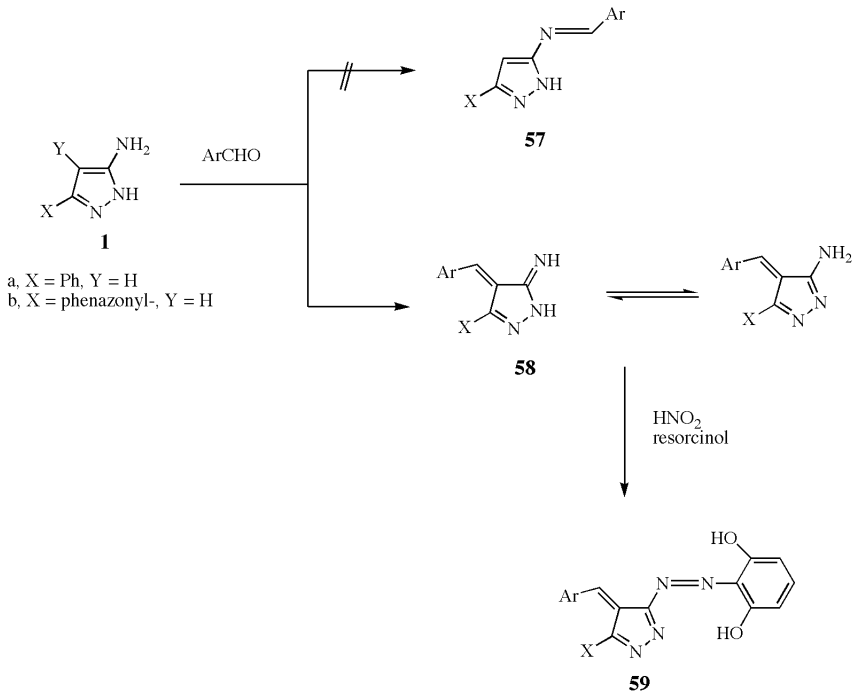
1	X	Y
o	H	CO_2Et
p	Me	-CHO
q	H	CN
r	SMe	CN
s	H	
t	H	CH_3
u	Me	NO
v	NH_2	$-CH_2SPh$
y	-COBt	CN
x	$-CH_2Ph$	-N=NAr
w	Me	SH

Figure 1

Scheme 9



Scheme 10

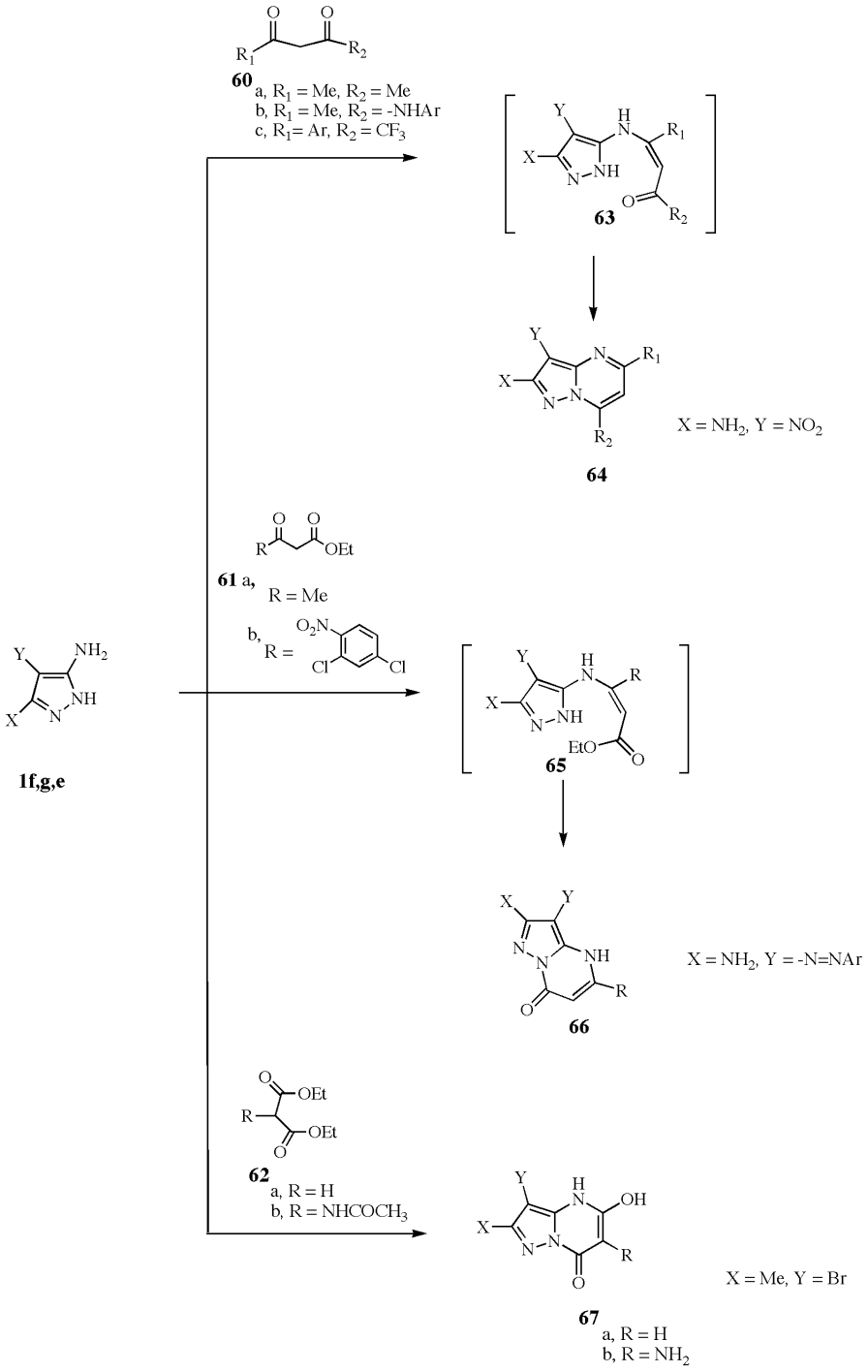


It has been proven that [41,42], by condensation reaction of 5-aminolpyrazoles **1a,b** with aromatic aldehydes only 4-arylidene derivatives are formed. Spectral analysis were in complete agreement with the proposed structures that further elucidated by the formation of diazonium salts and coupling with resorcinol to give the azo products **59** (Scheme 10).

V. THE SYNTHETIC POTENTIALITY OF 5-AMINO-PYRAZOLES.

In the following review emphasis will be placed on the reactions leading to the formation of fused azoles as a great advance in the chemistry of 5-aminopyrazoles. In addition to the potential biological importance of fused pyrazoles

Scheme 11



the synthetic approaches to the latter's might also be of interest to be extended to other amino heterocyclic derivatives, thus prompting ideas in this field [6].

A- Synthesis of Pyrazolo[1,5-*a*]pyrimidines.

5-Aminopyrazoles **1** have been extensively utilized for the synthesis of pyrazolo[1,5-a]pyrimidines [13,15,42-46]. With only a few exceptions, all reported syntheses of pyrazolo[1,5-*a*]pyrimidines utilize the cyclocondensation reaction of 5-aminopyrazoles **1** with β-bifunctional reagents [13,15,42-46]. Thus, pyrazolo[1,5-*a*]pyrimidines were isolated from reactions of **1** with β–diketones **60**, β-keto esters **61**, malonic acid derivatives **62**, α,β–unsaturated nitriles **20**, **70** and enaminones **72**, **74**, respectively (Schemes 11, 12 and 13).

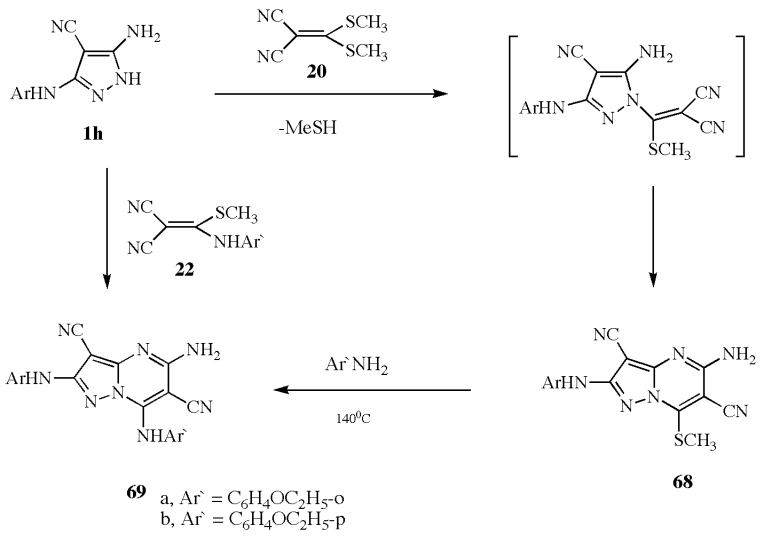
Although the reaction of asymmetric β-diketones **60** with **1f** may lead theoretically [1-3] to the promotion of two isomeric derivatives, in all the reported reactions of this type only one product could be isolated which is the pyrazolo[1,5-*a*]pyrimidine derivative **64**. Generally, the reaction was assumed to proceed *via* the interaction of the most active carbonyl moiety of the diketone with the exocyclic amino function followed by cyclisation (Scheme 11).

Several pyrazolo[1,5-*a*]pyrimidine derivatives have recently been synthesized *via* condensation of 5-aminopyrazole **1g** with β-ketoesters **61** and their structures were identified as **66** [42,43,47,48].

On the other hand, reaction of malonic acid derivatives **62a,b** with **1e** afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **67a,b** (Scheme 11).

The addition of suitably substituted reagents to 5-aminopyrazoles has been extensively utilized as a route for the synthesis of pyrazolo[1,5-*a*]pyrimidines [49,50]. Thus, reaction of compound **20** with 5-aminopyrazole **1h** in refluxing DMF gave the corresponding pyrazolo[1,5-*a*]-pyrimidine **68**. The formation of **68** from dithioacetals **20** proceeds *via* intial alkylation of the ring nitrogen [51] in **1h** followed by cyclisation to give **68** (Scheme 12). Fusion

Scheme 12



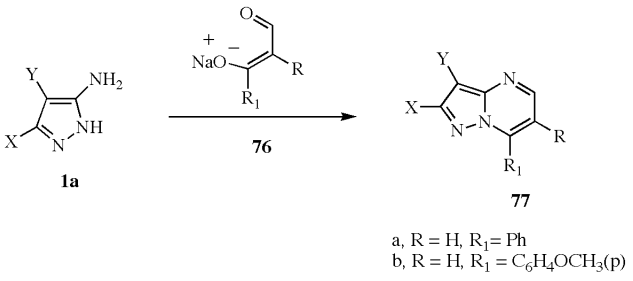
70,71	X	Y	R_1	R_2	R_3
a	NH_2	-N=N-Ar	H	Ar`	CN
b	$-CH_2Ph$	-N=N-Ar	H	H	H

of **62** with aromatic amines at 140 °C furnished the corresponding anilino derivatives **69a,b**. Compounds **69** were also, prepared from reaction of **1h** with **22**.

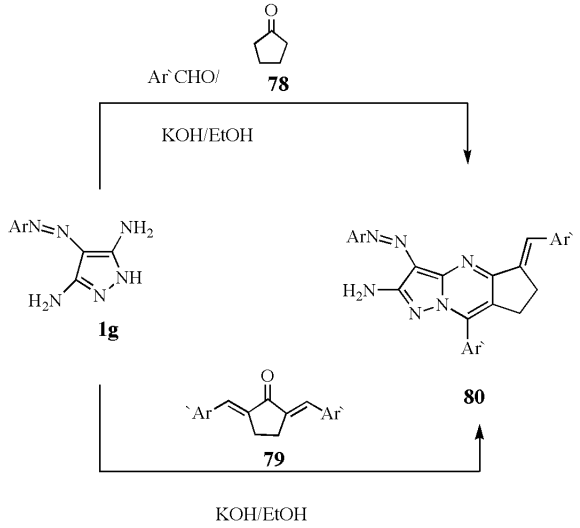
Similarly, 5-aminopyrazoles **1g,y** reacted with aryliden-emalononitriles **63a,b** to give the pyrazolo[1,5-*a*]pyrimidines derivatives **71a,b** [49,52] (Scheme 12).

5-Aminopyrazoles have also been reported to react with β-enaminones **72** and **74** to yield pyrazolo[1,5-*a*]pyrimidines **73** and **75**, respectively [53-57] (Scheme 13).

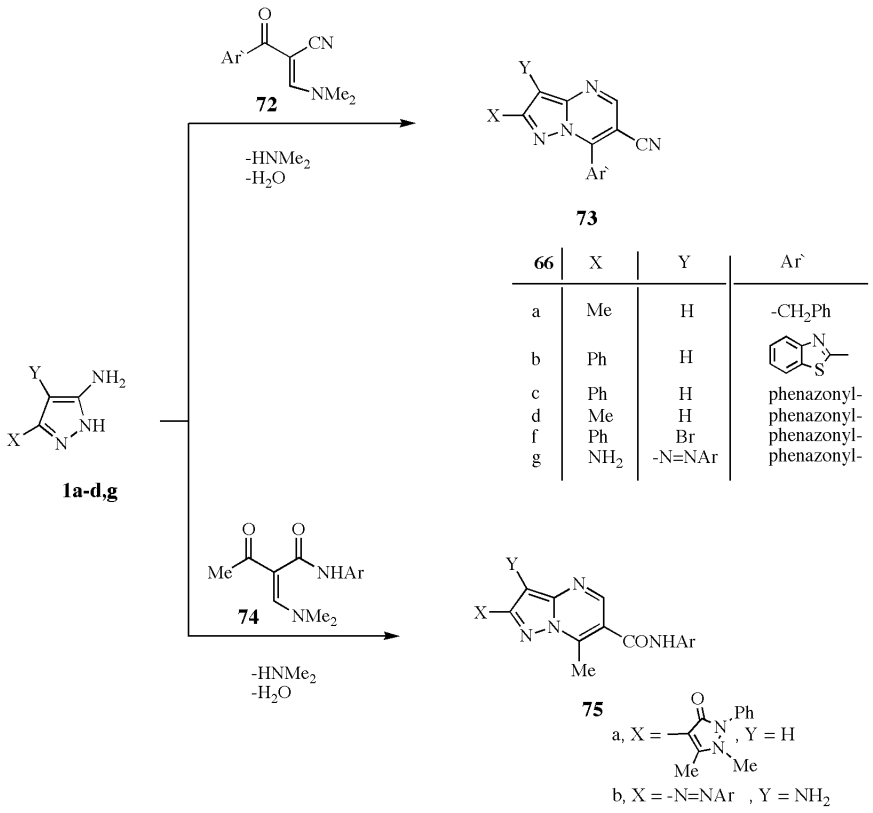
Also, It was found that [58] 5-aminopyrazole **1a** reacts with sodium salts of 3-hydroxymethylene-2-alkanones (**76**) to yield pyrazolo[1,5-*a*]pyrimidine derivatives **77**.



Elgemeie *et al.* [59] have recently reported the synthesis pyrazolo[1,5-*a*]pyrimidine derivatives utilizing 5-aminopyrazoles as starting materials. Thus, 3,5-diaminopyrazole **1g** react with a mixture of aromatic aldehydes and cyclopentanone (**78**) in ethanolic potassium hydroxide to afford pyrazolo[1,5-*a*]pyrimidine derivatives **80**. The same products have also been



Scheme 13



66	X	Y	Ar`
a	Me	H	-CH_2Ph
b	Ph	H	
c	Ph	H	phenazonyl-
d	Me	H	phenazonyl-
f	Ph	Br	phenazonyl-
g	NH_2	-N=NAr	phenazonyl-

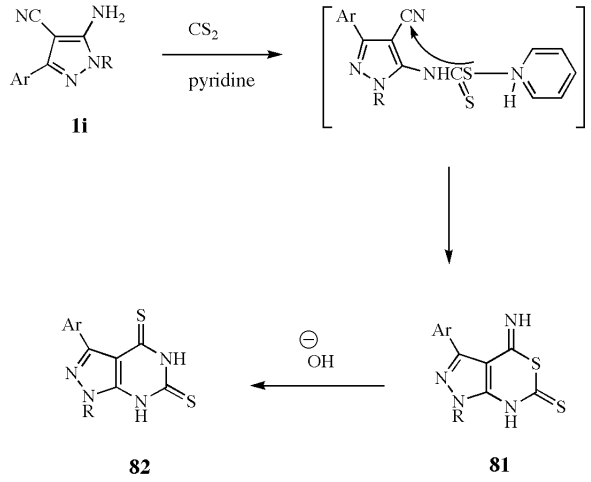
obtained *via* reaction of **1g** with 2,5-((*E*,*E*)-diarylidene)cyclopentanone **79**.

B- Synthesis of pyrazolo[3,4-*d*]pyrimidines.

Because of their biological importance, many recent methods for the synthesis of pyrazolo[3,4-*d*]pyrimidines have been described in the literature [1,2,29,60-64]. Most of these methods utilized the readily available 5-aminopyrazoles as starting materials.

Treatment of **1i** with carbon disulphide in pyridine solution afforded the pyrazolo[3,4-*d*]pyrimidine derivatives **82**. The reaction was considered to proceed *via* the

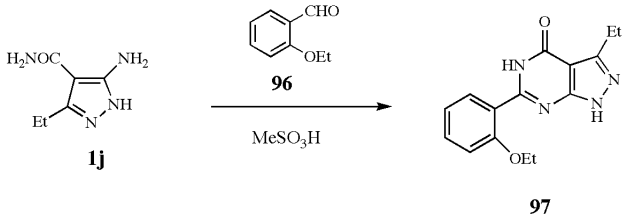
Scheme 14



intermediate formation of the 4-imino-pyrazolo[3,4-*d*]-[1,3]thiazine derivative **81** which rearrange rapidly and irrevesibly by a base catalysed (pyridine) ring –opening and ring closure sequence to yield the final products [1] (Scheme 14).

Simple nitriles were also reported [1,2] to react with **1i** to yield the pyrazolo[3,4-*d*]pyrimidine derivatives **88**. Another route for the synthesis involves the reaction of **1i** with ethyl orthoformate (**85**) to afford the corresponding Schiff's bases **89** which were cyclised by ammonia, amines and guanidine to yield the final pyrimidine derivatives **90**, **91** and **92** respectively. Similarly, **1i** reacts with diethyl oxalate (**84**) to yield **93** which could be converted into the pyrazolo[3,4-*d*]-pyrimidine derivative **95** by the action of diazomethane followed by boiling in ethanolic/ammonia (Scheme 15).

Condensation of compound **1j** with 2-ethoxybenzaldehyde (**96**) afforded the pyrazolo[3,4-*d*]pyrimidine **97** [64].



Also, pyrazolo[3,4-*d*]pyrimidine derivatives **98**, **100**, **102** could be obtained *via* reacting the 5-aminopyrazoles **1k-o** with formamide, aryl isothiocyanate and amide-diacetal reagents respectively, [29,60-63] (Scheme 16).

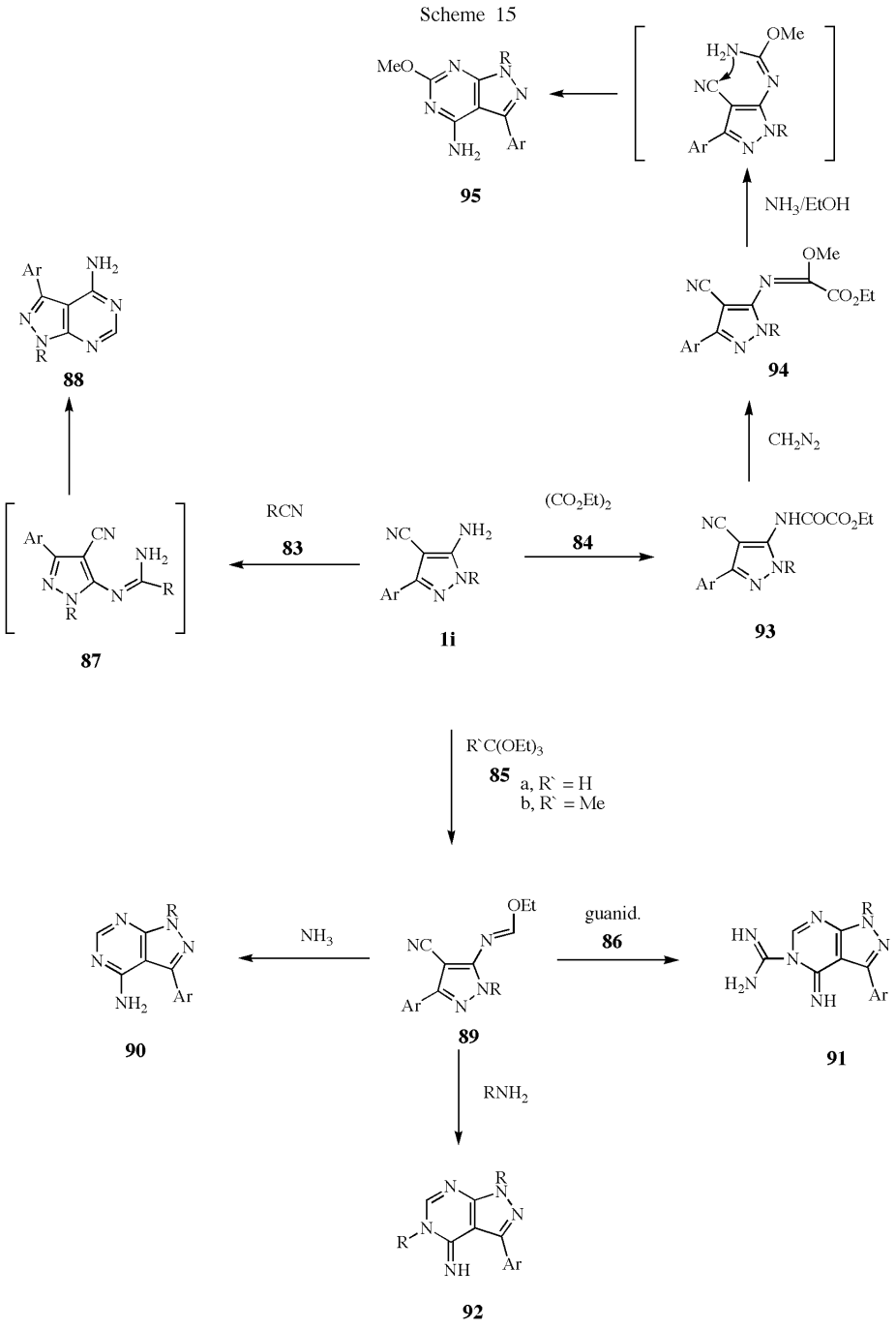
C- Synthesis of Pyrazolo[3,4-*b*]pyridines.

The reactions of 5-aminopyrazoles with β-functional reagents have been shown to afford substituted aminopyrazole derivatives which can be cyclised under a variety of reaction conditions to yield pyrazolo[3,4-*b*]pyridines [64-69]. Thus, cyclocondensation of 5-aminopyrazole derivatives **1p** with active methylene reagents **103** afforded the pyrazolo[3,4-*b*]pyridine derivatives **105a**-**d** (Scheme 17).

Another route for the synthesis of pyrazolo[3,4-*b*]-pyridines has been recently reported [70,71]. This includes the reaction of 5-aminopyrazole-4-carbonitriles **1q,r** with dimethyl acetylenedicarboxylate (**106**) in DMSO to afford the pyrazolo[3,4-*b*]pyridine derivative **107a,b**. The oxidation [71] of **107b** with one equivalent of *m*-chloroperbenzoic acid (**108**) gave the desired sulfoxide products **109** in good yields. Use of excess *m*-chloroperbenzoic acid in this reaction, of course, gave the corresponding sulfons **110** (Scheme 17).

Later on, the same author reported [72-75] the reaction of 5-aminopyrazole **1q,r** with acetylenedicarboxylate (**106**) in the presence of potassium carbonate and subsquent traetment of the filterate with 10 % HCl to afford the pyrazolo[3,4-*b*]pyridine derivative **113**. The mechanism of formation of **113** can be postulated as shown in (Scheme 18). Evidently, the Michael addition adduct produced by addition of dimethyl acetylenedicaroxylate to **1q,r**, in the first step of the process, was then dimerized, followed first by 1,6-cyclization of the cyano group and the enamino carbon and then a second cyclization of the amino group and ester group to give the 3-iminopyrazolo[3,4-*b*]pyridine derivative **112**,

Scheme 15

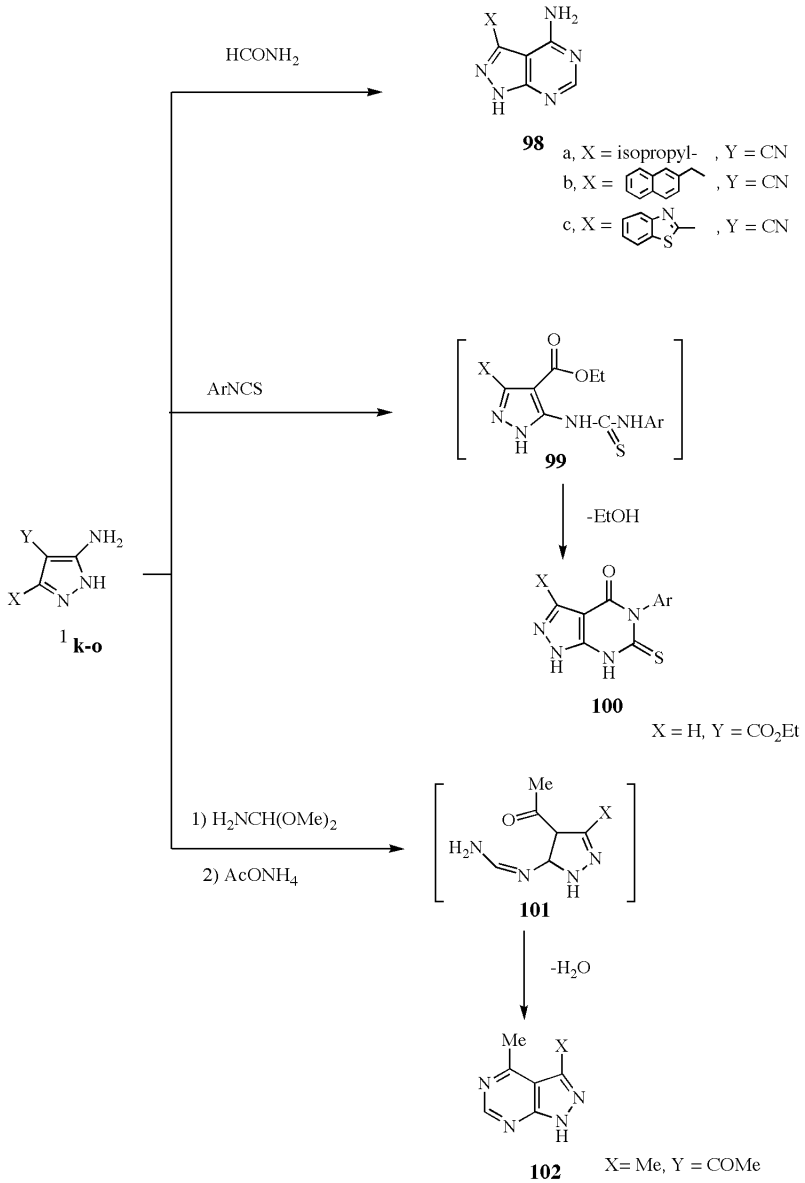


followed by hydrolysis of the imino group to the final product **113**.

Also, pyrazolo[3,4-*b*]pyridines have been synthesized *via* reaction of 5-aminopyrazoles with α,β-unsaturated nitriles [76-79]. Thus 3(5)-aminopyrazole derivatives **114** react with ethoxymethylene malononitrile (**115**) and with dithioketal **20a** to afford the pyrazolo[3,4-*b*]pyridine derivatives **117**, **118**, respectively (Scheme 19).

On the other hand, when the *N*1-nitrogen in 5-aminopyrazole **1d** is substituted by a methyl or aryl group, the reactions of these heterocycles with **119** gave 4,7-dihydropyrazolo[3,4-*b*]pyridines **120a-d** (Scheme 19) as a result of

Scheme 16



pyrazole *C*4-alkylation followed by intramolecular cyclisation [79]. It has been found that the reaction conditions of **119** with *N*1-substituted 5-aminopyrazoles depended profoundly on the electrophilicity of ethylenes. Indeed, the reaction of alkene **119a** with **1d** went to completion within 24 h in acetonitrile at room temperature.

Alkenes **119b,f** reacted similarly. At the same time short time heating was needed for alkylation by alkene **119c** to be brought to completion.

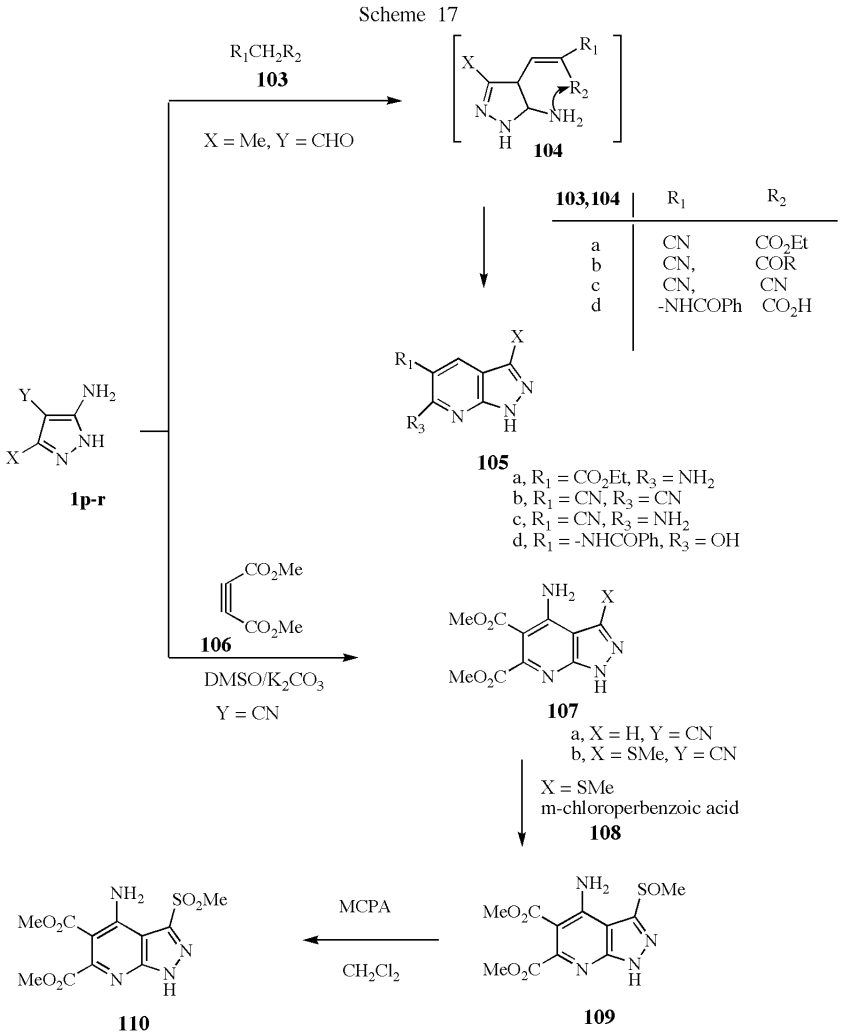
Quiroga *et al.* [80] have reported a new direct and simple synthetic entry into the pyrazolo[3,4-*b*]pyridine ring system. They have found that the 5-aminopyrazole derivative **1d** reacts with β-dimethylaminopropiophenones hydrochloride (**121**) in refluxing pyridine to yield a product of condensation *via* elimination of dimethylamine hydrochloride and water. These products can thus be formulated as **122** or the isomeric **124**. Addition of aryl vinyl ketone, resulting from elimination of

dimethylamine hydrochloride from **121**, to the *C*-4 atom of the pyrazole ring and subsequent cyclization with water elimination gives **123**. On the other hand, addition of an exocyclic amino group to the β-carbon atom of an aryl vinyl ketone followed by cyclization can afford **122**. β-Aminopropiophenones are relatively unstable in basic medium and easily lose the amino group forming aryl vinyl ketones [81,82], a fact which proved the formation of structure **123**. The new dihydropyrazolopyridines **123** are smoothly oxidized to compound **124** by treatment with *N*-bromosuccinimide in ethanol (Scheme 20).

D- Synthesis of Pyrazolo[1,5-*a*]-1,3,5-triazine.

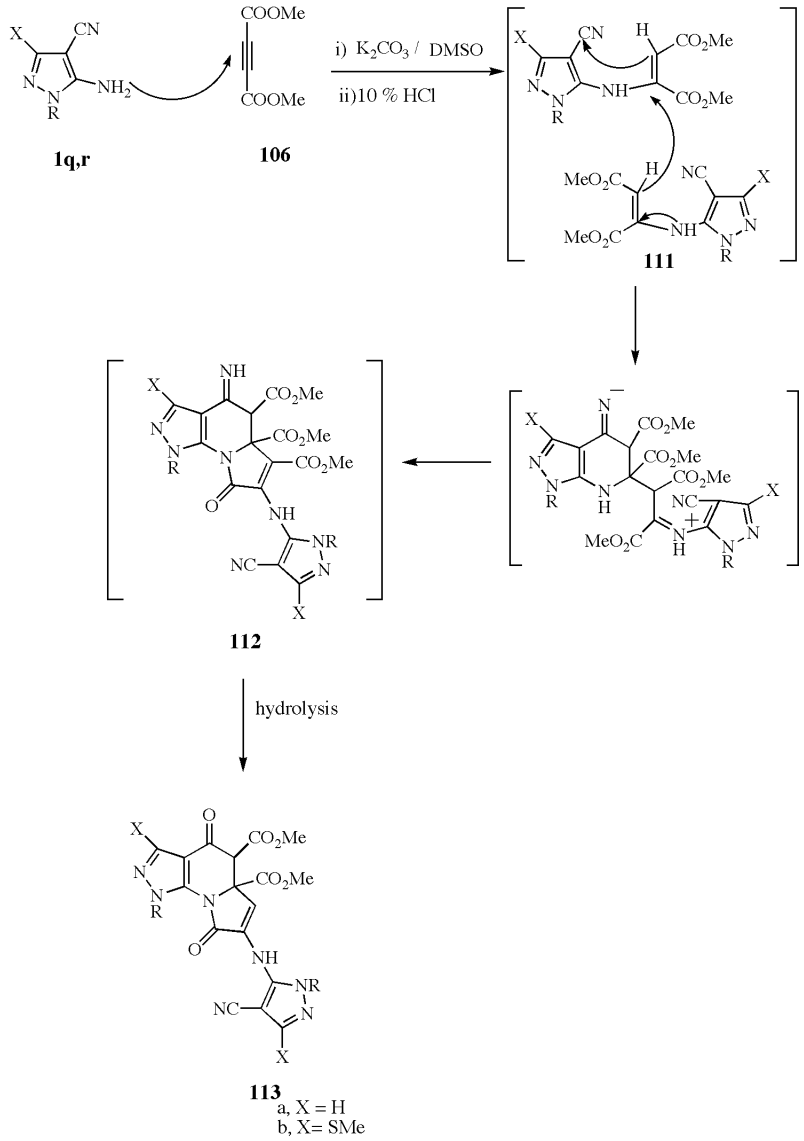
It has been stated that [1,78,79,80] derivatives of this ring system may be considered isomeric with the corresponding purines and might be expected to inhibit various nucleic acid-enzyme systems.

Scheme 17



Moreover, anticancer activity has been reported [83-84] for several pyrazolo[1,5-*a*]-1,3,5-triazines. Pyrazolo-

Scheme 18



[1,5-*a*]-1,3,5-triazines have been generally synthesized *via* the action of ethoxycarbonyl isocyanate **125a** or its thio analogue **125b** on 5-aminopyrazoles to yield *N*-carboethoxy-*N*-(pyrazol-5-yl)ureas **126** [1,85]. Compounds **126** were then either directly cyclised into the corresponding pyrazolo[1,5-*a*]-1,3,5-triazine derivatives **128** or hydrolysed to the corresponding *N*-(pyrazol-5-yl)-urea derivatives **127**. Cyclization of **127** with triethyl orthoacetate **85b** gave the corresponding pyrazolo[1,5-*a*]-1,3,5-triazine derivatives **128** [86] (Scheme 21).

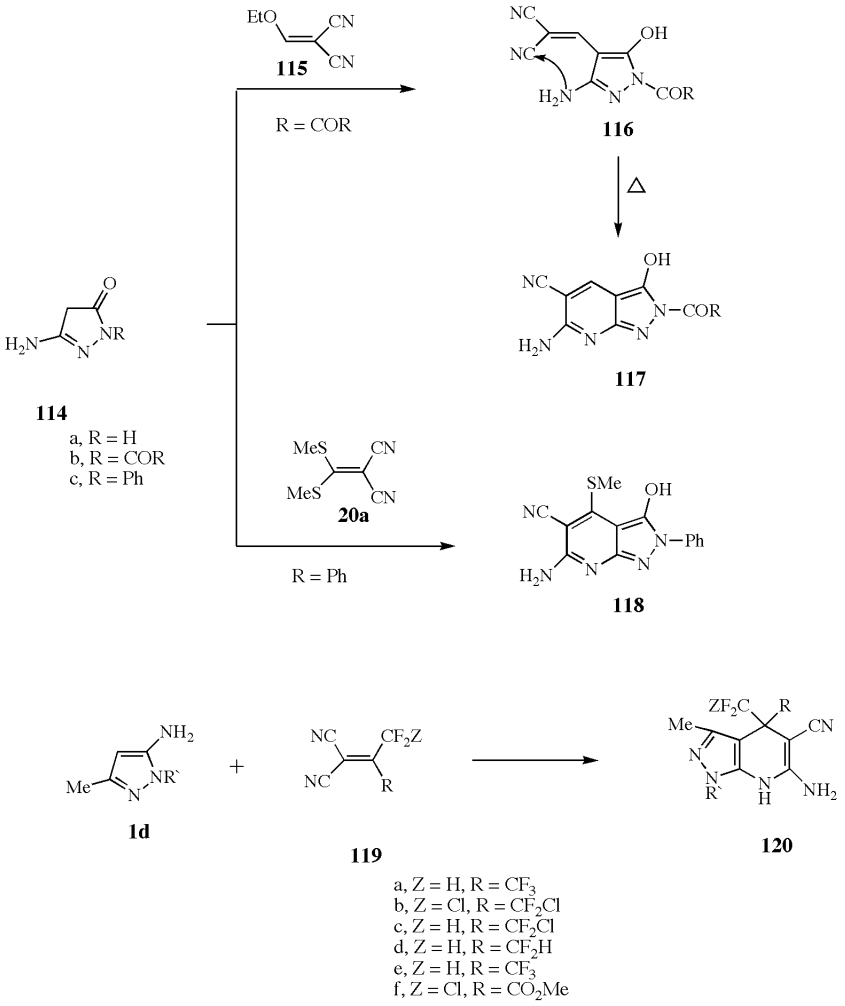
Also, Elgemeie *et al*. [87] have reported the reaction of diaminopyrazole derivatives **1g** with sulfuryl chloride isocyanate (**129**) to afford 7-amino-8-arylazo-1*H*-pyrazolo[1,5-*a*]-1,3,5-triazines (**130**).

Another route for the synthesis of these compounds was recently reported [88]. Thus *N*-cyanodithiocarbonimidic

acid dimethylester **131** was reacted with diaminopyrazole derivative **1g** to afford the pyrazolo[1,5-*a*]-1,3,5-triazine derivative **132**.

An alternative approach for the synthesis of pyrazolo[1,5-*a*]-1,3,5-triazines is reported [90] utilizing 3(5)-aminopyrazoles as the key intermediate. In this

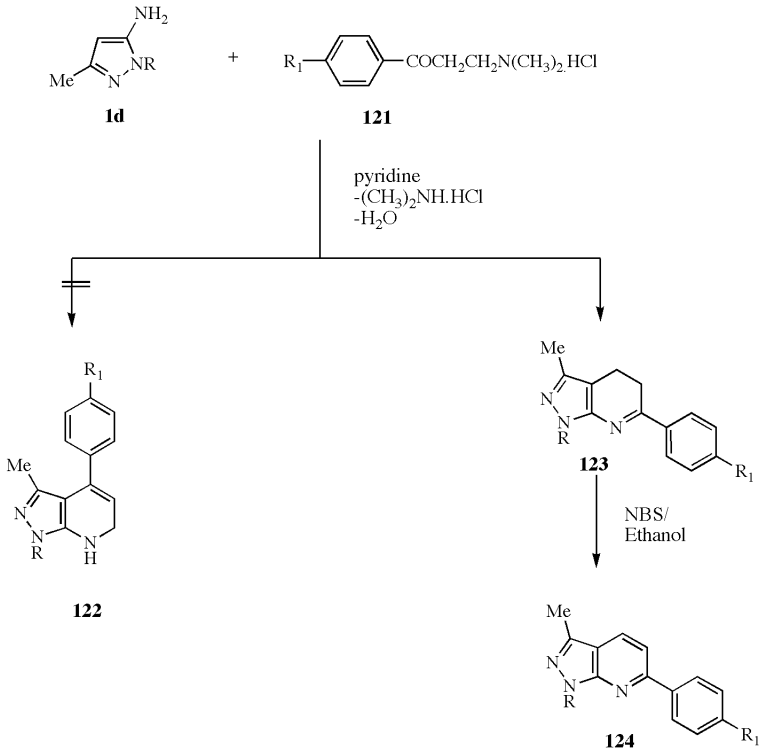
Scheme 19



Reaction of 5-aminopyrazole derivative **1r** with biselectrophilic reagent **133** leads to the formation of the pyrazolo[1,5-*a*]-1,3,5-triazine derivatives **134** [89].

approach, *C*-nucleoside derivatives of the pyrazolo[1,5-*a*]-1,3,5-triazines are synthesized as an important class of compounds that contain a C-C bond instead of the

Scheme 20



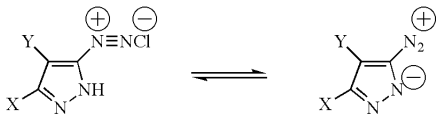
C-N bond between the carbohydrate and the heterocyclic moiety, which stabilizes the glycosylic bond, resulting in a different biological profile. Liang *et al.* [90] reported the formation of pyrazolotriazines **137**, **138** as a mixture of α- and β- isomers. The reaction of **1s** with alkyl *N*-cyanoformamidate **135** gave the anomeric mixture **136** that was deprotected in acidic medium to afford the free nucleosides **137a** and it's α-isomer **137b** (Scheme 22).

E- Synthesis of Pyrazolo[1,5-*c*]-1,2,4-triazines.

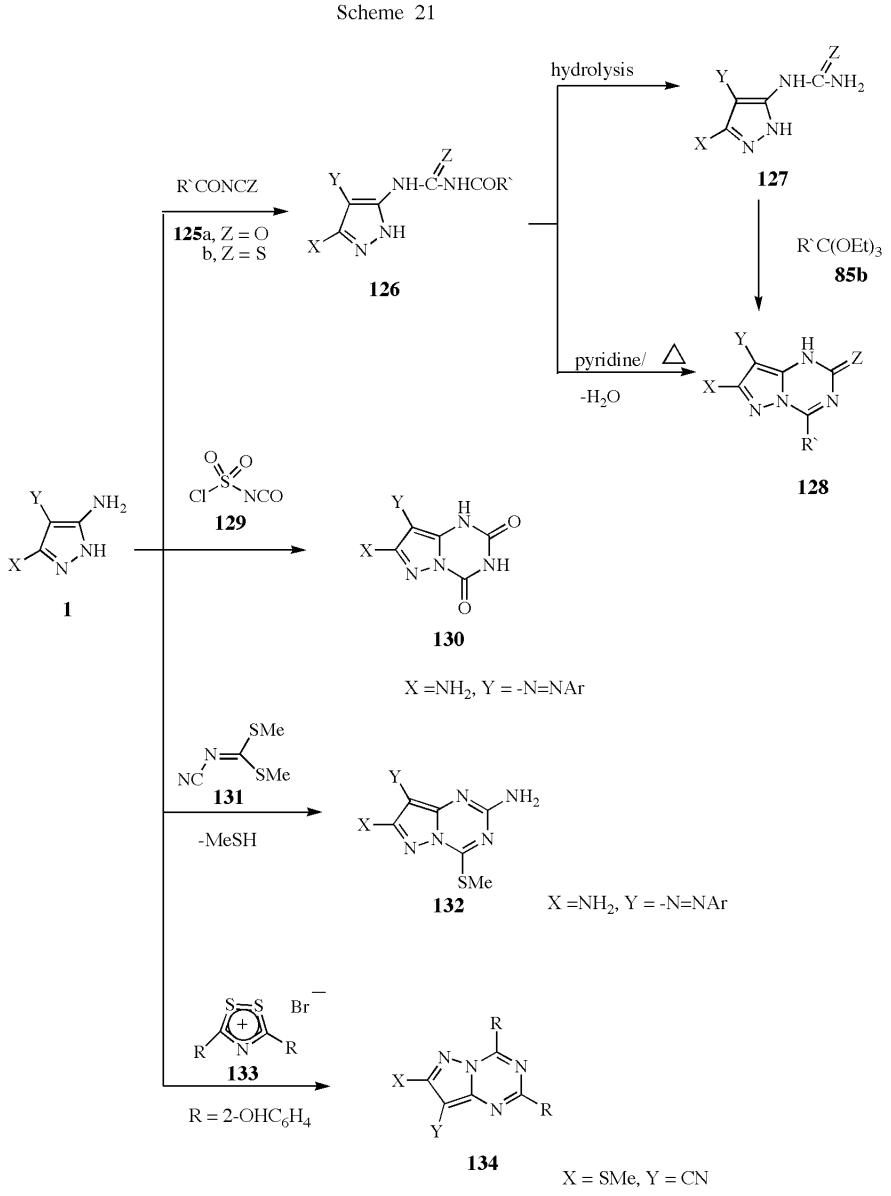
Particular interest has been aroused by tricyclic ring systems bearing a pyrazole moiety, which have shown high affinity for the BDZ receptor, with agonist, antagonist and inverse agonist activity [83-85].

Previous syntheses of this ring system have been carried out exclusively on the reactivity of diazopyrazole as it has been used as a template for the building up of pyrazolo[1,5-*c*]-1,2,4-triazines through [4+2] atom combination either *via* cycloaddition reaction or *via* coupling reaction followed by cyclization.

Ege *et al.* [91] have reported that diazotized aminopyrazoles **138** exist in equilibrium with isolable diazobetaines **139**. The diazobetaines **139** have added a variety of electron-poor and electron–rich systems affording pyrazolo[1,5-*c*]-1,2,4-triazines. Thus, depending on the nature of the reagent and exact reaction conditions either cycloaddition or coupling may take place.



Scheme 21

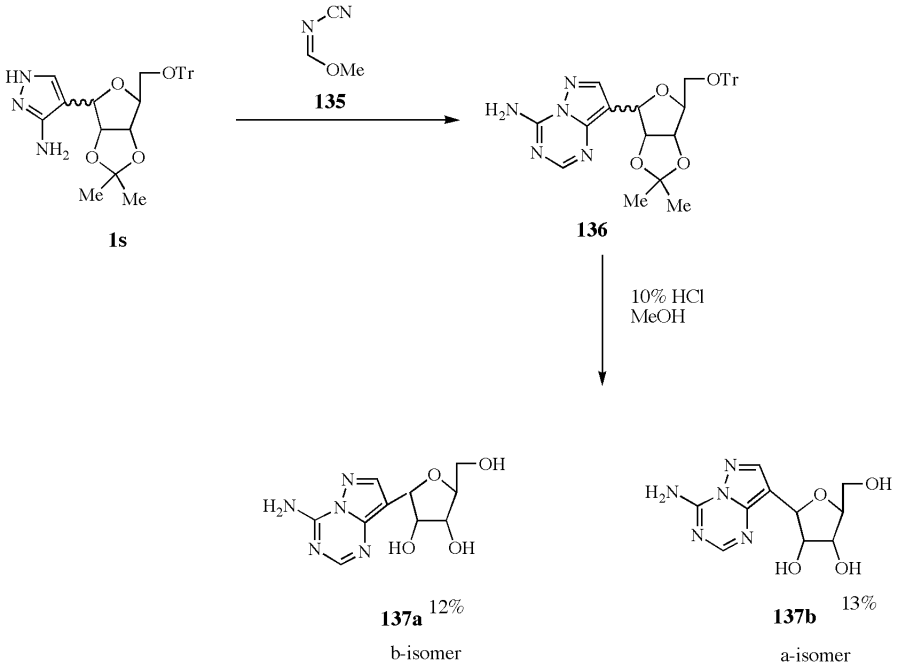


Recent reactions of diazobetaines **139** with enaminones **140**, [92,93] β-naphthol (**142**) [52] and resorcinol (**144**) [52] can be looked at as cycloaddition reactions, that afforded the corresponding target ring systems **141**, **143** and **145** (Scheme 23).

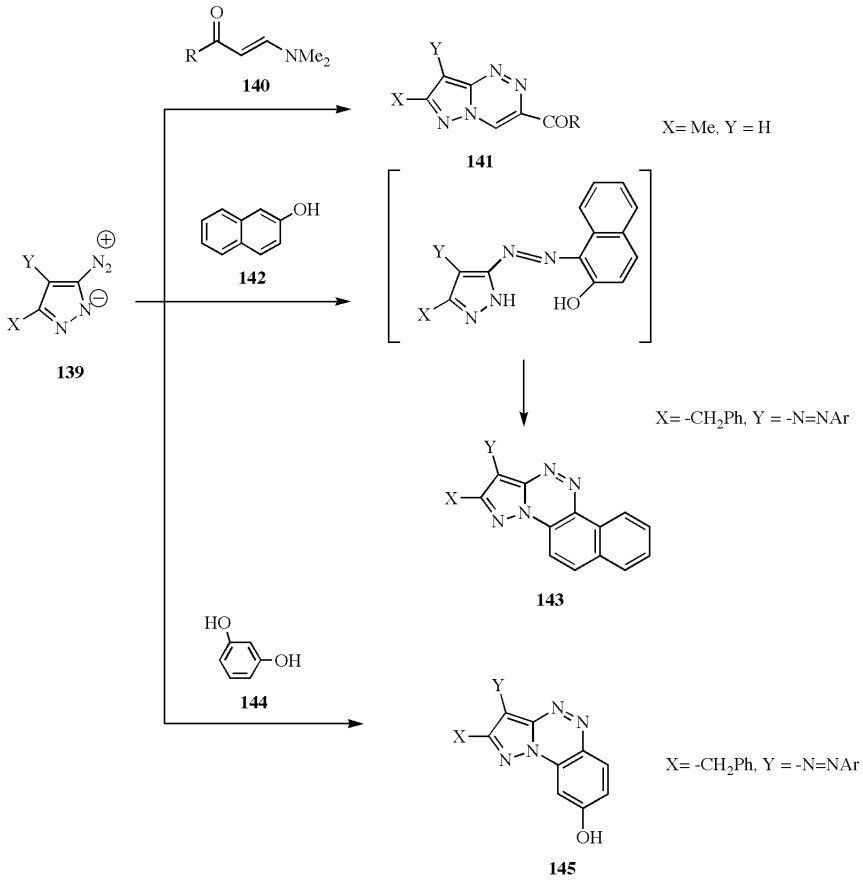
Pyrazolotriazines with phosphonate substituents in position 3 are reported by Ankenbrand *et al*. [94] *via* [4+2] cycloaddition using diazobetaines **139** and phosphonoacetic acid derivatives **146** or nitrile- and benzoylethylphosphonic acid diethylesters **148**, **150**, to give the 3-diethylphosphonatopyrazolo[1,5-*c*]-1,2,4-triazine derivatives **147, 149** and **151** respectively (Scheme 24).

A variety of pyrazolo[1,5-*c*]triazines **153a-d** have been prepared *via* coupling diazotized aminopyrazoles **138** with

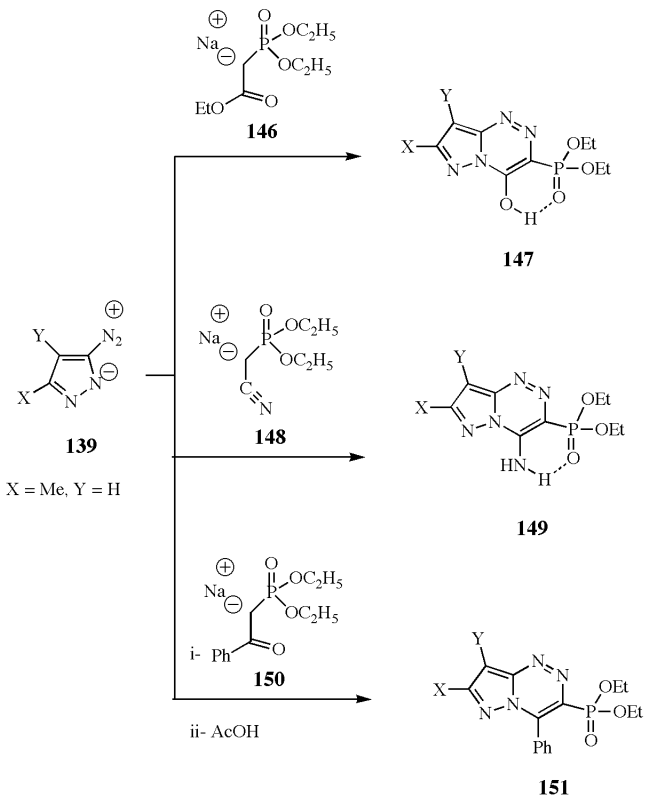
Scheme 22



Scheme 23



Scheme 24



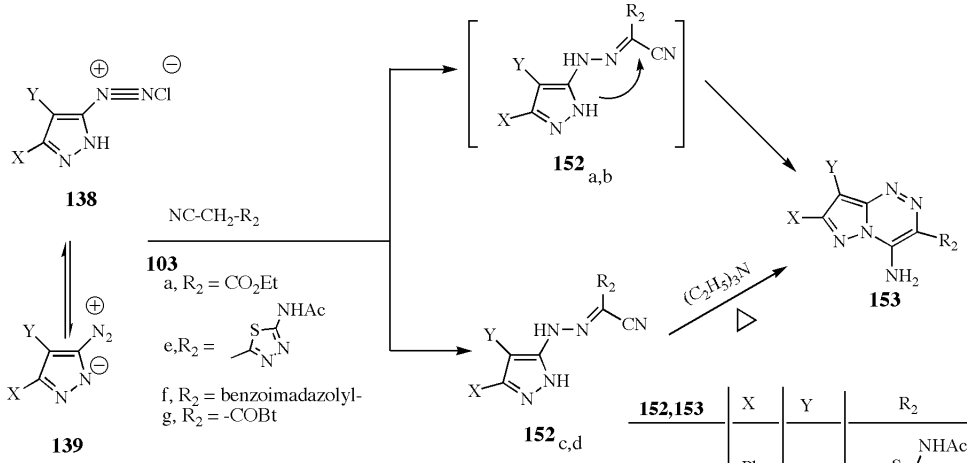
active methylene nitriles **103a,e-g** followed by cyclisation [21,95,96]. The formation of cyclic or acyclic products from the coupling reactions of active methylene compounds with diazotized aminopyrazoles **138** was explained by the mechanistic pathway for the reactions. Coupling with reagents which lead to the direct formation of cyclic products can take place with diazonium salts which exist in equilibrium with diazobetaines **139** *via* a dipolar cycloaddition. When the usual coupling takes place the hydrazones are formed.

Thus, aminopyrazole **138** diazotized with 1,3,4-thiadiazole-2-yl-acetonitrile (**103e**) [97] and benzoimidazolyl acetonitrile (**103f**) yielding the pyrazolo[1,5-*c*]-1,2,4-triazine derivatives **153a,b**. While the reaction of ethyl cyanoacetate (**103a**) and 3-(benzothiazol-2-yl)-3-propionitrile (**103g**) [98] with **138**, afforded the pyrazolotriazine **153c,d** *via* isolable hydrazone **152c,d** (Scheme 25).

In the following reaction the acyclic intermediate **155** could be isolated from the reaction of diazotized aminopyrazole **138** with 2-phenyloxazol-5-(4*H*)-one (**154**) yielding the pyrazolo[1,5-*c*]-1,2,4-triazine derivative **157** *via* ring opening of **155** to form the intermediate **156**, by the action of phenol [99] (Scheme 26).

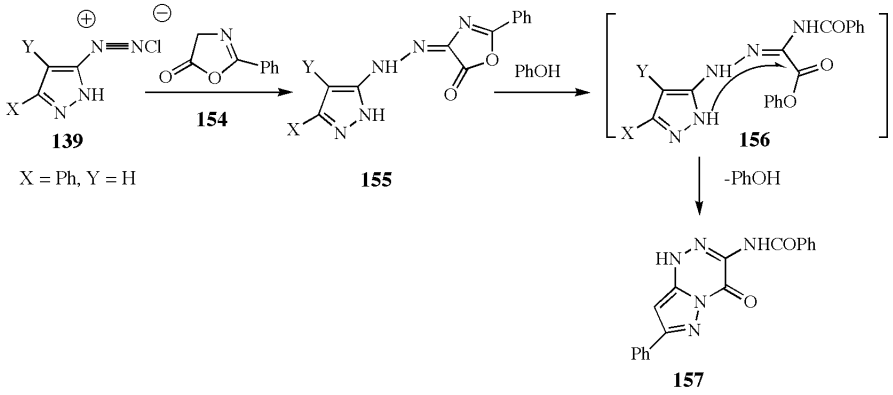
A series of pyrazolo[1,5-*c*]-1,2,4-triazine-5-oxides **158** have been synthesized [89] from 1-(2-nitrophenyl-5-aminopyrazole derivative **1t** which cyclized to the triazine system **158** in 10% NaOH at room temperature.

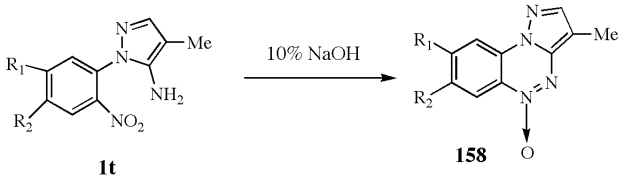
Scheme 25



152,153	X	Y	R_2
a	Ph	H	
b	Ph	H	benzoimadozolyl-
c	SMe	CN	CO_2Et
d	Ph	H	COBt

Scheme 26





F- Synthesis of other Pyrazolotriazines.

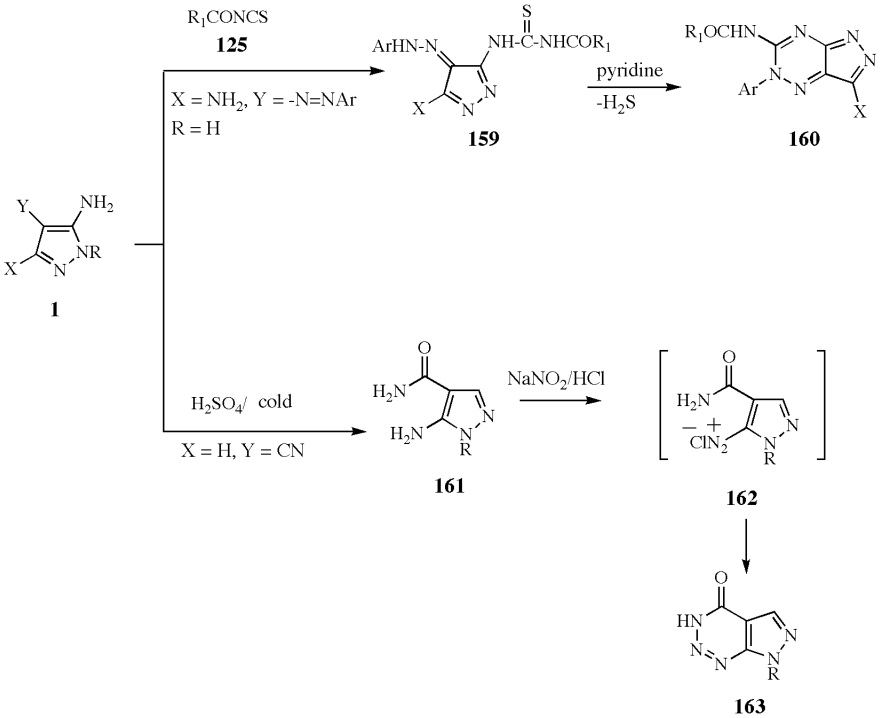
It has been reported that the thiourea derivative **159**, obtained *via* the reaction of 5-aminopyrazole **1g** with benzoyl or ethoxycarbonyl isothiocyanates **125** cyclises into the pyrazolo[3,4-*e*]-1,2,4-triazine derivatives **160** on treatment with pyridine [1].

On the other hand, pyrazolo[4,3-*e*]-1,2,3-triazine-4-ones **163** [100-102] were synthesized *via* diazotizing **161**, obtained by treatment of **1q** with sulfuric acid. The formation of these products were assumed to proceed *via* the sequence demonstrated in (Scheme 27).

G- Synthesis of Pyrazolo[3,4-*b*]pyrazines.

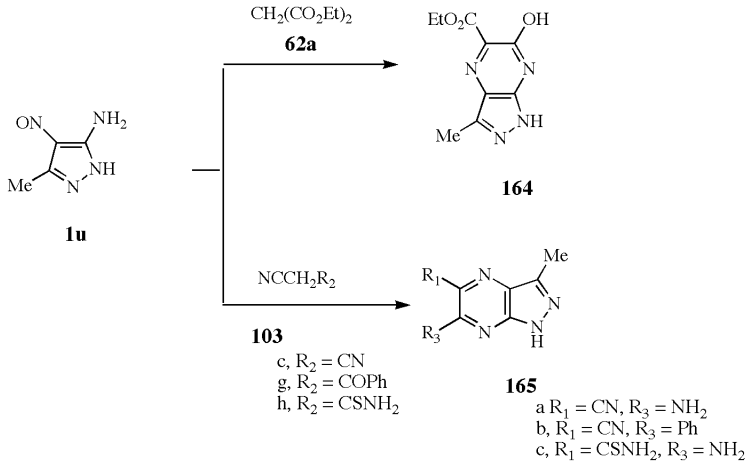
Derivatives of this ring system are obtained by condensing 5-aminopyrazole **1u** with diethylmalonate (**62a**) to yield pyrazolo[3,4-*b*]pyrazine **164** [103]. Also, treatment of **1u** with active methylene nitriles **103c,g,h** afforded

Scheme 27



pyrazolo[3,4-*b*]pyrazine derivatives **165a-c** [104] (Scheme 28).

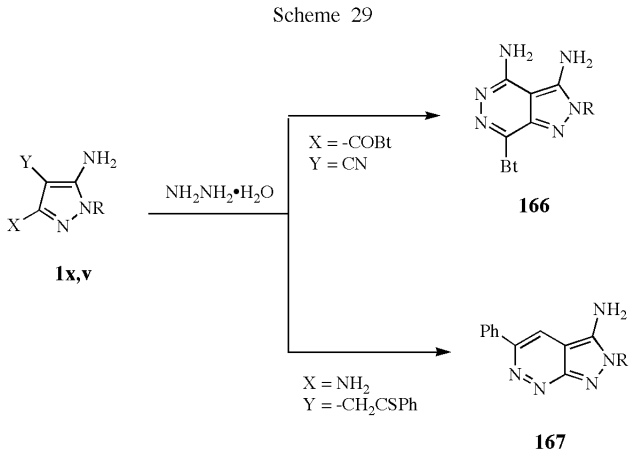
Scheme 28



H- Synthesis of Pyrazolopyridazines.

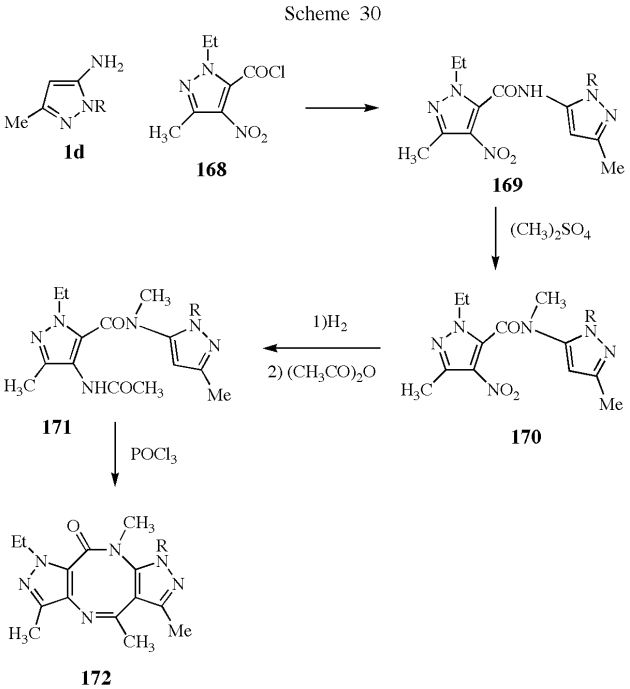
Derivatives of this ring system are reported [61,105] from 5-aminopyrazole intermediate. Thus, 5-aminopyrazole **1x** is converted into pyrazolo[3,4-*d*]pyridazine [59] derivative **166** upon cyclocondensation with hydrazine hydrate in DMF, while refluxing **1v** with the same reagent afforded the pyrazolo[3,4-*c*]pyridazine derivative **167** [106] (Scheme 29).

Scheme 29



novel route [109,110] for the synthesis is obtained by the Bischler-Napieralski cyclization reaction on pyrazol-4-carboxamides **171**. Thus, the reaction of 5-pyrazolecarbonyl chloride **168** with 5-aminopyrazoles **1d** gave, 5-pyrazoleamides **169**, key intermediate in the synthesis of the tricyclic system **172**. Treatment of **169** with dimethylsulfate followed by hydrogenation and acetylation afforded **171** which gave the pyrazolo[3,4-*b*:4',3'-*f*]-[1,5]diazocin derivative **172** upon treatment with $POCl_3$ (Scheme 30).

Scheme 30



I- Synthesis of Pyrazolo[3,4-*b*:4',3'-*f*][1,5]diazocin.

This class of fused pyrazoles has acquired considerable importance because of their interesting pharmaceutical and microbiological properties [10,106-108]. An interesting

J-Synthesis of Benzimidazo[1,2-*b*]pyridine.

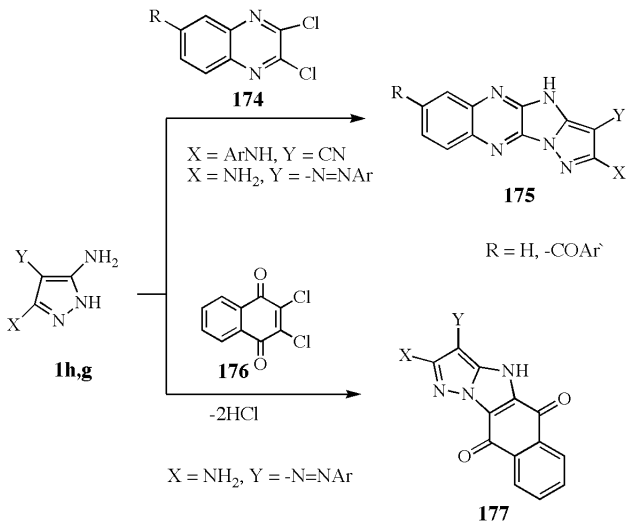
It has been reported [30] that 5-aminopyrazole **1h** can be converted to the corresponding triazacyclopenta[*a*]indene derivative **173** upon heating with lead oxide in dioxane for 30 min.

1h **173**

K-Synthesis of Pyrazolo[2,5-*d*]imidazo[4',5'-*b*]quinoxaline and Naphtho[3,2-*e*]imidazo[1',2'-*b*']pyrazole.

5-Aminopyrazoles **1g,h** react with 2,3-dichloroquinoxalines **174** to afford the pyrazolo[2,5-*d*]imidazo[4',5'-*b*]-quinoxaline derivatives **175** [111]. While reacting 3,5-diaminopyrazole **1g** with 2,3-dichloronaphthoquinone **176** afforded the naphtho[3,2-*e*]imidazo[1',2'-*b*']pyrazole derivative **177** [50].

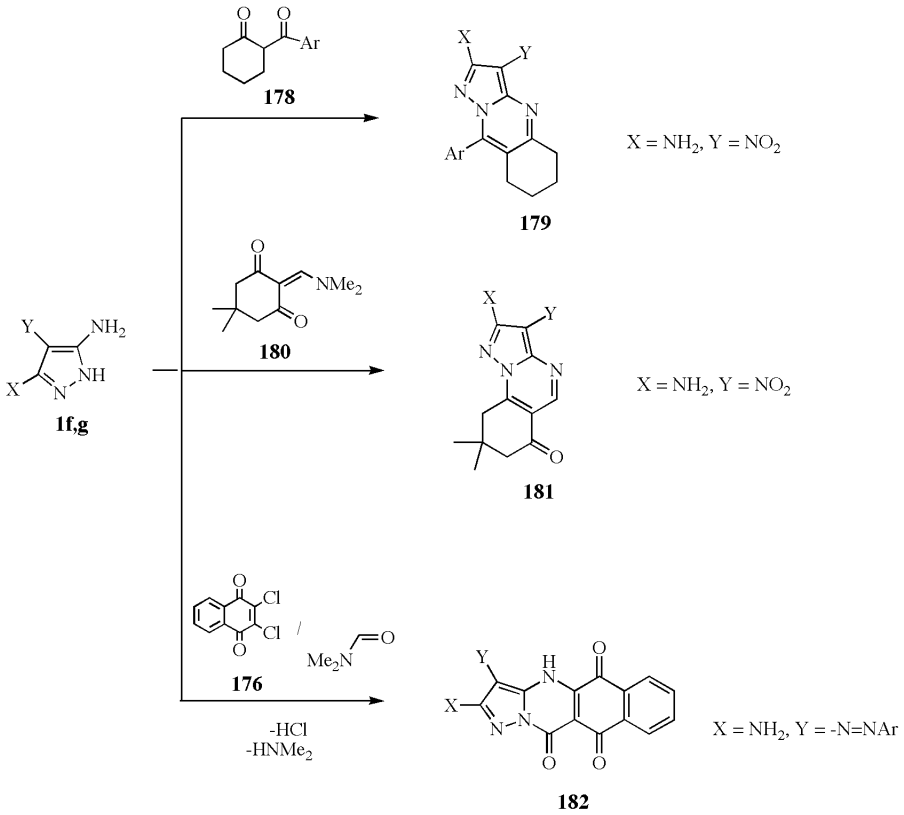
Scheme 31



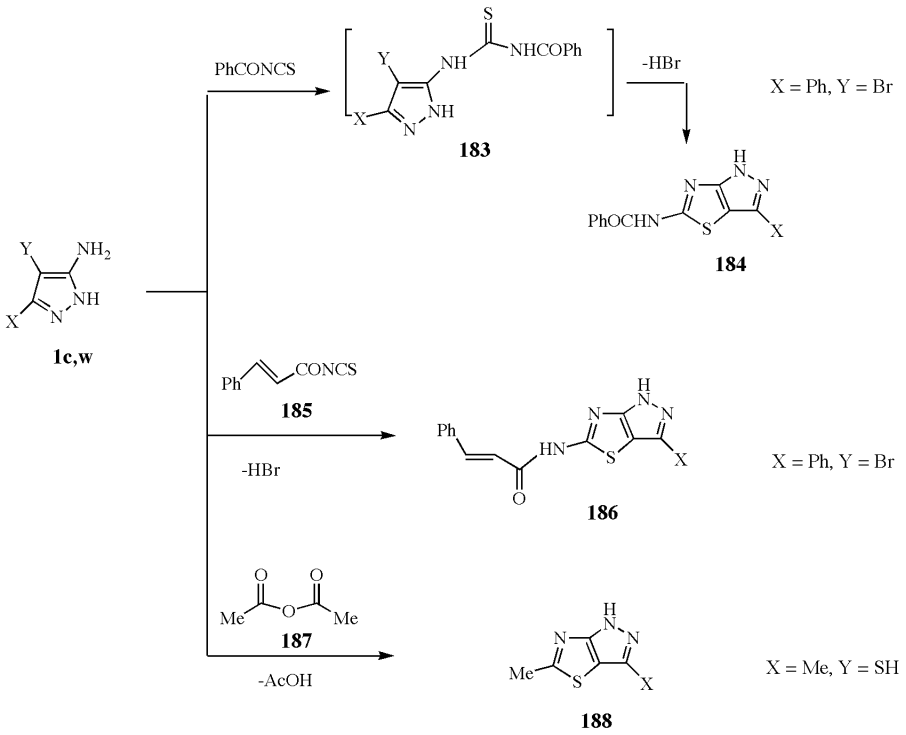
L- Synthesis of Pyrazoloquinazolines.

The reaction of 5-aminopyrazoles **1** with cyclic ketones is a well established route [44,112,113] for the synthesis of this ring system. Thus 3,5-diaminopyrazole **1f** reacted with aroylcyclohexanone **178** to yield the pyrazolo[5,1-*b*]-

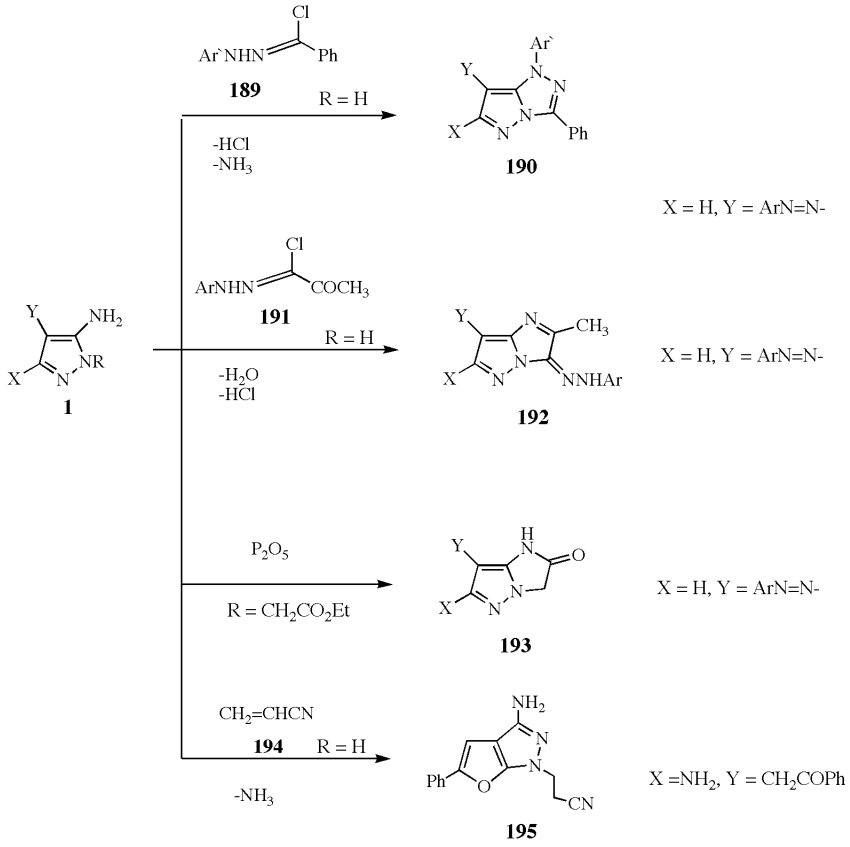
Scheme 32



Scheme 33



Scheme 34



quinazoline derivative **179** [44].

On the other hand, reacting **1f** with dimethylcyclohexane-1,3-dione derivative **180** gave the corresponding pyrazolo[1,5-*a*]quinazoline derivative **181** [112].

Another route for the synthesis of the targeted compound was achieved by reacting **1g** with 2,3-dichloronaphthoquinone (**176**) and DMF to yield the pyrazolo[2,3-*a*]-quinazoline derivative **182** [113] (Scheme 32).

M- Synthesis of Pyrazoles fused to five Membered Rings.

It has been reported [1] that 5-aminopyrazole **1c** reacted with benzoyl isothiocyanate to afford the pyrazolo[4,5-*d*]-thiazole derivative **184**. On the other hand, compound **1c** reacted with 3-phenylacryloyl isothiocynate (**185**) to yield the pyrazolo[3,4-*d*]thiazole derivative **186** [114].

Also, 5-aminopyrazole **1w** reacted with acetic anhydride (**187**) to yield the pyrazolo[3,4-*d*]thiazole derivative **188** [115] (Scheme 33).

Several synthesis of pyrazolo[1,5-*c*]-1,2,4-triazoles, imidazo[1,2-*b*]pyrazoles and furo[2,3-*c*]pyrazoles have been reported [1,116] in the literature and are summarized in (Scheme 34).

VI. REFERENCES

[1] M. H. Elnagdi, F. M. Abdel-Galil, B. Y. Riad and G. H. Elgemeie, *Heterocycles*, **20**, 2437 (1983) and references cited therein.

[2] M. H. Elnagdi, F. A. Abd-Elaal and G. H. Elgemeie, *Heterocycles*, **23**, 3121 (1985) and references cited therein.

[3] M. H. Elnagdi, M. R. Elmoghayar and G. H. Elgemeie, *Adv. Heterocycl. Chem.*, **41**, 319 (1988) and references cited therein.

[4] M. H. Elnagdi, M. R. Elmoghayar and K. U. Sadek, *Adv. Heterocycl. Chem.*, **48**, 223 (1991) and references cited therein.

[5] R. H. Wiley and P. Wiley, 'Pyrazolones, Pyrazolidones and Derivatives', John Wiley and Sons, New York, 1964.

[6] L. C. Behr, R. Fusco and C. H. Jarboe, 'The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings', eds. By A. Weissberger, Interscience Publishers, New York, 1967.

[7] R. M. Mohareb, S. M. Sherif and H. F. Zohdi, *J. Chin. Chem. Soc.*, **40**, 181 (1993).

[8] S. A. El-Hawash and A. I. El-Malla, *Pharmazie*, **53**, 368 (1998).

[9] M. Takahashi and K. Chigira, *J. Heterocyclic Chem.*, **32**, 207 (1995).

[10] C. P. Kordik, C. Luo, B. C. Zanoni, S. L. Dax, J. J. McNally, T. W. Lovenberg, S. J. Wilson and A. B. Reitz, *Bioorg. Med. Chem. Lett.*, **11**, 2283 (2001).

[11] M. A. Youngman, J. J. McNally, T. W. Lovenberg, A. B. Reitz, N. M. Willard, D. H. Nepomuceno, S. J. Wilson, J. J. Crook, D. Rosenthal, A. H. Vaidya and S. L. Dax, *J. Med. Chem.*, **43**, 346 (2000).

[12] S. P. Watson, R. D. Wilson, D. B. Judd and S. A. Richards, *Tetrahedron Lett.*, **38**, 9065 (1997).

[13] M. Jachak, U. Krießmann, M. Mittlbach and H. Junek, *Monatsh. Chem.*, **124**, 199 (1993).

[14] A. A. Hassanien, A. E. Amr and S. A. S. Ghozlan, *J. Chin. Chem. Soc.*, **47**, 1273 (2000).

[15] Z. E. Kandeel, *J. Chem. Res. (S)*, 290 (1995).

[16] M. G. A. Shvekhgeimer and O. A. Ushakova, *Chem. Heterocyl. Compd.*, **37**, 370 (2001).

[17] A. Echevarria, M. Martin, C. Perez and I. Rozas, *Arch. Pharm.(Weinheim Ger.)*, **327**, 303 (1994).

[18] T. Ryckmans, H. Viehe, J. Feneau-Dupont, B. Tinant and J. Declerq, *Tetrahedron*, **53**, 1729 (1997).

[19] D. Fouque, E. About-Jaudet and N. Collingnon, *Synth. Commun.*, **25**, 3443 (1995).

[20] N. P. Solov'eva, V. A. Makarov and V. G. Granik, *Chem. Heterocycl. Compd.*, **33**, 85 (1997).

[21] M. A. Raslan, R. M. Abd El-Aal, M. E. Hassan, N. A. Ahmed and K. U. Sadek, *J. Chin. Chem. Soc.*, **48**, 91 (2001).

[22] J. S. Larsen, M. A. Zahran, E. B. Pedersen and C. Nielsen, *Monatsh. Chem.*, **130**, 1167 (1999).

[23] H. G. Krug, R. Neildein, R. Boese and W. Kramer, *Heterocycles*, **41**, 721 (1995).

[24] G. H. Elgemeie, A. H. Elghandour, A. M. Elzanate and S. A. Ahmed, *J. Chem. Soc. Perkin Trans.1*, **21**, 3285 (1997).

[25] P. Traxler, G. Bold, J. Frei, M. Lang and N. Lydon, *J. Med. Chem.*, **40**, 3601 (1997).

[26] N. K. Mohamed, A. A. Hassan, Y. R. Ibrahim and A. E. Mourad, *Arch. Pharm.(Weinheim Ger.)*, **326**, 245 (1993).

[27] R. J. Lu and H. Z. Yang, *Tetrahedron Lett.*, **38**, 5201 (1997).

[28] D. B. Nilov, N. P. Solov'eva, I. S. Nikolaeva, V. V. Peters and L. Yu. Krylova, *Pharm. Chem. J.*, **32**, 7, 16 (1998).

[29] B. C. Kraybill, L. L. Elkin, J. D. Blethrow, D. O. Morgan and K. M. Shokat, *J. Amer. Chem. Soc.*, **124**, 12118 (2002).

[30] R. Kluge, M. Schulz, M. Pobisova and M. Nuechter, *Chem. Ber.*, **127**, 1729 (1994).

[31] C. F. Beam, S. E. Davis, T. L. Cordray, K. W. Chan, C. M. Kassis, J. G. Freeman Davis, G. M. Latham, T. S. Guion, K. C. Hilderbran, A. Cameron Church, M. U. Koller, C. R. Metz, W. T. Pennington and K. L. Schey, *J. Heterocyclic Chem.*, **34**, 1549 (1997).

[32] R. D. Wilson, S. P. Watson and S. A. Richards, *Tetrahedron Lett.*, **39**, 2827 (1998).

[33] D. E. Tupper and M. R. Bray, *Synthesis*, **3**, 337 (1997).

[34] A. W. Erian, S. I. Aziz, A. M. Negm and S. M. Sherif, *J. Chem. Res.(M)*, 9, 2301 (1993).

[35] D. H. Hutaud, M. Baudy-Floch'h, P. Gougeon, P. Gall and P. Le Grel, *Synthesis*, **16**, 2435 (2001).

[36] N. Bodor, M. J. S. Dewar and A. J. Harjet, *J. Amer. Chem. Soc.*, **92**, 2929 (1970).

[37] J. Elguero, R. Jacquier and S. Magonae-Mondon, *Bull. Soc. Chim. France*, 4436 (1970).

[38] R. S. Sagitullin, A. N. Kost and N. N. Borisov, *Chem. Heterocycl. Compd.*, **8**, 1237 (1972).

[39] A. S. Bailey and A. J. Buckley, *J. Chem. Soc., Perkin Trans.1*, 1973 (1943).

[40] L. R. Swett, J. D. Ratajcsyk, C. W. Nordeen and G. H. Aynillan, *J. Heterocyclic Chem.*, **12**, 1137 (1975).

[41] M. A. Sofan, F. M. El-Taweel, T. M. Abu Elmaati and A. A. Elagamey, *Pharmazie*, **49**, 482 (1994).

[42] T. M. Abu Elmaati and F. M. El-Taweel, *J. Chin. Chem. Soc.*, **50**, 413 (2003).

[43] F. M. El-Taweel and T. M. Abu Elmaati, *J. Chin. Chem. Soc.*, **49**, 1051 (2002).

[44] V. A. Makarov, V. A. Tafeenko and V. G. Granic, *Chem. Heterocycl. Compd.*, **34**, 1423 (1998).

[45] R. A. Nugent, C. J. Dunn, N. D. Staite, M. J. Murphy and S. T. Schlachter, *Phosphorus, Sulfur Silicon Relat. Elem.*, **109**, 229 (1996).

[46] V. V. Chernyshev, A. N. Fitch, E. J. Sonneveld, A. I. Kurbakov, V. A. Makarov and V. A. Tafeenko, *Acta Crystalogr. Sect.B*, **44**, 554 (1999).

[47] M. A. Sofan, F. M. El-Taweel, T. M. Abu Elmaati and A. A. Elagamey, *Indian. J. Chem.*, **33B**, 738 (1994).

[48] V. I. Filyakova, O. A. Kuznetsova, E. N. Ulomskii, T. V. Rybalova, Yu. V. Gatilov, M. I. Kodess, V. I. Rusinov and K. I. Pashkevich, *Russ. Chem*, **51**, 332 (2002).

[49] M. A. Zahran, A. M. El-Sherif, M. S. El-Gaby, Y. A. Ammar and U. H. El-Said, *Farmaco*, **56**, 277 (2001).

[50] M. S. El-Gaby, Z. A. Sayed, F. A. Abu-Shanab and A. M. Hussein, *Phosphorous, Sulfur Relat. Elem*., **164**, 1 (2000).

[51] G. H. Elgemeie, S. E. Elezaby, H. A. Ali and A. Mansour, *Bull. Chem. Soc. Jpn*., **67**, 738 (1994).

[52] M. M. Abdel Khalik, *J. Chem. Res. (M)*, 6, 1377 (1997).

[53] I. E. Al-Afaleq, *Synth. Commun*., **30**, 1985 (2000).

[54] M. A. Al-Shiekh, K. M. Al-Zaydi and E. A. Hafez, *J. Chem. Res.(M)*, **1**, 173 (2000).

[55] K. M. Dawood, A. M. Farag and Z. E. Kandeel, *J. Chem. Res.(M)*, 537 (1999).

[56] T. M. Abu Elmaati, *Acta Chim. Slov*., **49**, 721 (2002).

[57] T. M. Abu Elmaati, S. B. Said, N. S. Abu Elenein, M. A. Sofan and M. N. Khodeir, *Polish J. Chem*., **76**, 945 (2002).

[58] G. H. Elgemeie and N. H. Metwally, *Monatsh. Chem*., **131**, 779 (2000).

[59] G. H. Elgemeie and H. A. Ali, *Synth. Commun*., **32**, 253 (2002).

[60] A. M. Farag and K. Dawood, *Heteroat. Chem*., **8**, 45 (1997).

[61] R. H. Khan and R. C. Rastogi, *J. Chem. Res. (S)*, 410 (1993).

[62] V. A. Dorokhov, A. V. Komkov and B. I. Ugrak, *Izv. Akad. Nauk. Ser. Khim*., **8**, 1429 (1996).

[63] S. Guccione, L. M. Scolaro and F. Russo, *J. Heterocylic Chem*., **33**, 459 (1996).

[64] E. R. Bacon and B. Singh, *Inc. USA PCT Int. Appl. W. O*. 9628, 448 (1996); *Chem. Abstr*., **126**, 117991k (1997).

[65] M. H. Elnagdi, A. M. Negm and K. U. Sadek, *Synlett*, 27 (1994) and references cited therein.

[66] A. Z. A. Elassar, Y. M. Elkholy and M. H. Elnagdi, *J. Prakt. Chem*., **340**, 491 (1998) and references cited therein.

[67] A. M. Hussein and T. I. El-Emary, *J. Chem. Res. (S)*, 20 (1998).

[68] G. Sabitha, R. Srividya, B. Archana and J. S. Yadav, *Synth. Commun*., **29**, 655 (1999).

[69] V. K. Ahluwalia and B. Goyal, *Synth. Commun*., **26**, 1341 (1996).

[70] Y. Tominaga, N. Yoshinori, S. Kataoka, N. Aoyama, T. Masonari and A. Miike, *Tetrahedron Lett*., **36**, 8641 (1995).

[71] Y. Tominaga, K. Sasaki and R. N. Castle, *J. Heterocyclic Chem*., **35**, 1219 (1998).

[72] Y. Tominaga and K. Nomoto, *Heterocycles*, **37**, 235 (1994).

[73] Y. Tominaga, J. K. Luo, L. W. Castle and R. N. Castle, *J. Heterocyclic Chem*., **30**, 267 (1993).

[74] Y. Tominaga, R. N. Castle and N. K. Daily, *J. Heterocyclic Chem*., **30**, 295 (1993).

[75] Y. Tominaga, N. Yoshioka, R. N. Castle, J. Luo and T. Hata, *J. Heterocyclic Chem*., **34**, 613 (1997).

[76] Y. Matsuda, H. Matsumoto, S. Ide, K. Furuno, T. Kazuki, I. Katsura, T. Itou and C. Motokawa, *Yakugaku Zasshi*, **113**, 32 (1993).

[77] G. H. Elgemeie, A. H. Elghandour and A. M. Alzanate, *J. Chem. Res. (S)*, 256 (1997).

[78] M. T. Cocco, C. Congiu and V. Onnis, *J. Heterocyclic Chem*., **31**, 925 (1994).

[79] A. S. Golubev, P. V. Pasternak, A. F. Shidlovskii, L. N. Saveleva, B. B. Averkiev, V. N. Nestrov, M. Yu. Antipin, A. S. Peregudov and N. D. Chkanikov, *J. Fluorine Chem*., **114**, 63 (2002).

[80] J. Quiroga, B. Insuasty, S. Cruz, P. Hernandez, A. Bolanos, R. Moreno, A. Hormaza and R. H. de Almeida, *J. Heterocyclic Chem*., **35**, 333 (1998).

[81] H. Helmann and G. Optiz and Alpha-aminoalkylurung, *Verlag Chemie, Weinheim*, 246 (1960).

[82] S. Piroelle and P. Rollin, *Bull. Soc. Chim. France*, 2543 (1973).

[83] S. Selleri, F. Bruni, A. Costanzo, G. Guerrini, P. M. Aiello, G. Lavarone and C. Martini, *Eur. J. Med. Chem*., **27**, 985 (1992).

[84] A. Costanzo, F. Bruni, G. Guerrini, S. Selleri, P. M. Aiello, G. Lavarone and C. Martini, *J. Heterocyclic Chem*., **29**, 1499 (1992).

[85] T. Lübbers, P. Angehrn, H. Gmunder, S. Herzig and J. Kulhanek, *Biorg. Med. Chem. Lett*., **12**, 821 (2001).

[86] A. M. Kamal El-Dean and A. A. Geies, *J. Chem. Res. (S)*, 352 (1997).

[87] G. H. Elgemeie, S. R. El-Ezbawy and H. A. Ali, *Synth. Commun*., **31**, 3456 (2001).

[88] G. H. Elgemeie and S. A. Sood, *J. Chem. Res*. (*S*), **10**, 439 (2001).

[89] D. Briel, *Pharmazie*, **50**, 675 (1995).

[90] C. Liang, T. Ma, J. S. Cooperwood, J. Du and C. K. Chu, *Carbohydrate Research*, **303**, 33 (1997).

[91] G. Ege, K. Gilbert and H. Franz, *Synthesis*, 556 (1977).

[92] S. M. Agamey, *J. Chem. Res. (S)*, 349 (2001).

[93] F. M. El-Taweel, *Alex. J. Pharm. Sci*., **12**, 11 (1998).

[94] T. Ankenbrand and R. Neidlein, *Heterocycles*, **51**, 513 (1999).

[95] K. U. Sadek, A. S. Maghraby and M. H. Elnagdi, *Bull. Chem. Soc. Jpn*., **66**, 2927 (1993).

[96] O. A. Fathalla and M. E. Zaki, *Indian J. Chem*., **37B**, 484 (1998).

[97] A. M. Farag, *J. Chem. Res. (S)*, 432 (1994).

[98] A. M. Farag, K. M. Dawood and Z. E. Kandeel, *Tetrahedron*, **52**, 7893 (1996).

[99] A. M. Farag, Z. E. Kandeel and M. H. Elnagdi, *J. Chem. Res. (S)*, 10 (1994).

[100] M. M. El-Abadelah, *Heterocycles*, **45**, 1255 (1997).

[101] P. R. Huddleston, J. M. Barker, Y. Z. Adamczewska, M. L. Wood and D. Holmes, *J. Chem. Res. (S)*, 72 (1993).

[102] J. L. Kelley, D. C. Wilson, V. L. Styles, F. E. Soroko and B. Cooper, *J. Heterocyclic Chem*., **32**, 1417 (1995).

[103] G. Guarneri, P. Giori, R. Ferroni, R. Tomatis and C. A. Benassi, *Gazz. Chim. Ital*., **103**, 1105 (1973).

[104] H. S. El-Kashef, T. I. El-Emary, M. Gasquet, P. Timon-David, J. Maldonado and P. Vanelle, *Pharmazie*, **55**, 572 (2000).

[105] N. H. Metwally and F. M. Abdelrazek, *Egypt J. Chem*, **42**, 491 (1999).

[106] O. Migliara and V. Spiro, *J. Heterocyclic Chem*., **18**, 271 (1981).

[107] L. Lamartina and O. Migliara, *Boll. Chim. Farm*., **129**, 314 (1990).

[108] O. Migliara, D. Schillaci and B. Maggio, *Boll. Chim. Farm*., **131**, 331 (1992).

[109] O. Migliara, L. Lamartina, M. Timoneri and S. Plescia, *J. Heterocyclic Chem*., **32**, 835 (1995).

[110] O. Migliara, L. Lamartina and R. Rainieri, *J. Heterocyclic Chem*., **32**, 1589 (1995).

[111] A. A. Hassan, N. K. Mohammed, A. A. Aly and A. E. Mourad, *Bull. Soc. Chim. Belg*., **105**, 159 (1996).

[112] V. A. Makarov, N. P. Solov'eva and V. G. Granik, *Chem. Heterocycl. Compd*., **33**, 535 (1997).

[113] A. A. Hassan, N. K. Mohammed, Y. R. Ibrahim and A. E. Mourad, *Liebigs Ann. Chem*., **6**, 695 (1993).

[114] E. A. Hafez, M. R. Elmoghayar and M. M. Ramiz, *Liebigs Ann. Chem*., 65 (1987).

[115] S. V. Thiruvikraman and S. Seshadri, *Bull. Chem. Soc. Jpn*., **58**, 785 (1985).

[116] M. H. Elnagdi, I. El-Ghamry, E. Kandeel, A. H. Abdel Rahman and A. A. El-Naggar, *Gazz. Chim. Ital*., **127**, 791 (1997).