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RESEARCH ARTICLE

Pyrazolopyrimidines: Synthesis, Chemical reactions and Biological activity

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Abstract

Synthesis, chemical reactivity and biological activity of different pyrazolopyrimidines derivatives are reviewed.

1- Introduction.

Chemistry associated with genes has attracted a great public interest during the last two decades. Nucleotides are the backbone of the nucleic acid molecule. The common pyrimidine bases in the nucleotides are cytosine, thymine and uracil. The two common purine bases in nucleic acids are adenine and guanine. Pyrazolopyrimidine and their analogs are very important in the fields of medicinal chemistry and chemotherapy, as they have antimetabolite properties, (anticancer, antiviral, antitumor activities and can be used in the treatment of gout), microbiological and pharmacological effects[1-10].

Synthetic analogues of purines and pyrimidines nucleosides, and nucleotides are widely used in the medical science and clinical medicine. Typically, most uses exploit the role of nucleotides as components of the nucleic acids essential for cellular growth and division. For a cell to divide, its DNA must be replicated.

The normal purine and pyrimidine deoxyribonucleotides must therefore be available. One of the most important components of an oncologist pharmacopoeia is the group of synthetic analogues of purines, pyrimidines, and their nucleosides.

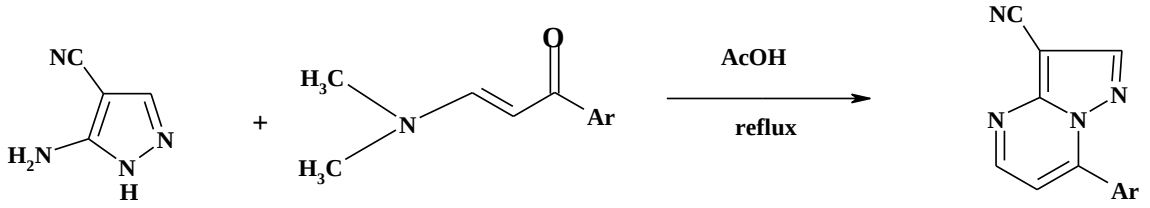
The pharmacological approach uses an analogue in which either the heterocyclic ring structure, the position of different groups or the sugar moiety has been altered so as to induce toxic effects when the analogue is incorporated into specific cellular constituents. Many of these effects reflect one of two processes: - **(1)** inhibition by the drug of specific enzymes essential for nucleic acid synthesis, or **(2)** incorporation of metabolites of the drug into nucleic acids where they effect the base pairing essential to accurate transfer of information Examples include 6-thioguanine and 6-mercaptopurine which are widely used clinically and have different effects.

The following contains an up to date survey of their most important chemical properties, and biological activities including compounds of pyrazolopyrimidines and their analogous.

2. Synthesis of Pyrazolopyrimidines derivatives.

2.1. Synthesis of Pyrazolo[1,5-a]pyrimidine derivatives.

5-Unsubstituted-7-arylpyrazolo [1,5-*a*] pyrimidines **3a-c** could be constructed through the reaction of substituted 3-aminopyrazole **1** with arylenaminones **2** in refluxing acetic acid[11-13]. (Scheme 1).



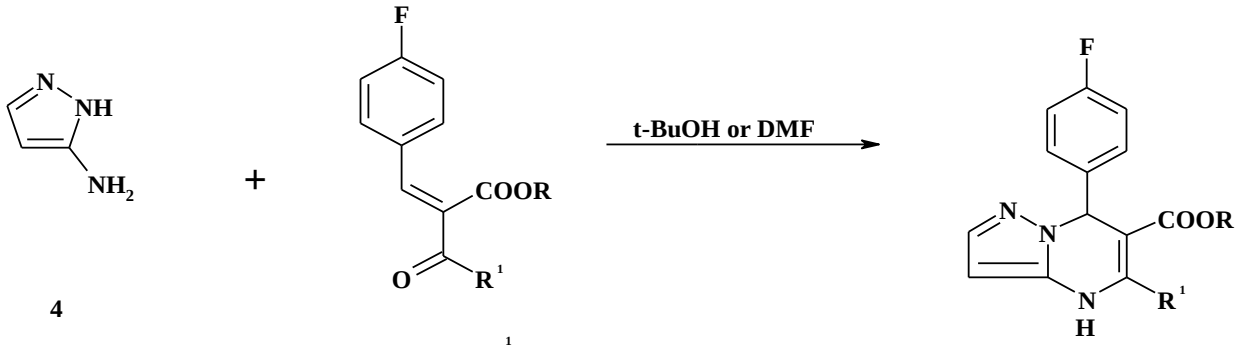
1

2a ,Ar = 3- pyridyl
b ,Ar = 3- CF_3-phenyl
c ,Ar = phenyl

3 (a-c)

Scheme (1)

Condensation of position 2 of the substituted aminopyrazoles **4** with benzylideneketo esters **5** resulted in preparation of pyrazolopyrimidine derivatives **6**[14]. (Scheme 2).



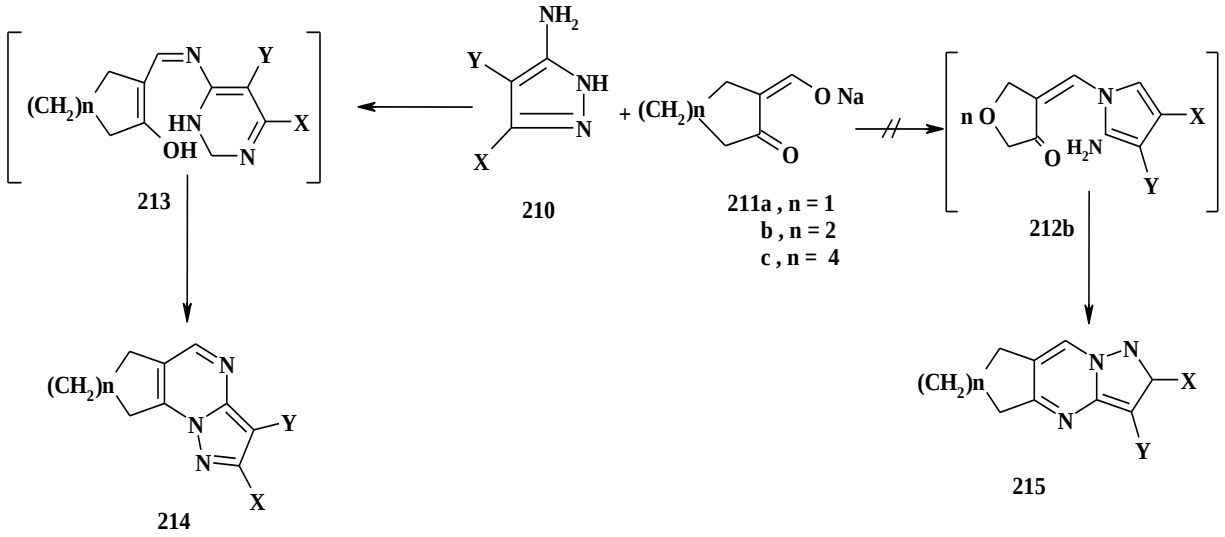
4

5a, ,R' = C_2H_5 R^1 = i-pr
b, R' = CH_3 R^1 =c-Pr

6

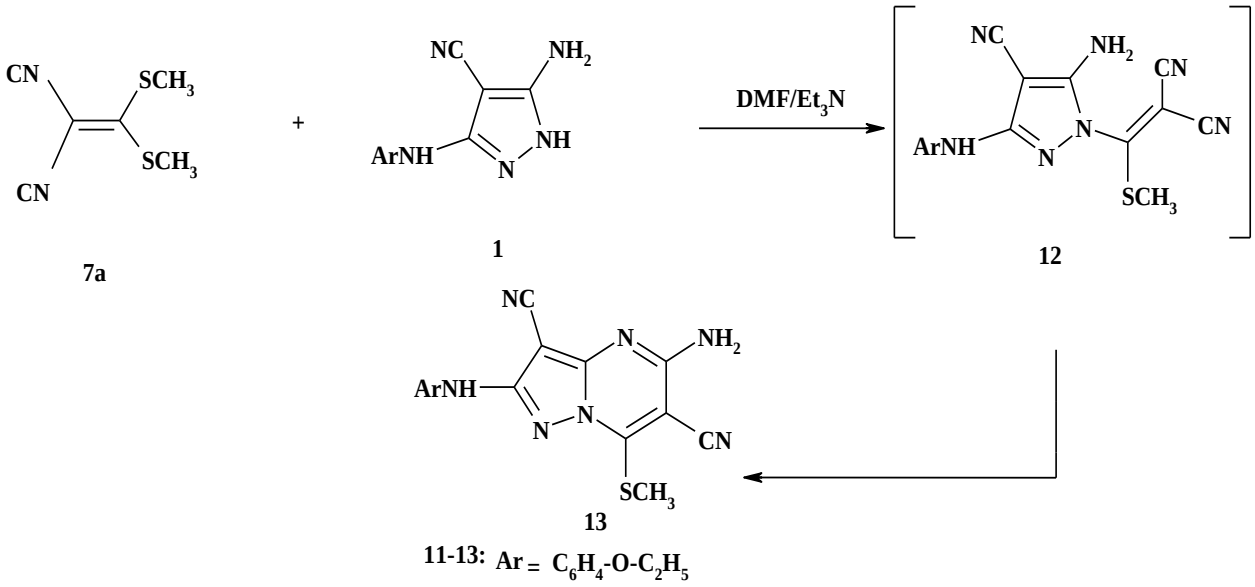
(Scheme 2)

Elgemeie et al[15,16] , reported that the reaction of ketene dithioacetals **7a,b** with aminopyrazole **8** afforded the 7-methylthiopyrazolo[1,5-*a*]pyrimidines **10a,b** through the intermediate of **9a,b**. (Scheme 3).



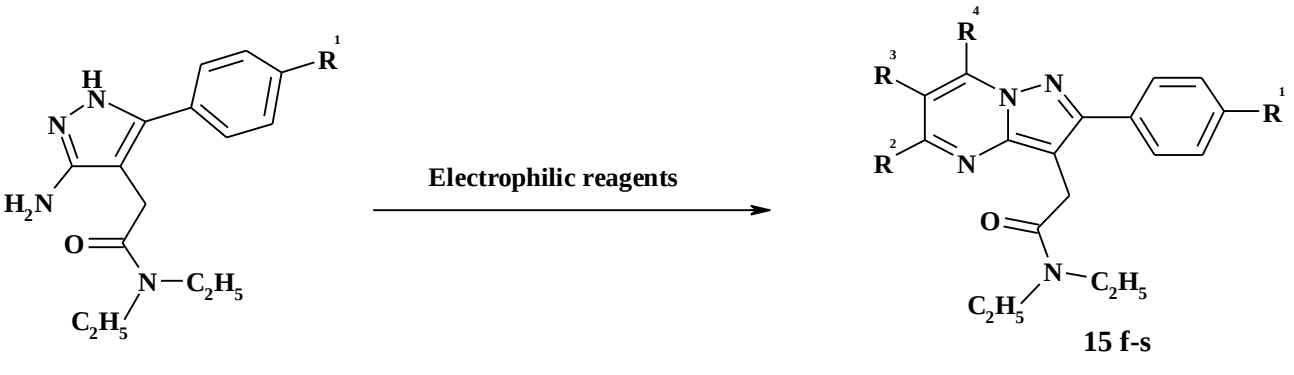
(Scheme 3)

Similarly, Zaharan et al[17-20], have reported that the reaction of ketene dithioacetals **7a** with aminopyrazoles **11** by initial alkylation of the ring nitrogen in **11** to give **12** as an intermediate which underwent cyclization giving pyrazolo[1,5-*a*]pyrimidines**13**. (Scheme 4).



(Scheme 4)

Condensation of **14** with the suitable electrophilic reagents (such as: *β*-diketones, *β*-ketoaldehydes or their acetals) led to the closure of the pyrimidine ring affording the pyrazolo[1,5-*a*]pyrimidin-3-yl-acetamides **15**[21]. (Scheme 5).



14

15 f-s

15	R^1	R^2	R^3	R^4	15	R^1	R^2	R^3	R^4
f	H	CH_3	H	H	m	OCH_3	CH_3	H	CH_3
g	H	H	H	CH_3	n	F	CH_3	H	H
h	H	H	H	H	o	Cl	H	H	CH_3
i	H	CH_3	H	CH_3	p	Cl_3	CH_3	H	CF_3
j	Cl	CH_3	H	CH_3	q	OCH_3	CF_3	H	CH_3
k	F	CH_3	H	CH_3	r	OCH_3	CF_3	H	CF_3
l	CH_3	CH_3	H	CH_3	s	Cl	CH_3	H	C_6H_5

(Scheme 5).

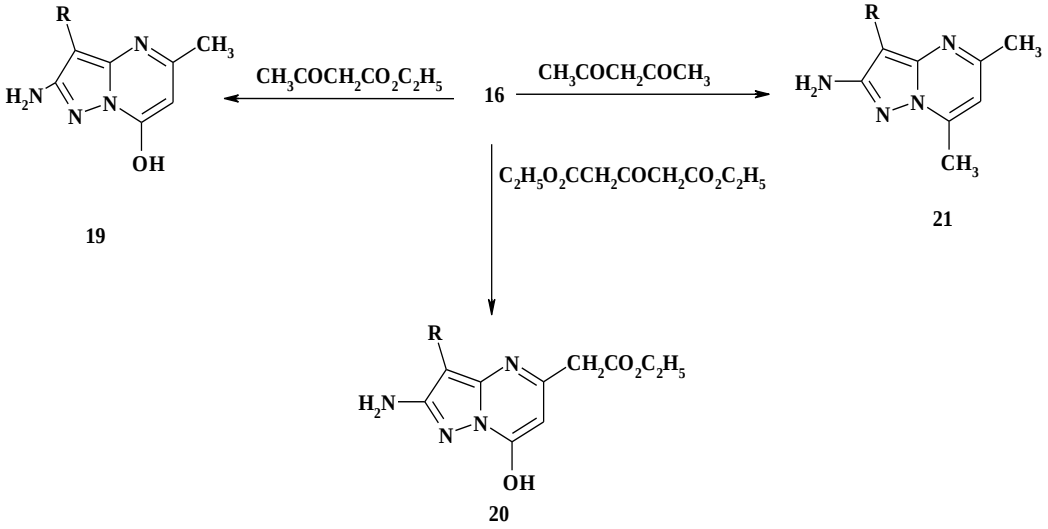
The reaction of pyrazole derivative **16** with an equimolar amounts of a substituted cinnamonitrile derivatives **17** in DMF and piperidine provided pyrazolopyrimidine derivatives **18**[22]. (Scheme 6).

16 17 18

R = OH, NH_2, C_6H_5

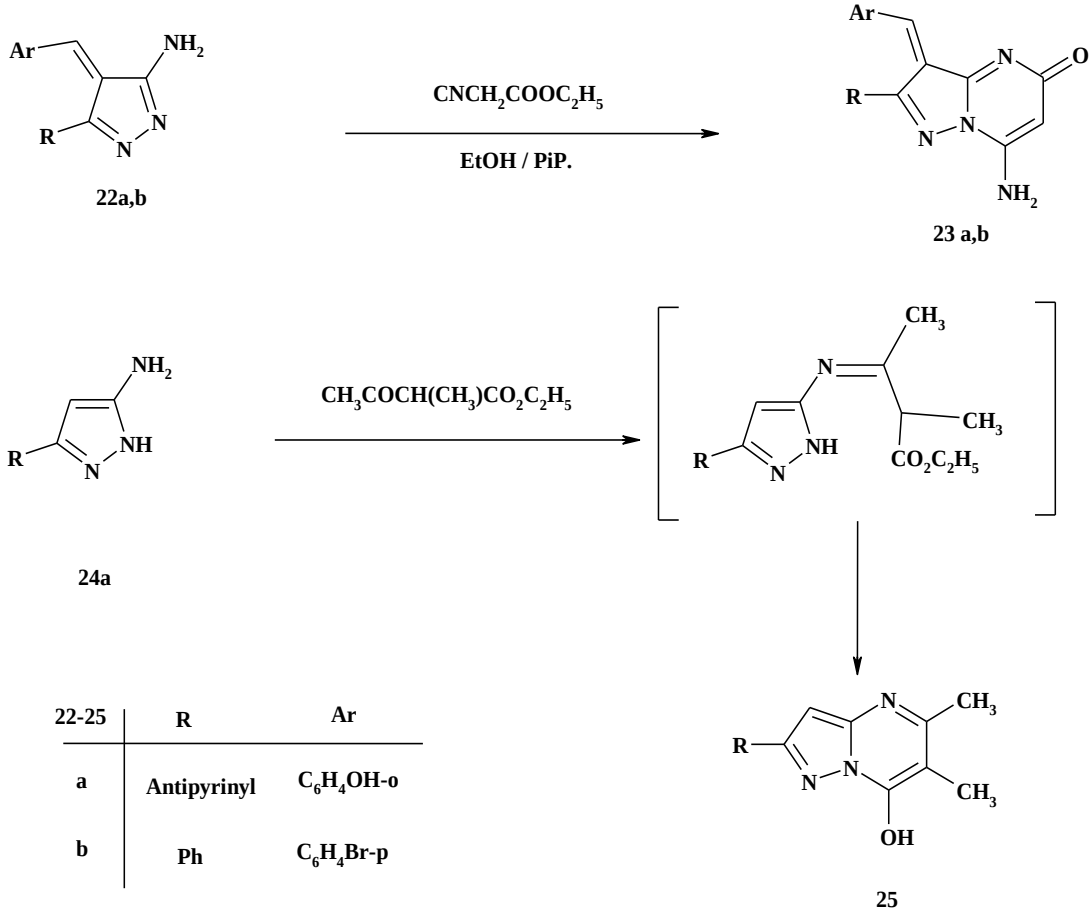
(Scheme 6)

Compound **16** could be condensed with ethy1 acetoacetate, diethyl acetonedicarboxylate and acetyl acetone to yield the corresponding pyrazolo[1,5-*a*] pyrimidine derivatives **19, 20** and **21,** respectively [22]**.** (Scheme 7).



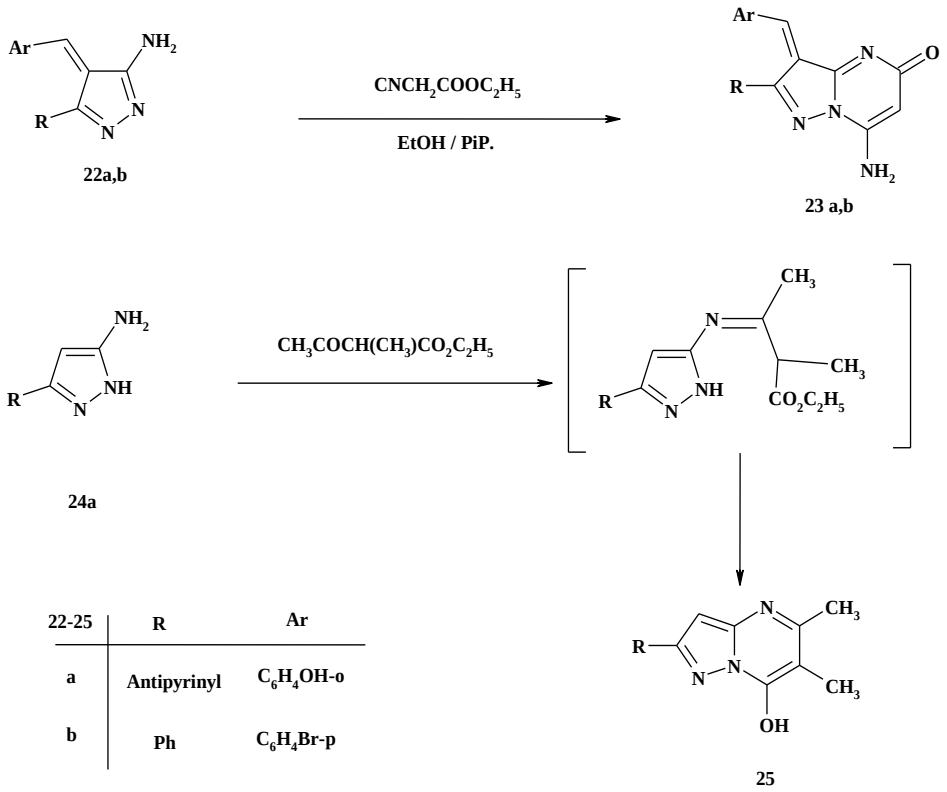
(Scheme 7)

Condensation of 5-amino-4-arylidenepyrazoles 22a,b with ethyl cyanoacetate afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **23a,b.** On the other hand, reaction between 5-amino-2-antipyrinylpyrazole **24a and** ethyl *β*-methyl acetoacetate in glacial acetic acid gives the pyrazolo[1,5-*a*]pyrimidines **25**[23]. (Scheme 8).



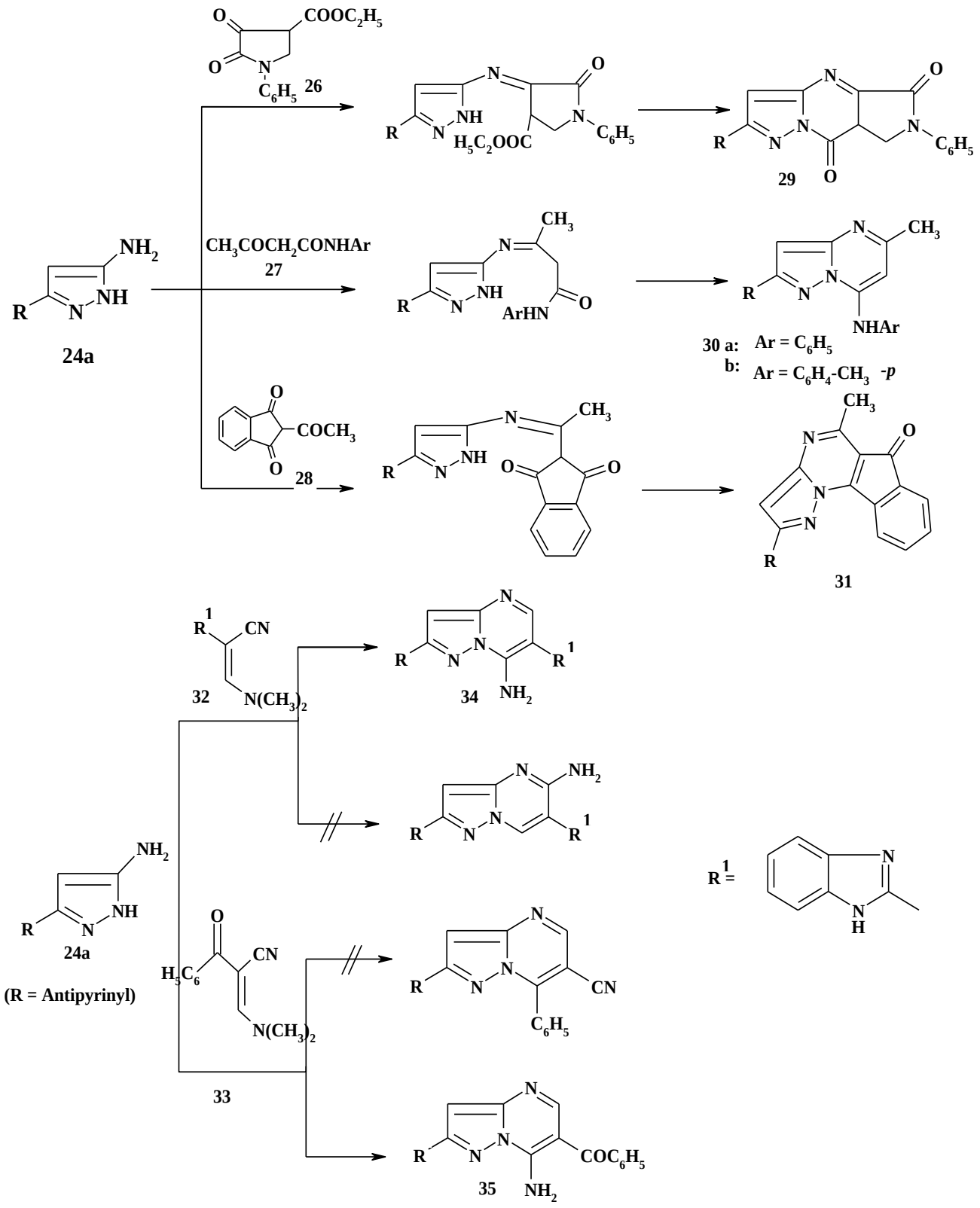
22-25	R	Ar
a	Antipyrinyl	C_6H_4OH-o
b	Ph	C_6H_4Br-p

(Scheme 8)



(Scheme 8)

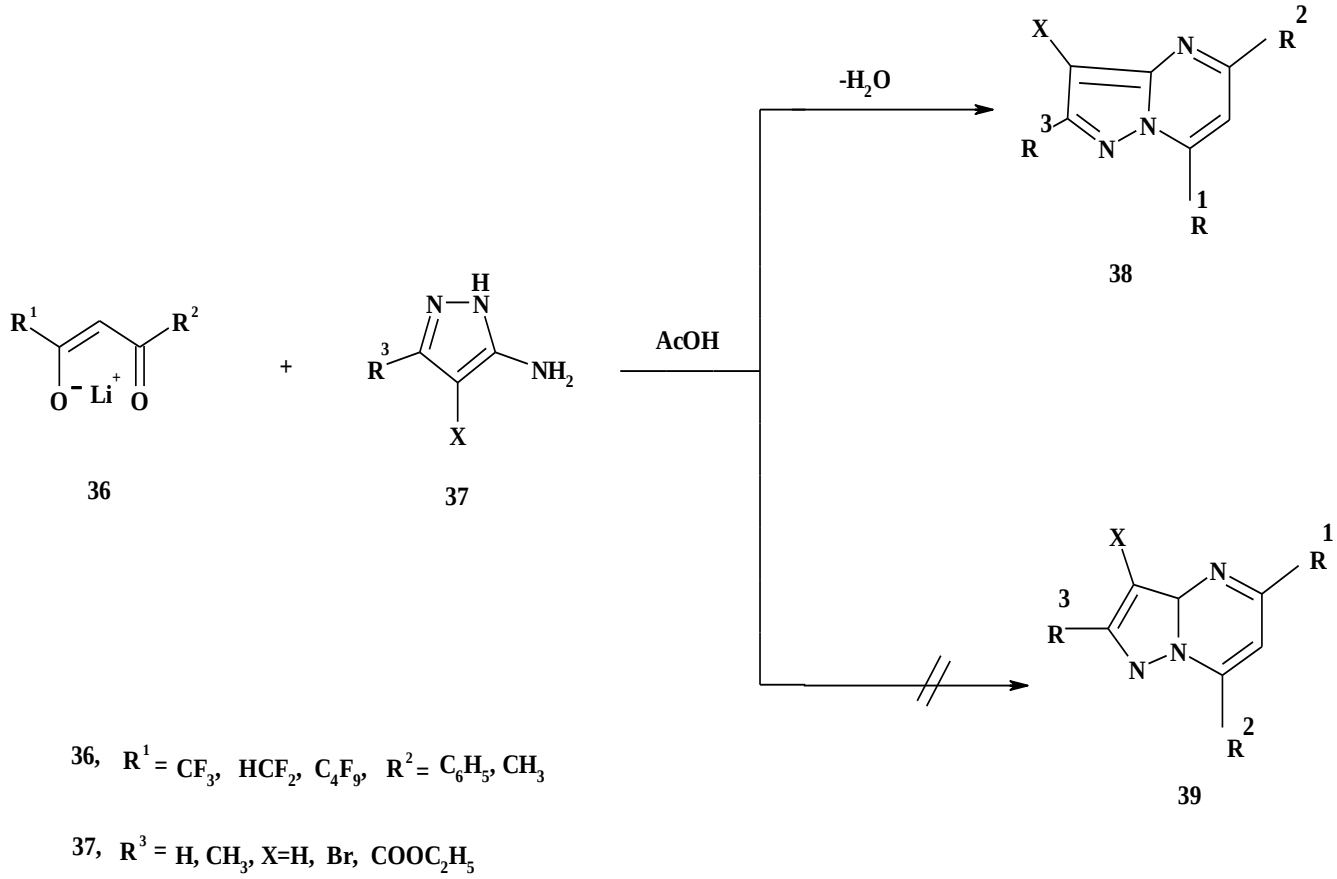
Also, it was reported that, compound **24a** reacted with the cyclic *β*-ketoester **26**, acetoacetanilides **27** in glacial acetic acid and 2-acetylindan-1,3-dione **28** in ethanol catalyzed by acetic acid under reflux to afford pyrazolopyrimidine derivatives **29**, **30** and **31,** respectively. On the other hand, compound **24a** reacted with 3-dimethylamino-2[benzimidazol-2-yl]prop-2-enenitrile **32** or 3-(dimethylamino)-2-benzoyl propenonitrile **33** in refluxing ethanol catalyzed by acetic acid to give the pyrazolo[1,5-*a*]pyrimidine derivatives **34** or **35,** respectively[23]. (Scheme 9).



(Scheme 9)

Filyakova et al[24], studied the reaction of lithium enolates of fluorine-containing *β*-diketones **36** with 3-

aminopyrazoles **37** that afforded (7-polyfluoroalkyl) pyrazolo[1,5-*a*]pyrimidines **38**. (Scheme 10).

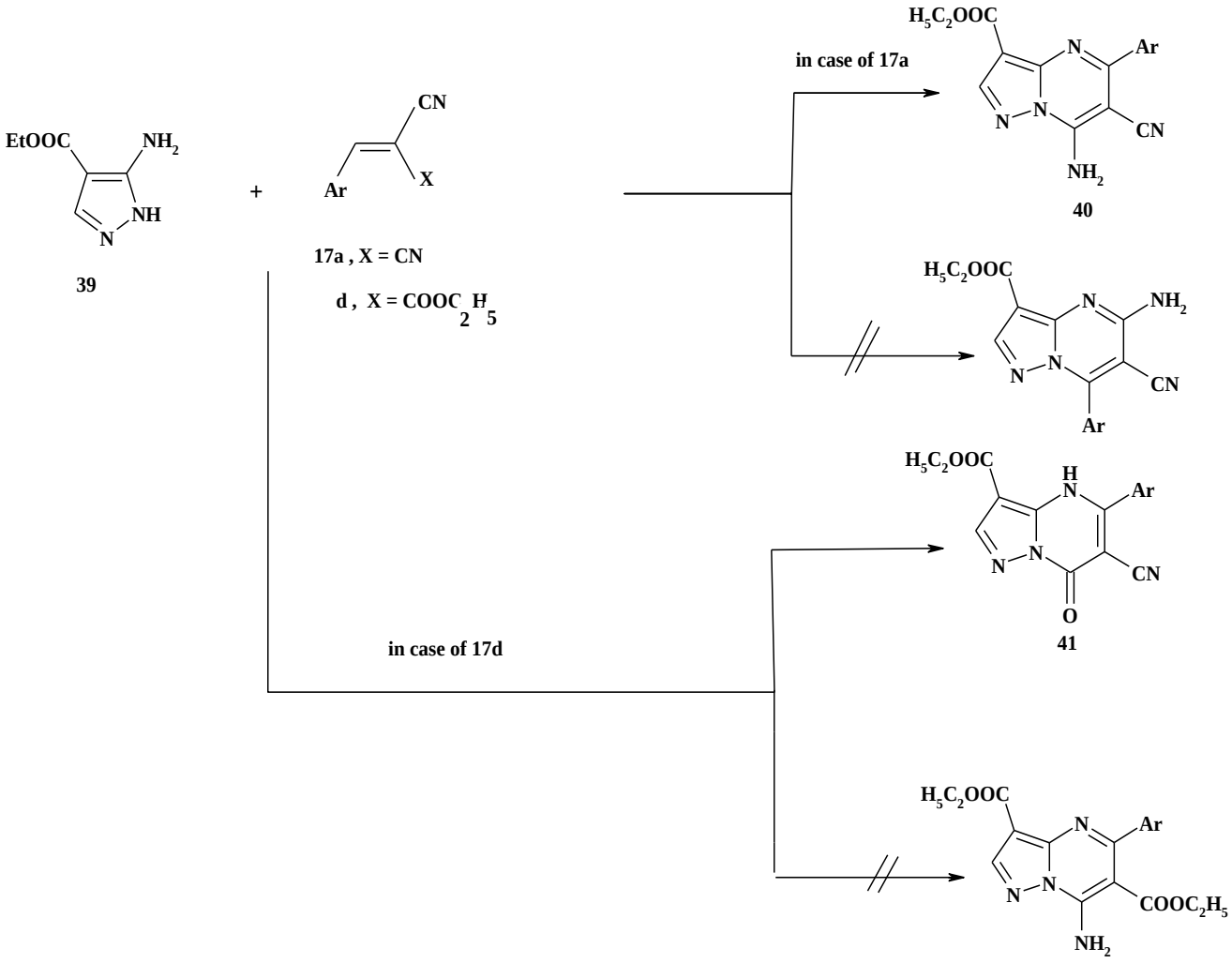


36, R^1 = CF_3, HCF_2, C_4F_9, R^2 = C_6H_5, CH_3

37, R^3 = H, CH_3, X=H, Br, $COOC_2H_5$

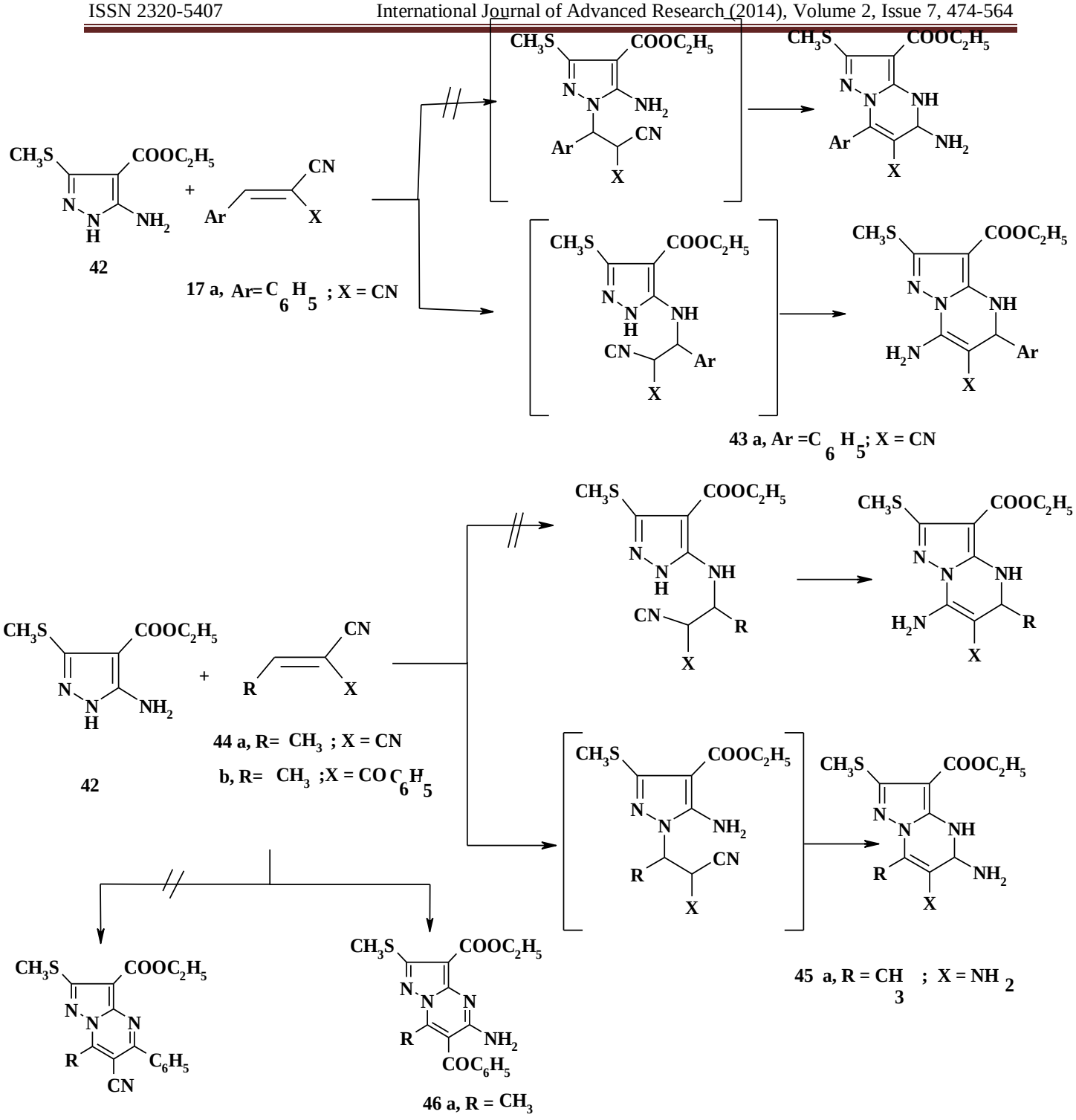
(Scheme 10)

Reflux of ethyl 3-amino-(lH)-pyrazole-4-carboxylate **39** with *β*-cyanocinnamonitriles **17a** or ethyl *β*-cyano cinnamates **17d** in pyridine led to the formation of ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-*a*]pyrimidine-5-carboxylates **40** or ethyl 5-aryl-6-cyano-7-oxo(4H, 7*H*)pyrazolo[1,5-*a*]pyrimidine-3-carboxylates **41** respectively[25]. (Scheme 11).



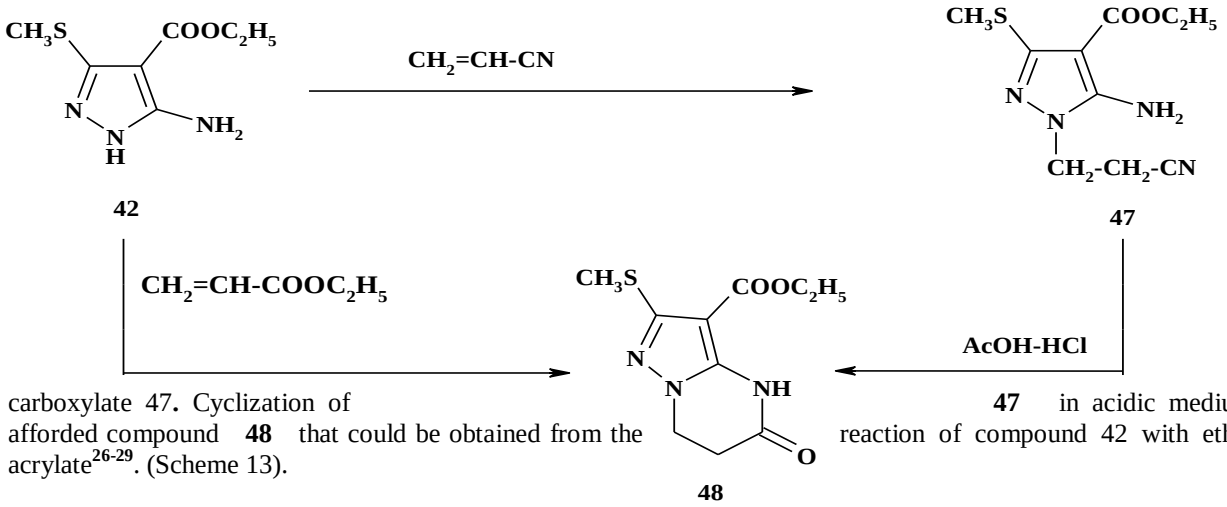
(Scheme 11)

Raslan et al[26-29], reinvestigated some earlier work that discussed the reaction of aminopyrazoles **42** with *β*-arylacrylonitriles **17** and has reported that the reaction of the aminopyrazole derivatives **42** with **17a** afforded 7-amino-pyrazolo[1,5-*a*]pyrimidine derivatives **43** . Also, compound **42** was found to react with **44** to yield 5-aminopyrazolo[1,5-*a*]pyrimidine derivatives **45** . The reaction of **42 with** 44 was reported to afford the 5-aminopyrazolo[1,5-*a*]pyrimidine derivatives **46**. (Scheme 12).


42
17 a, Ar= C6H5 ; X = CN
43 a, Ar =C6H5; X = CN
42
44 a, R= CH3 ; X = CN
b, R= CH3 ;X = CO C6H5
45 a, R = CH3 ; X = NH2
46 a, R = CH3

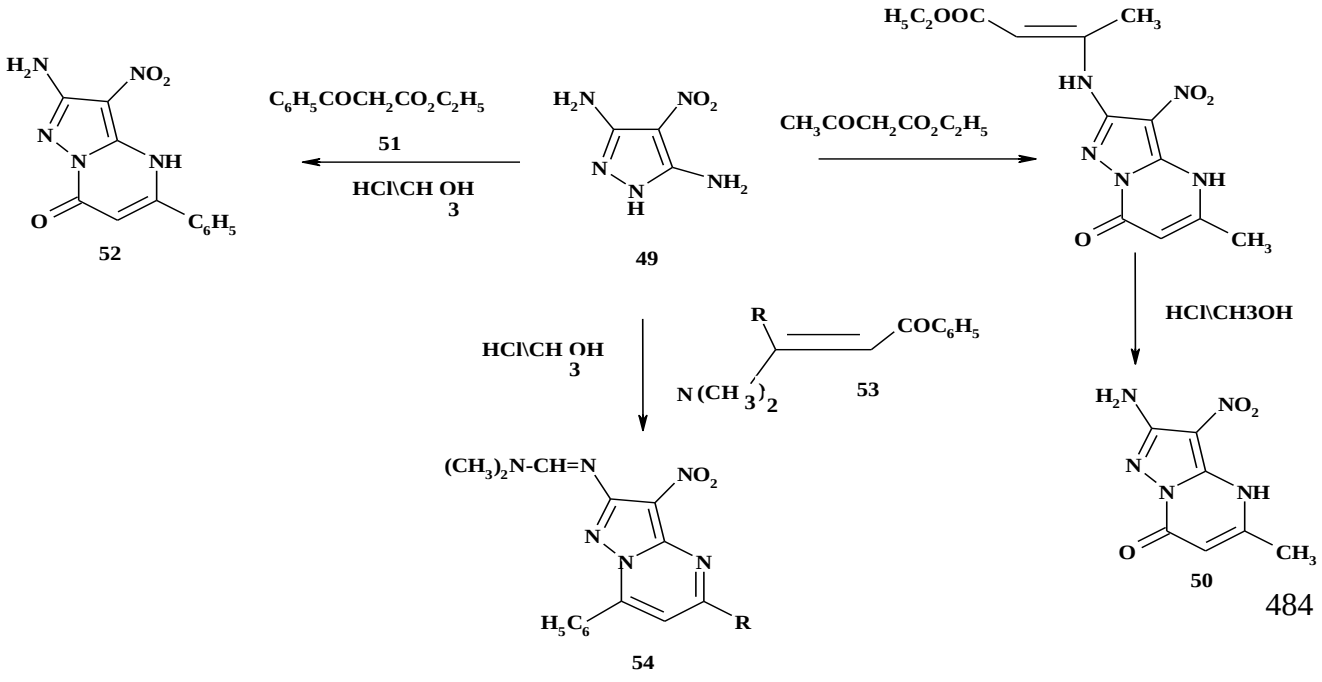
(Scheme 12)

Moreover, compound **42** reacted with acrylonitrile in the presence of potassium hydroxide to yield the pyrazole-4-carboxylate 47**.** Cyclization of **47** in acidic medium afforded compound **48** that could be obtained from the reaction of compound 42 with ethyl acrylate[26-29]. (Scheme 13).



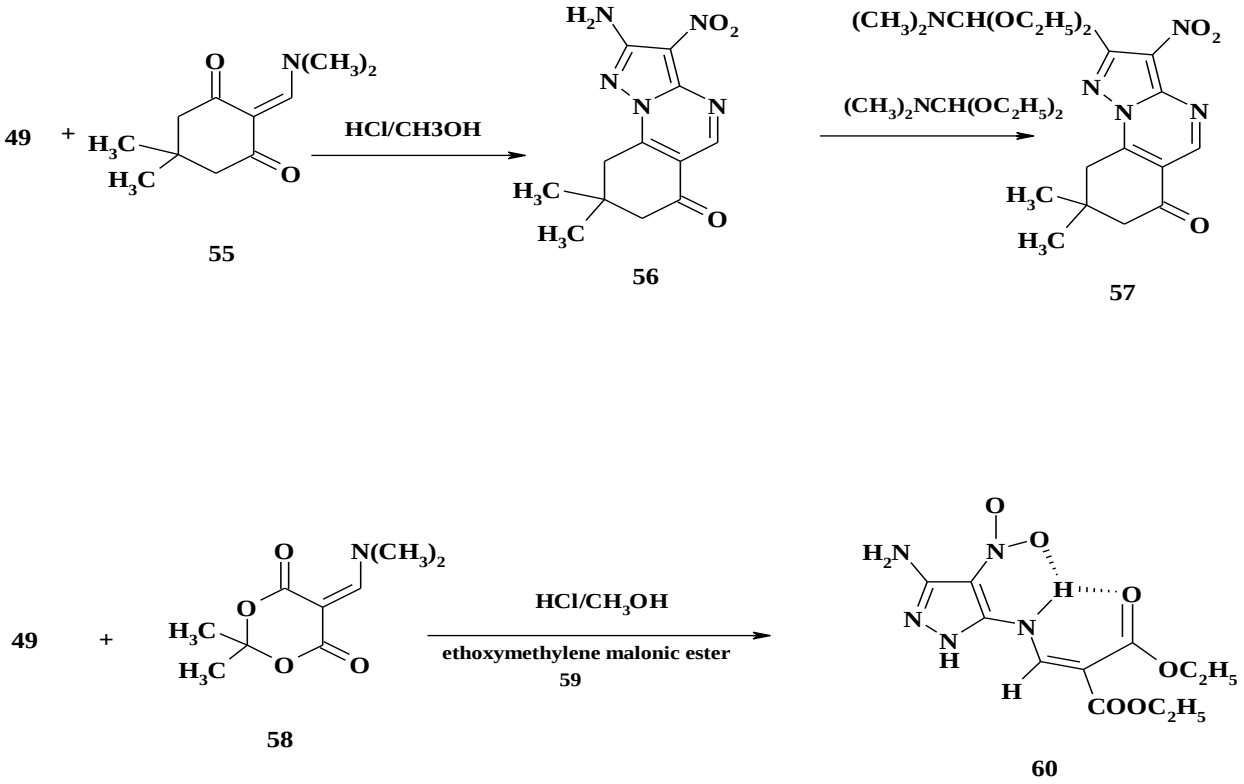
(Scheme 13)

It has been found that, 3,5-diamino-4-nitropyrazole **49** tended to react with ethyl acetoacetate in the presence of methanolic hydrochloric acid to form pyrazolo [1,5-*a*]pyrimidine derivative **50** . In a similar manner, compound **49** which reacted with ethyl benzoylacetate **51**and **53** to yield compounds **52,54** respectively[30-36]. (Scheme 14).



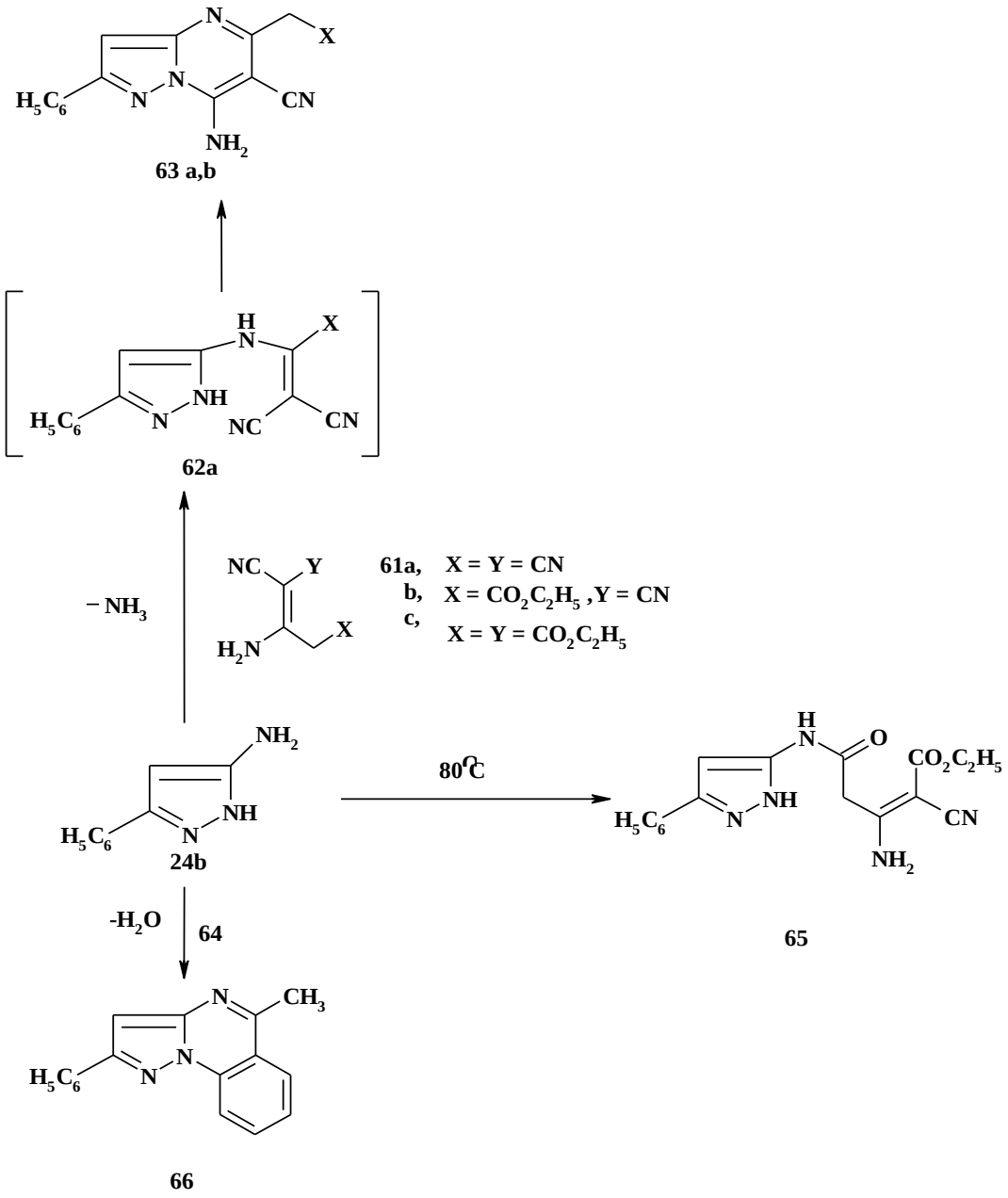
(Scheme 14)

Similarly, compound **49** reacted with 2-dimethylaminomethylene dimedone **55** to afford amidine **57.** Also, compound **49 could** be reacted with 5- dimethylaminomethylene-2,2-dimethyl-l,3-dioxane-4,6-dione **58** and ethoxymethyl- enemalonic ester **59** to give compound **60**[30-36]. (Scheme 15).



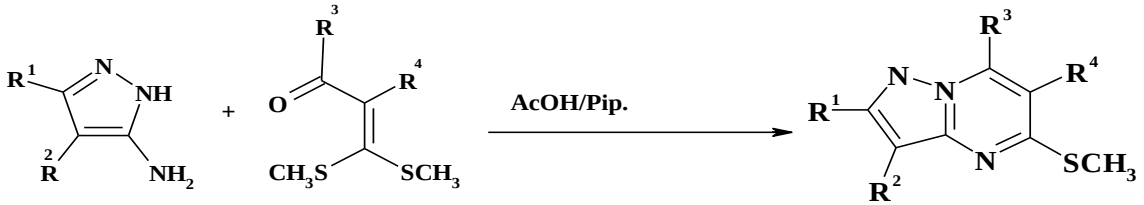
(Scheme 15)

Reaction of 5-amino-3-phenylpyrazole 24b with the malononitrile dimer **61a** or ethyl cyanoacetate diamer **61b** gave the intermediates 62a,b, which were cyclized to the pyrazolo[1,5-*a*]pyrimidine derivatives **63a** or **63b** respectively. Also, the reaction of **24b** at 80 °c or 2-hydroxyacetophenone **64** resulted in the formation of compound 65 **or** 66 respectively[37-39]. (Scheme 16).


63 a,b
62a
61a, X = Y = CN
b, X = CO2C2H5 ,Y = CN
c, X = Y = CO2C2H5
− NH3
24b
80°C
65
-H2O
64
66

(Scheme 16)

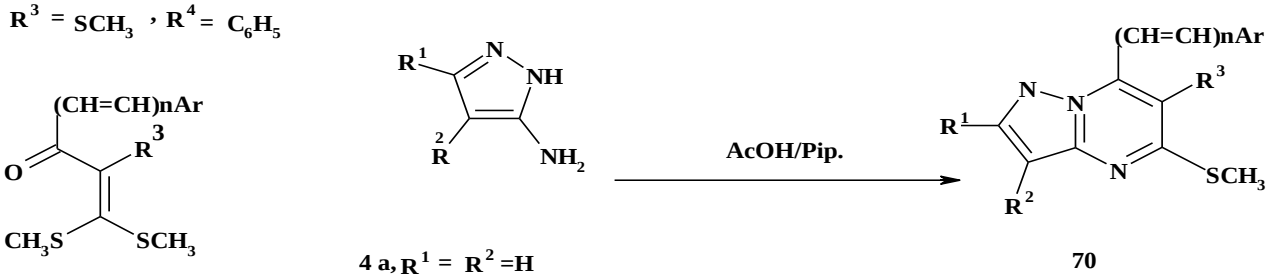
Cyclo condensation of 3-aminopyrazole derivatives **4** with *β*-oxoketene dithioacetals 67 afforded 5-methylthio-6,7-disubstituted pyrazolo[1,5-*a*]pyrimidines **68** . In addition, Compound 70 has been synthesized by condensation of compound 4 with dithioacetals **69**[40-43.] (Scheme 17).



4 a, $R^1 = R^2 = H$

b, $R^3 = SCH_3$, $R^4 = C_6H_5$

68



69a, Ar = 4- OCH_3-C_6H_4

b, Ar = C_6H_5 ;n=3

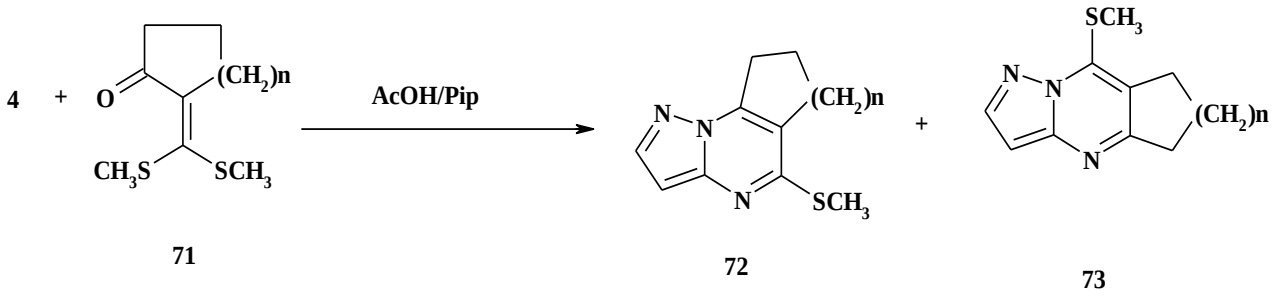
4 a, $R^1 = R^2 = H$ **b,** $R^3 = SCH_3$, $R^4 = C_6H_5$

70

67-70	R^1	R^2	R^3	R^4
a	H	H	CH_3	H
b	H	H	4- Cl-C_6H_4	H

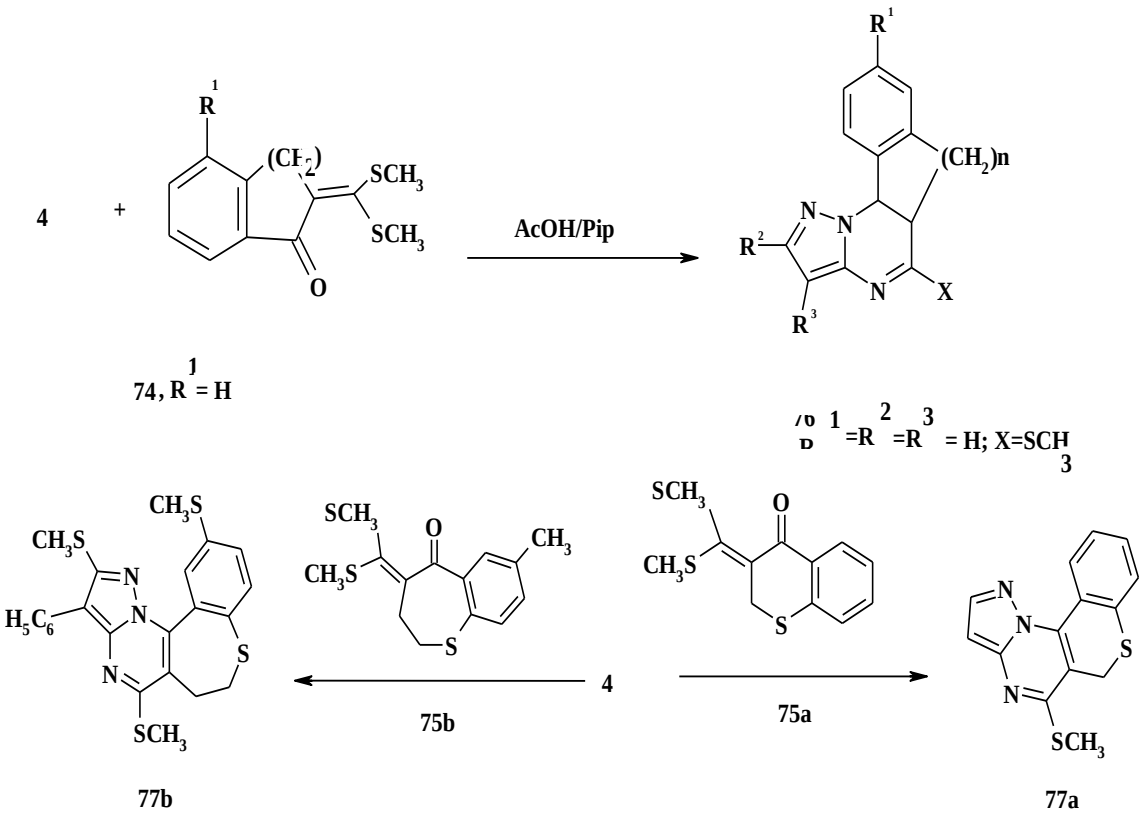
(Scheme 17)

when **4** is reacted with dithioacetal **71** derived from cyclopentanone Yielded a mixture of angular and linearly fused pyrimidines **72** and **73** are offeried[40]. (Scheme 18).



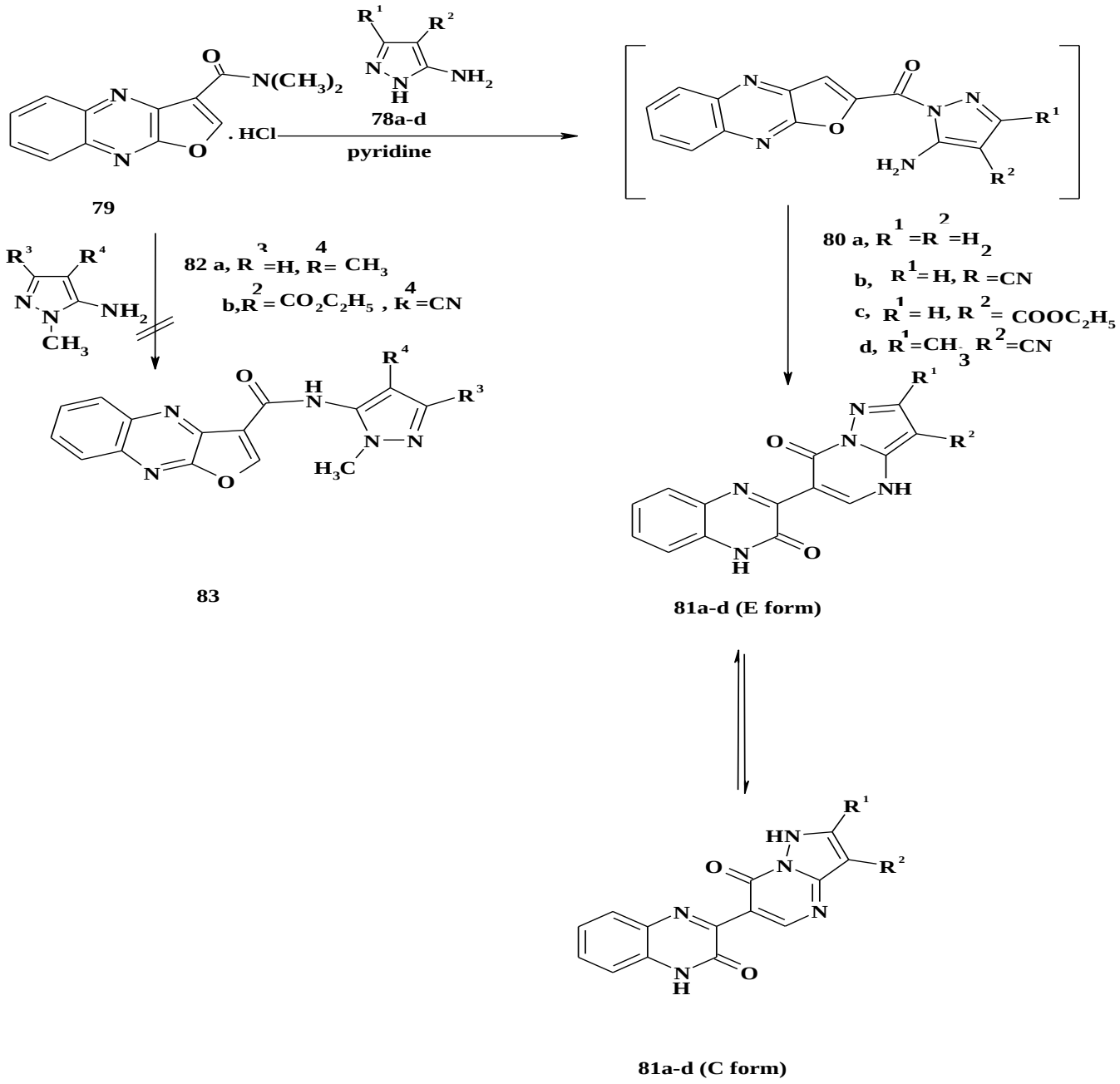
(Scheme 18)

Similarly, the reaction of **4 with** ketene dithioacetals 74 **and** 75a,b derived from benzocyclic ketones were investigated. Thus, a series of benzocyclo and benzohetero cyclopyrazolopyrimidines **76, 77a** and **77b** were obtained respectively[40-43]. (Scheme 19).



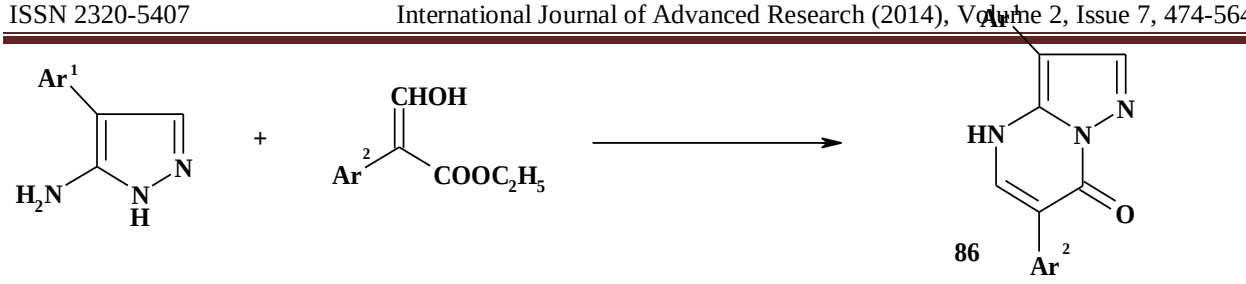
(Scheme 19)

Kurasawa et al[44], has reported the synthesis of novel 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **81a-d** by the reaction of 3-(*N*,*N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride **79** with 5-amino-(1*H*)pyrazoles **78a-d** in the presence of pyridine. The reaction of **79** with 5-amino-1-methylpyrazoles **82a,b** in the presence of pyridine did not afford the expected 3-[*N*-(l-methyl-pyrazol-5-yl)carbamyol]furo[2,3-*b*]quinoxalines **83** , but recovered the free base of **81**[44,45]. (Scheme 20).



(Scheme 20)

The synthesis of 4,7-dihydro-3,6-disubstituted pyrazolo[1,5-*a*]pyrimidin-7-ones **86** were performed by a one-step reaction between 3(5)-amino-4-aryl pyrazoles **84** and ethyl 2-aryl-3-hydroxypropenoates **85**[46]**.** (Scheme 21).

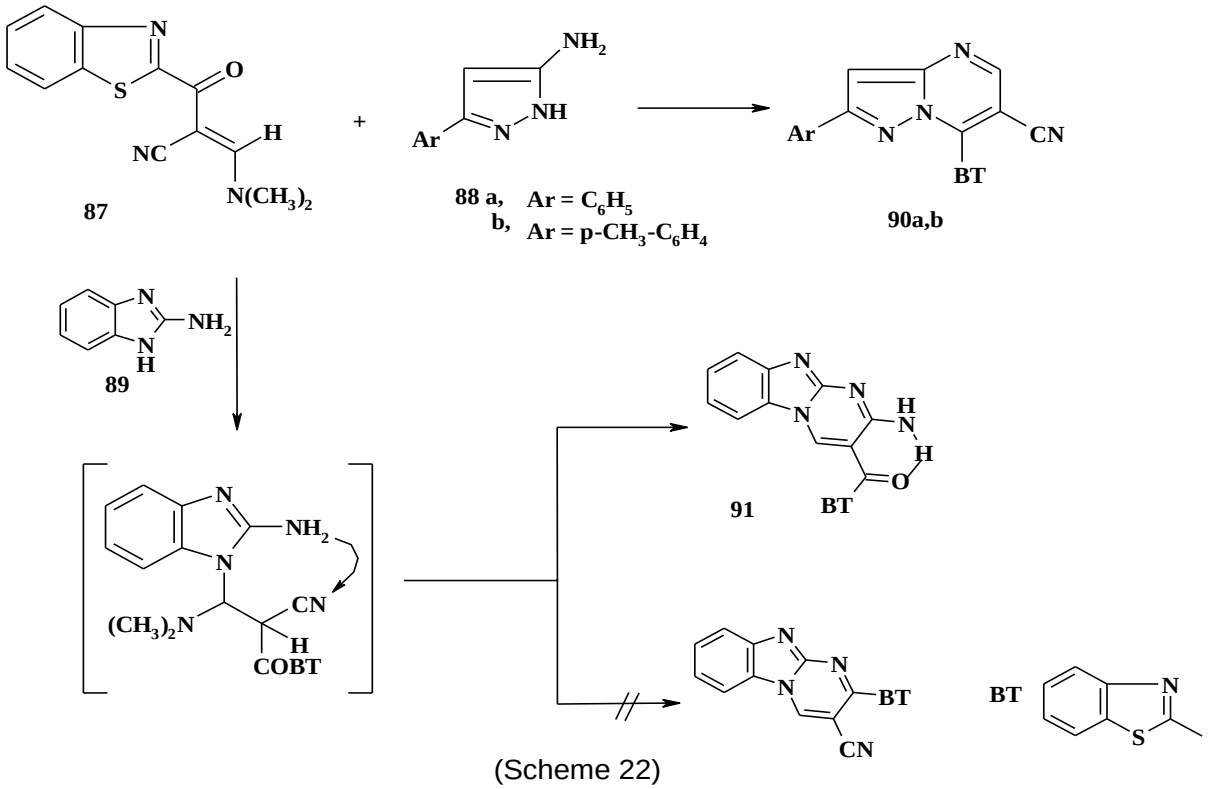


86	Ar^1	Ar^2
f	$_3$-$OCH_3C_6H_4$	$_3$-thienly
g	C_6H_5	$_3$-$OCH_3C_6H_4$
h	$_3$-thienyl	$_3$-thienyl
i	$_3$-thienyl	$_3$-thienyl

86	Ar^1	Ar^2
a	C_6H_5	C_6H_5
b	3 -thienyl	C_6H_5
c	3 -$OCH_3C_6H_4$	C_6H_5
d	C_6H_5	3 -thienyl
e	3 -$OCH_3C_6H_4$	3 -thienyl

(Scheme 21)

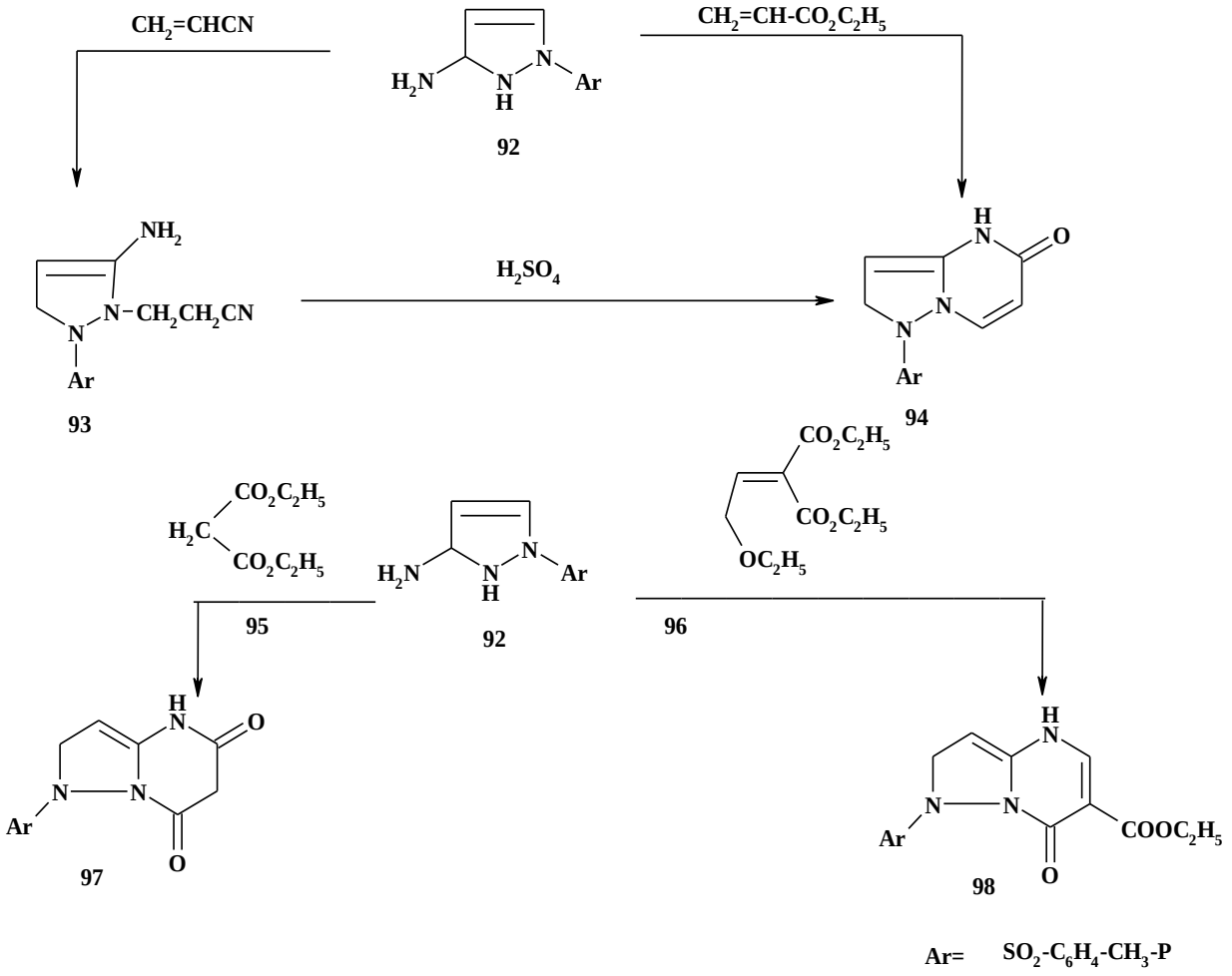
The reaction of 3-(benzothiazol-2-yl) -2-(*N,N*-dimethylamino)methylene-3-oxo-propanenitrile **87** with 5-amino-3-aryl-(1*H*)-pyrazoles **88$_{a,b}$** or 2-aminobenzimidazole **89** afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **90$_{a,b}$** and the pyrimido[1,2-*a*]benzimidazole derivatives **91** respectively [47-49] . (Scheme 22).



(Scheme 22)

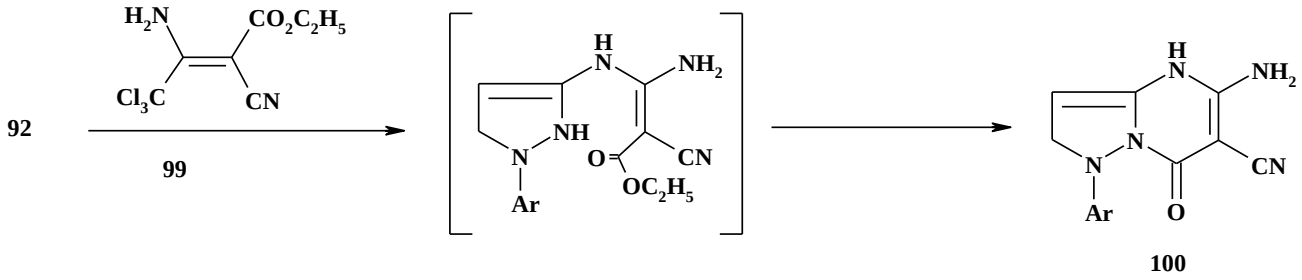
When (*N*-tosyl)-3-aminopyrazole derivative **92** treated with acrylonitrile, the corresponding 1-(*p*-tosyl)-3-amino-*β*-cyano ethylpyrazole **93** was obtained, which was cyclized to pyrazolo[1,5-*a*]pyrimidine derivative **94** by the action of concentrated sulphuric acid. Also, compound 94 could be obtained directly upon treatment of **92**

with ethyl acrylate. Compound **92** reacted with diethyl malonate **95** or its ethoxyethylene derivative **96** to yield the pyrazolo[1,5-*a*]pyrimidine derivatives **97** and **98** respectively[50]. (Scheme 23).



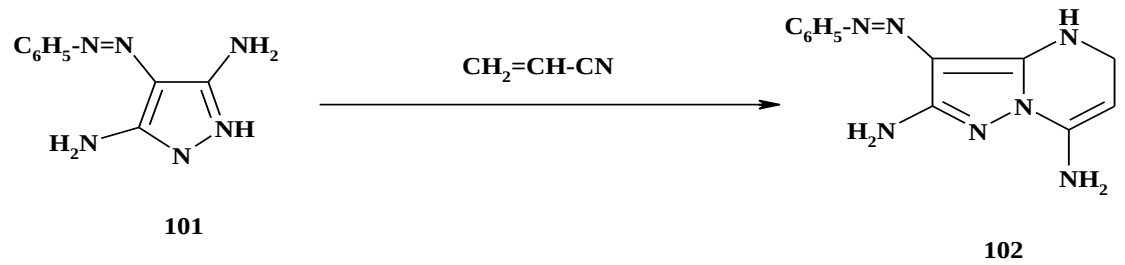
(Scheme 23)

Also, the condensation of compound 92 with ethyl 2-amino-3-trichloromethyl crotonate **99** in refluxing ethanol yielded the pyrazolo[1,5-*a*]pyrimidine **100**[50]**.** (Scheme 24).



(Scheme 24)

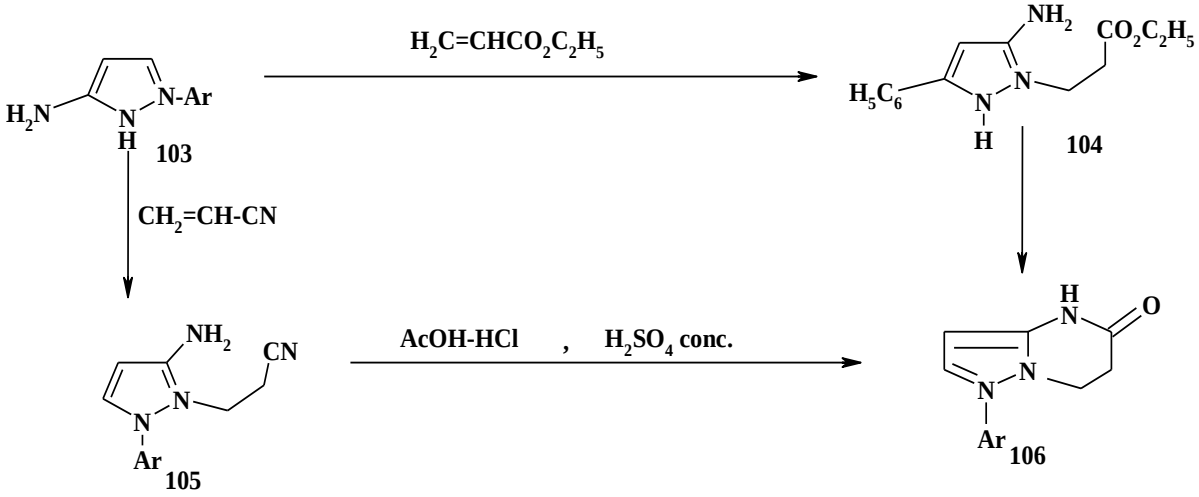
Elnagdi et al [51-54], found that pyrazolo[1,5-*a*]pyrimidine derivative **102**, were prepared by reaction of 3,5-diamine pyrazole **101** with acrylonitrile. (Scheme 25).



101 **102**

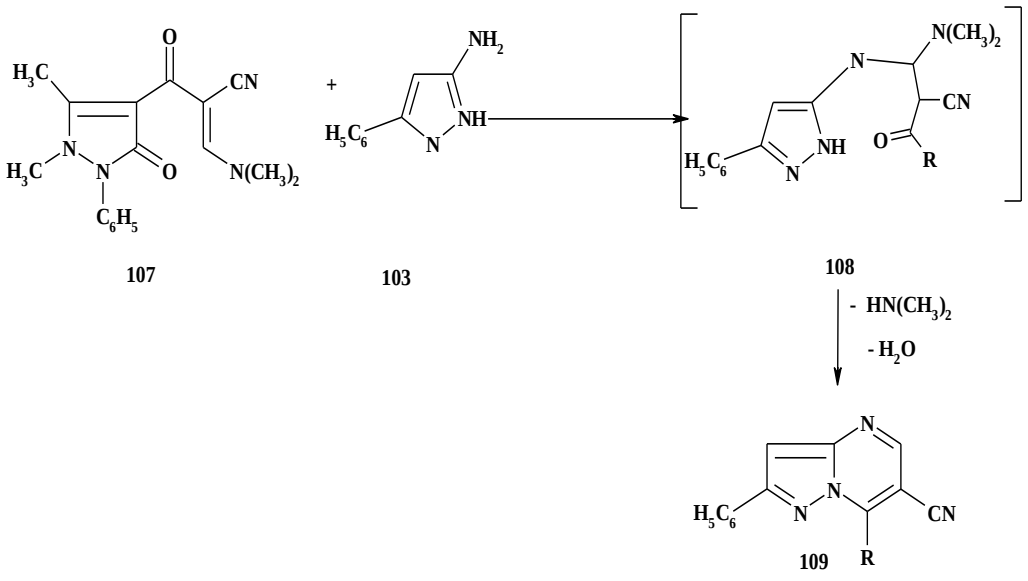
(Scheme 25)

On the other hand, 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine **106** can be prepared by the reaction of 5-aminopyrazolo **103** with ethylacrylate or with acrylonitrile via formation of intermediate **104, 105,** respectively[52]. (Scheme 26).



(Scheme 26)

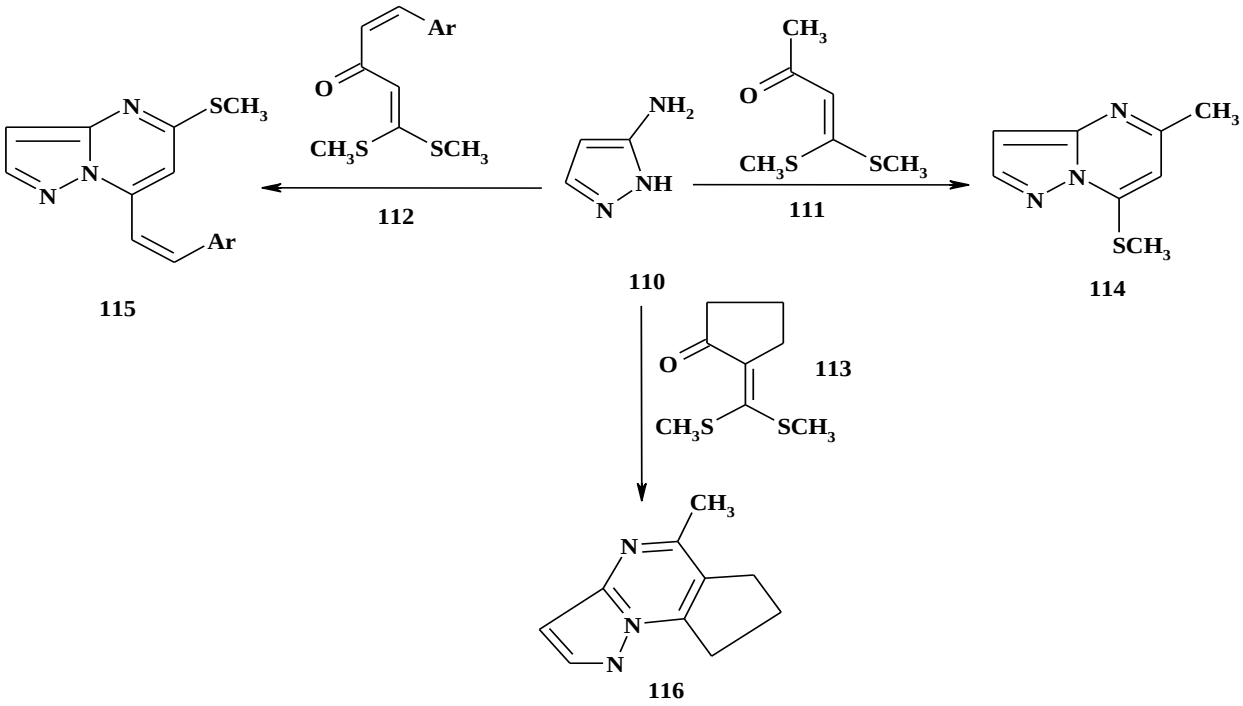
In addition, compound **107** reacted with 5-amino-*1H*-pyrazolo derivative **103,** to afford pyrazolo[1,5-*a*]pyrimidine derivative **109**[53-56]. (Scheme 27).



107 **103** **108** **109**

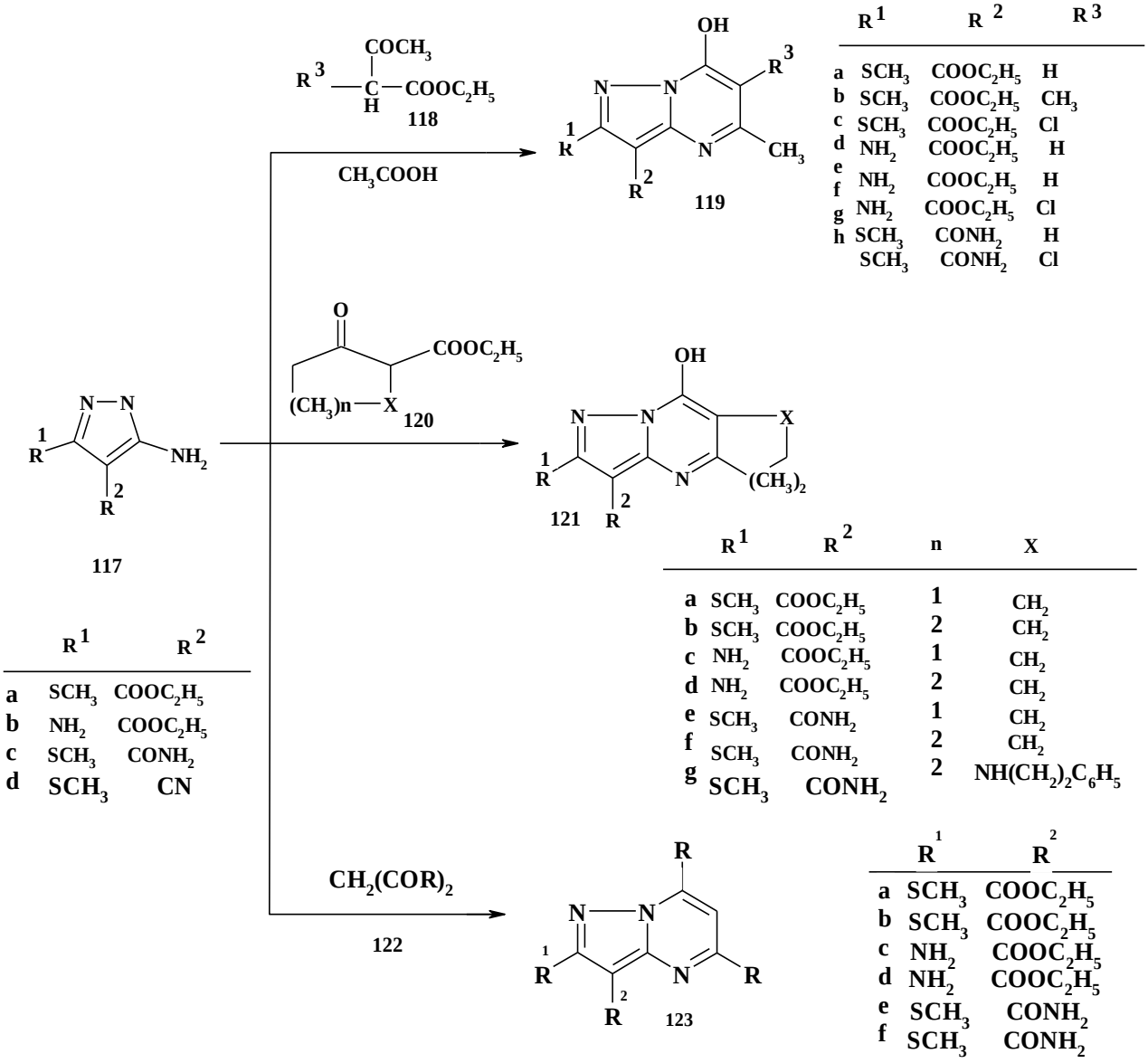
(Scheme 27)

Pyrazolo[1,5-*a*]pyrimidines **114-116**[57]**,** were prepared by the reaction of 5-(3)- amino pyrazole **110** with ketene dithioacetals **111, 112** and **113.** (Scheme 28).



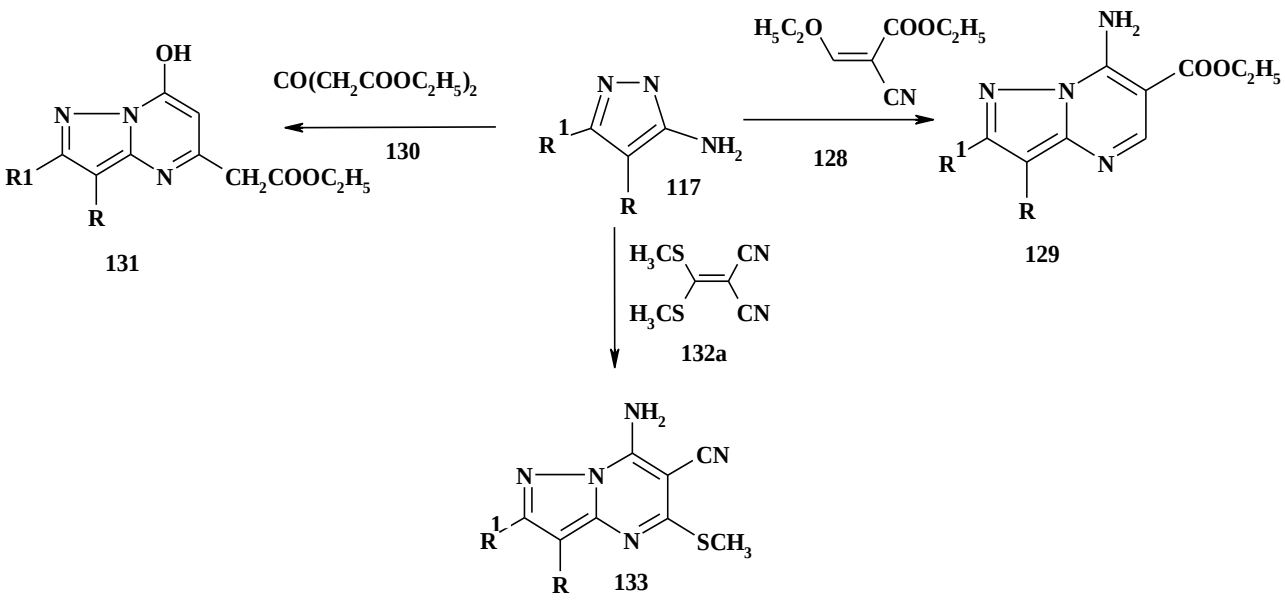
(Scheme 28)

Ram et al[58], have found that pyrazolo[1,5-*a*]pyrimidines **119, 121, 123, 125** and **127** can be prepared by reaction of 5-aminopyrazole **117a-d** with acrylic *β*-ketoester **118, 120**, *β*-diketones **122**, *β*-oxo ketene dithioacetate **124** and benzocyclic ketene dithioacetals **126**. (Scheme 29).



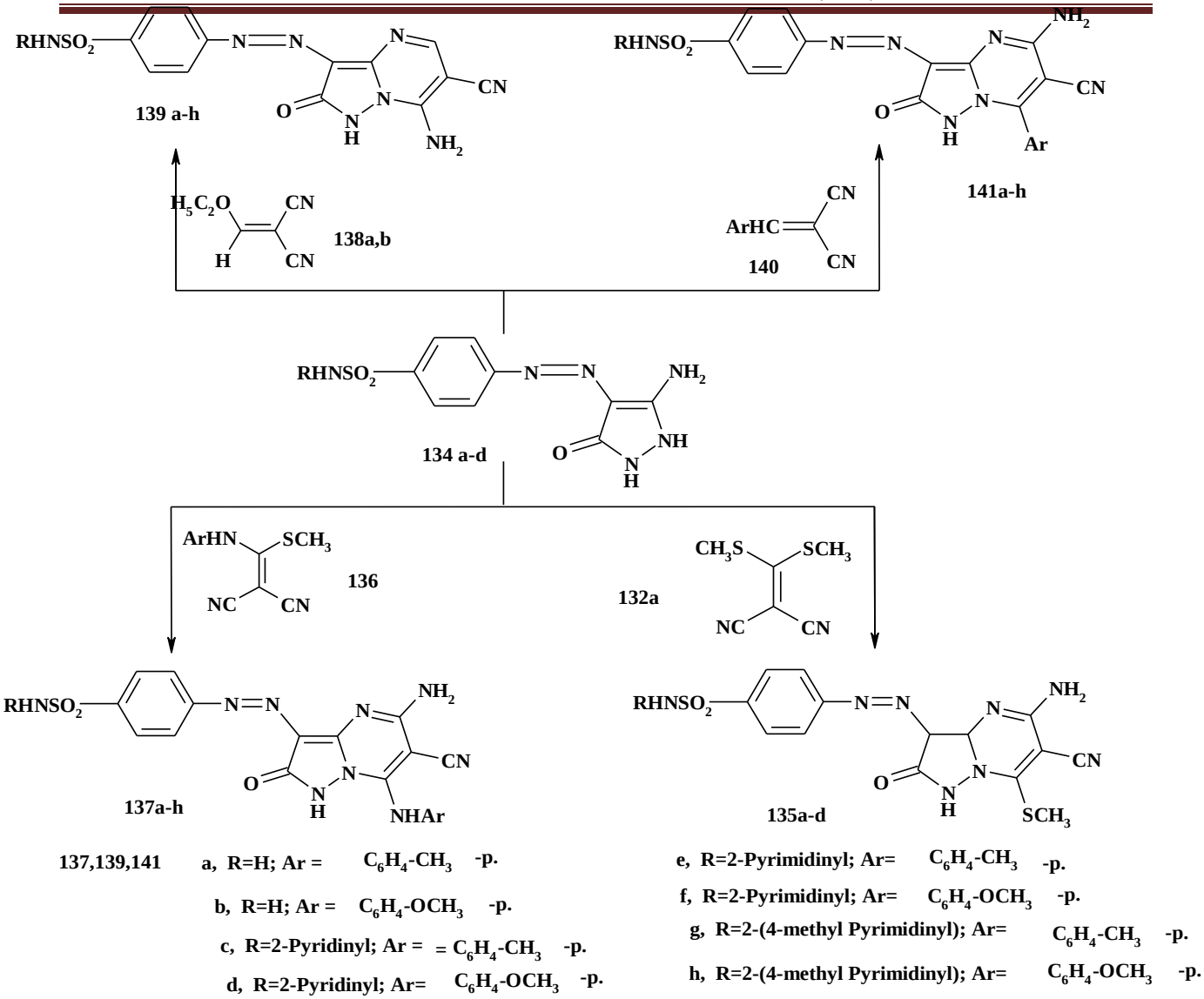
(Scheme 29)

Synthesis of pyrazolo[1,5-*a*]pyrimidines **129, 131** and **133** , were reported by the reaction of 5-aminopyrazole **117** with acyclic *β*-keto esters **128, 130 a**nd ketene dithioacetals **132** respectively[58]**.** (Scheme 30).



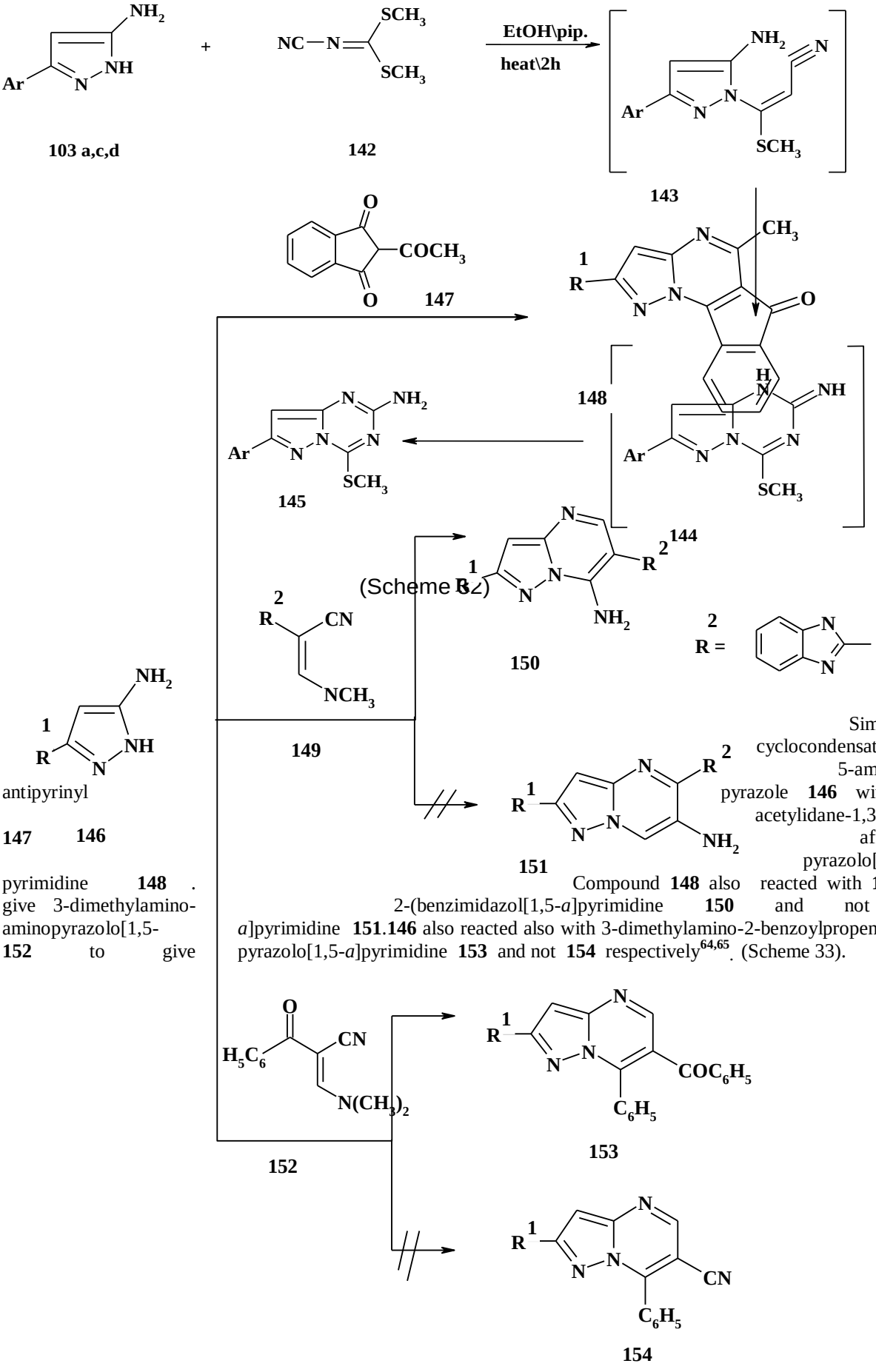
(Scheme 30)

El-Gaby et al[59], have found that compound **132a** reacted with aminopyrazole **134$_{a-d}$** to yield the corresponding pyrazolo[1,5-*a*]pyrimidine **137a-d** via formation of the intermediate **135a-d**. The aniline derivatives **139a-d** were synthesized by a one-pot reaction by refluxing aminopyrazole **134a-d** with [(aryl amino methylthio)methylene]malononitrile **140d,e** to yield pyrazolo[1,5-*a*]pyrimidine **141$_{a-h}$,** When ethoxymethylenemalono-nitrile **138a-d** was reacted with the amino pyrazole **134$_{a-d}$** the corresponding pyrazolo pyrimidine **139a-h** was offeried[60-62]. (Scheme 31).



(Scheme 31)

Elgemeie et al[63], reported that dimethyl *N*-cyano-dithioiminocarbonate **142** reacted with (3)5-aminopyrazole **103** to give the corresponding 4-methylthiopyrazolo [1,5-*a*]1,3,5-triazine **145** via the formation of intermediates **143, 144.** (Scheme 32).

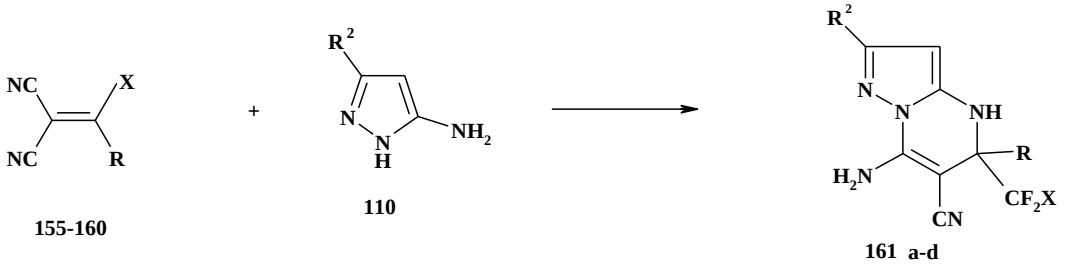


(Scheme 32)

antipyrinyl pyrimidine **148** . Similarly, cyclocondensation of 5-amino-2-pyrazole **146** with 2-acetylidane-1,3-dione afforded pyrazolo[1,5-*a*] pyrazolo[1,5-*a*]pyrimidine **150** and not 5-aminopyrazolo[1,5-*a*]pyrimidine **151**.**146** also reacted also with 3-dimethylamino-2-benzoylpropenonitril **152** to give Compound **148** also reacted with **149** to 2-(benzimidazol[1,5-*a*]pyrimidine **153** and not **154** respectively[64,65]. (Scheme 33).

(Scheme 33)

Golubev et al[66], found that alkenes **155-160** reacted with 5-amino-5(3)-methyl pyrazole **110** to give pyrazolo[1,5-*a*]pyrimidine **161$_{a-d}$**. (Scheme 34).



155-160

110

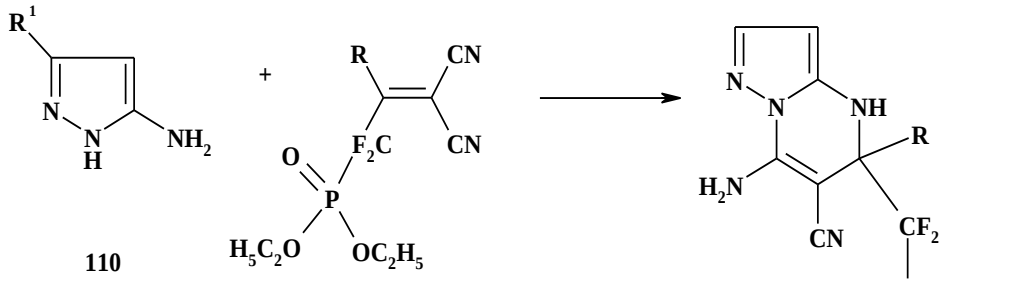
161 a-d

	R	X
155	Cl	CF_3
156	Cl	CF_2Cl
157	H	CF_2Cl
158	H	CF_2H
159	H	CF_3
160	Cl	CO_2CH_3

161	a	b	c	d
X	Cl	Cl	H	H
R	CF_3	CF_2Cl	CF_3	CF_2Cl

(Scheme 34)

Pasternak et al[67], found that the interaction between 1-aryl-3-methyl-5-amino pyrazole **110** and ethyl- 3,3-dicyano-2-[(diethoxyphosphoryl)difluoromethyl] acrylate **162a,b** formed 4,5-dihydropyrazolo[1,5-a]pyrimidine **163a,b**. (Scheme35).



110

162 a,b

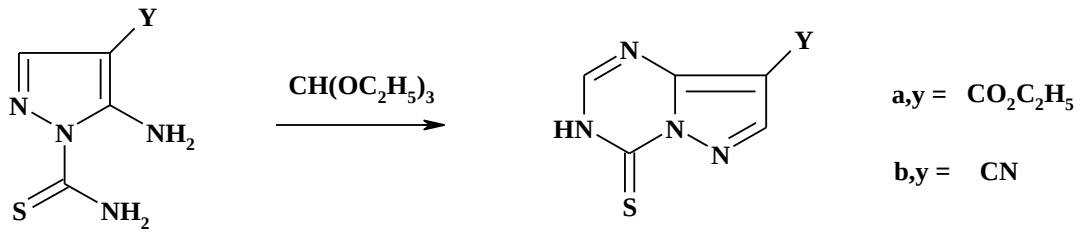
163 a,b

162 a, R = CF_3

b, R = $COOC_2H_5$

(Scheme 35)

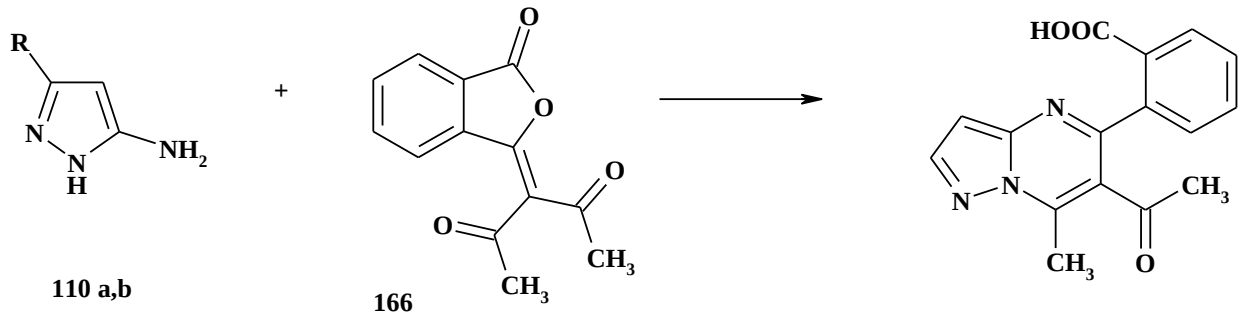
Condensation of 4-substituted 5-amino pyrazole-1-carbothioamides **164a,b** with triethylorthoformat lead to the formation of the pyrazolo[1,5-*a*]triazine derivative **$165_{a,b}$**[68]. (Scheme 36).



164 a,b **165 a,b**

(Scheme 36)

Reaction of 3-(3-oxo -2benzofuran-1(3*H*)-lidene) pentane2,4-diene **166** with aminopyrazole **110** to afford the desired 2-(6-acetyl-2- 7-methyl pyrazolo[1,5-*a*] pyrimidine-5-yl) benzoic acids **167a,b** after a few minutes[69]. (Scheme 37).

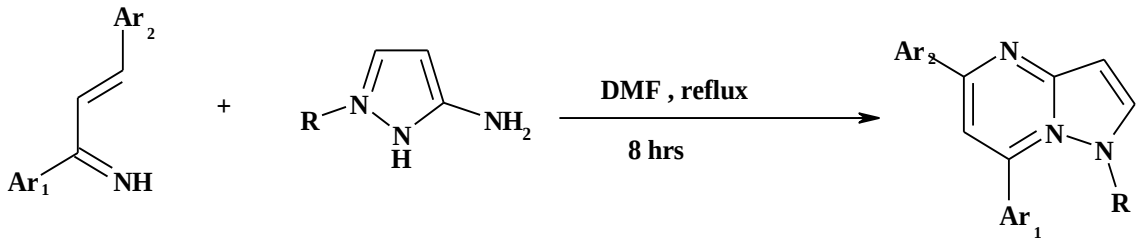


110 a,b **166** **167 a,b**

167	R
a	CH_3
b	$(CH_3)_3C$

(Scheme 37)

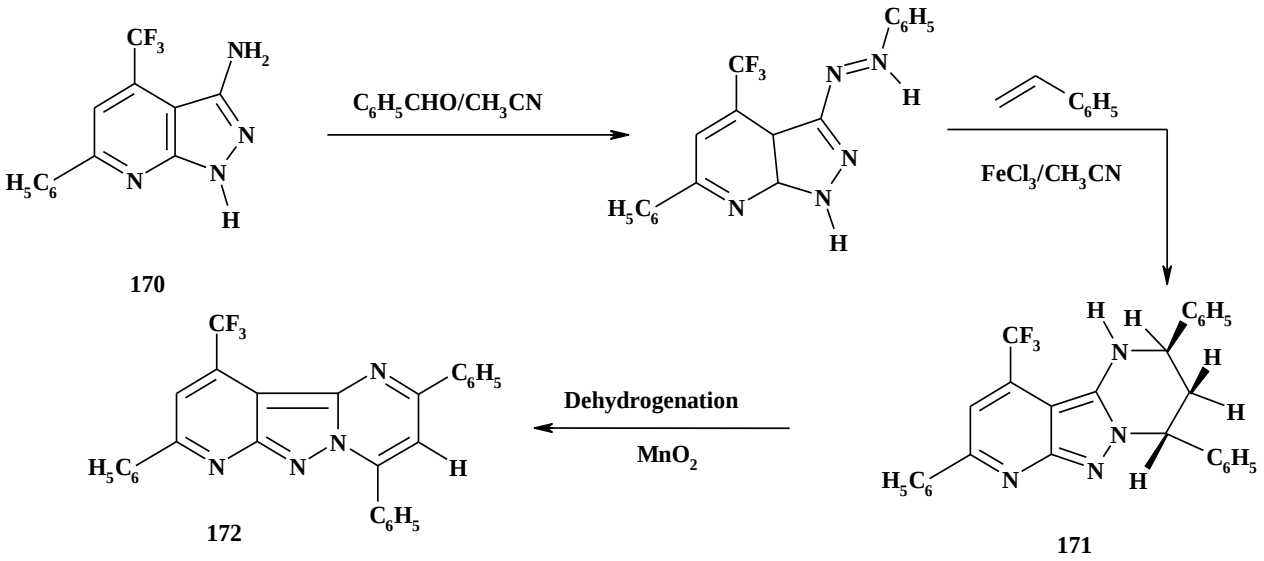
Reaction of *α,β*-unsaturated imines **168** with 5-aminopyrazoles, this one-pot procedure yielded the anticipated pyrazolo[1,5-a]pyrimidine **169**[70]. (Scheme 38).



168 **169**

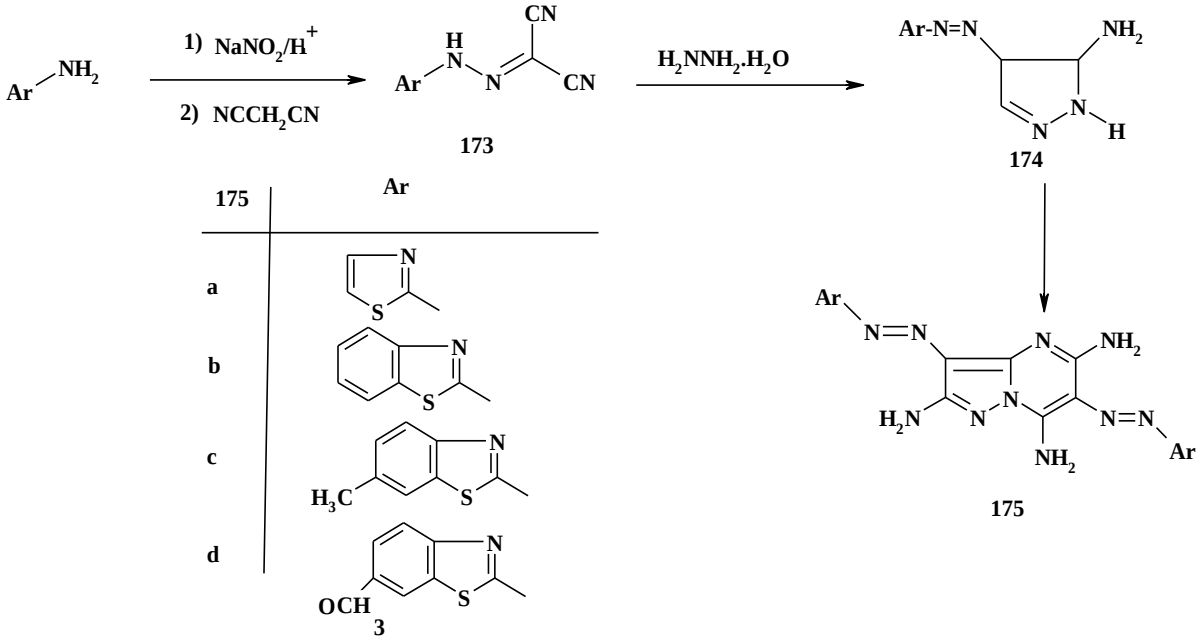
(Scheme 38)

Kanth et al[71], found that the compound **170** was reacted with benzaldehyde in acetonitrile at room temperature and isolated Schiff's base which reacted with styrene in presence of $FeCl_3$ to obtain compound **171** which was dehydrogenated with active MnO_2 to give pyrido[2\',3\':3\',4\']pyrazolo[1,5-*a*] pyrimidine/quinazoline **172**. (Scheme 39).



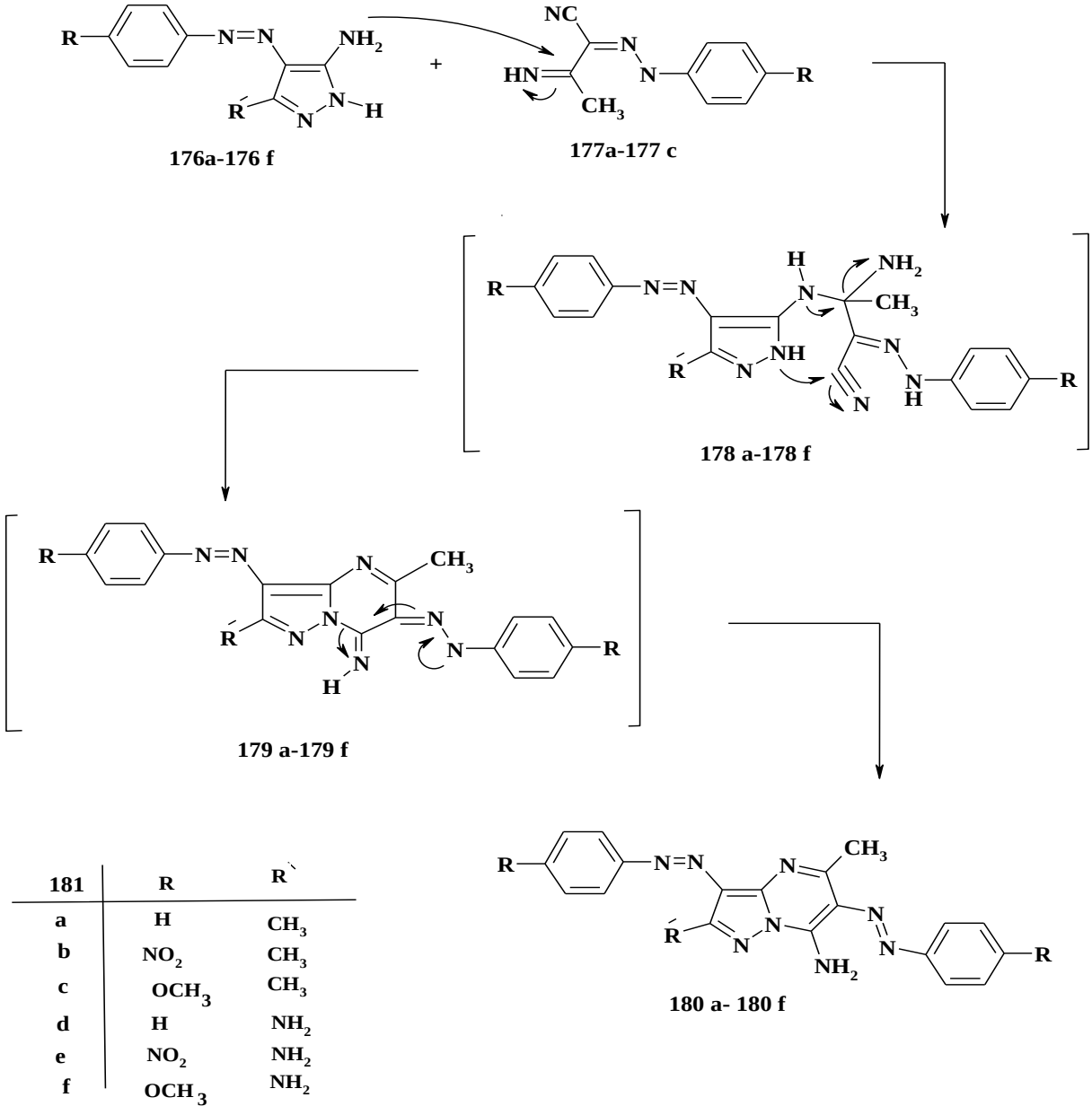
(Scheme 39)

Masoud et al[72], found that 3,6-bis-hetarlazo-2,5,7-triaminopyrazolo[1,5-*a*]pyrimidine heterocyclic diazo **175** was synthesized by the cyclization of **173** with hydrazine hydrate (65%) in molar ratio 2:1 in ethanol by reaction of **174** with equimolar amount of **173** being obtained as red-brown to purplesolid. (Scheme 40).



(Scheme 40)

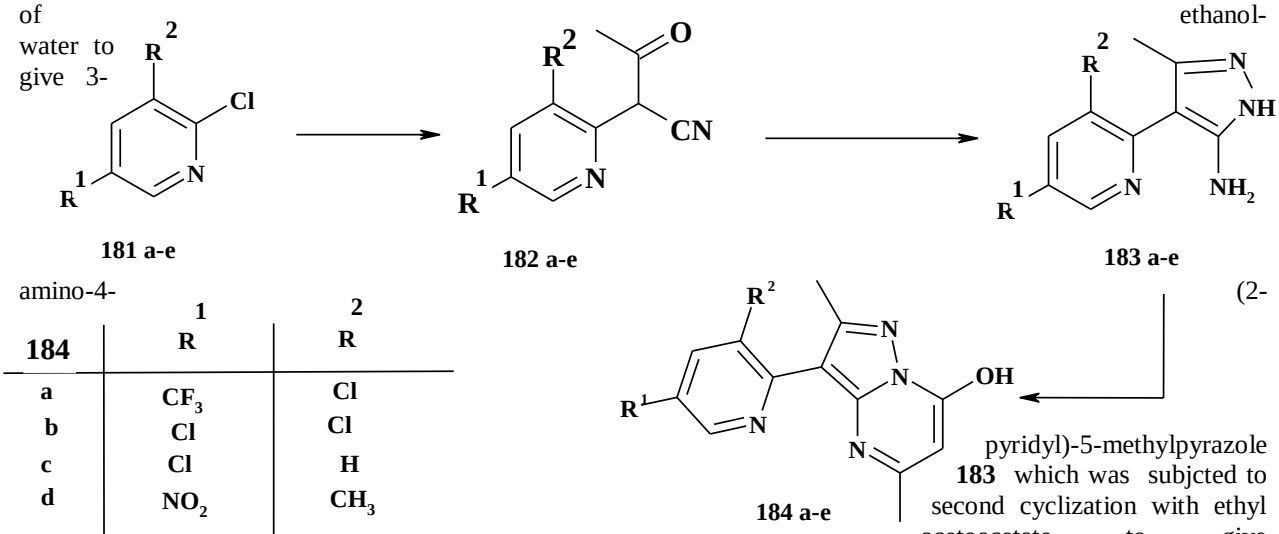
Reaction of 5-amino-4-acylazo -3-methyl-*1H*-pyrazole **176a-c** and 3,5-diamino-4-arylazo-pyrazole **176d-f** with 2-arylhydrazone-3-ketimino- butyronitrile **177a-c** in refluxing ethanol containing a catalytic amount of pyridine yielded 3,6-diarylazo-7-amino-2,5-dimethyl pyrazolo[1,5-*a*]pyrimidine **180a-c** and 3,6-diarylazo-2,7-diamino-5-methyl pyrazolo[1,5-*a*]pyrimidine[73]**.** (Scheme 41).



181	R	R`
a	H	CH_3
b	NO_2	CH_3
c	OCH_3	CH_3
d	H	NH_2
e	NO_2	NH_2
f	OCH_3	NH_2

(Scheme 41)

Reaction of 2,3-dichloro-5-trifluoromethylpyridine **181** with tetra-butylcyano acetate in presence of sodium hydride produced 2-(2-pyridyl) acetonitrile **182** which cyclized with hydrazine hydrobromide in mixture of ethanol-water to give 3-amino-4-(2-pyridyl)-5-methylpyrazole **183** which was subjcted to second cyclization with ethyl acetoacetate to give pyrazolo[1,5-*a*]pyrimidinones **184**[74]. (Scheme 42).

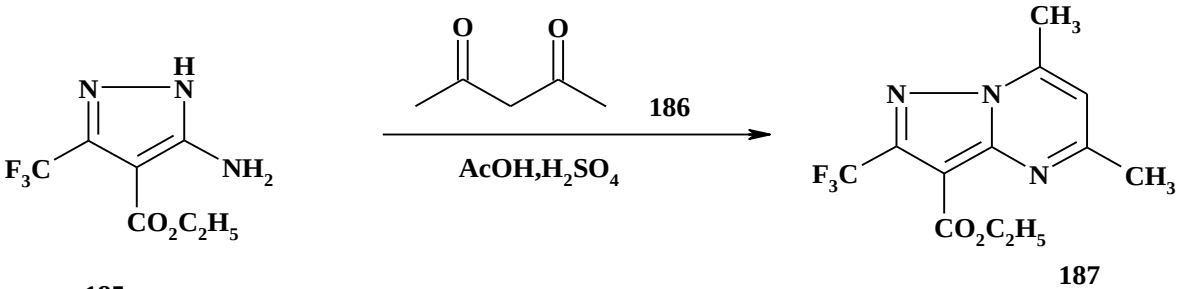


181 a-e **182 a-e** **183 a-e** **184 a-e**

184	R^1	R^2
a	CF_3	Cl
b	Cl	Cl
c	Cl	H
d	NO_2	CH_3
e	CH_3	NO_2

(Scheme 42)

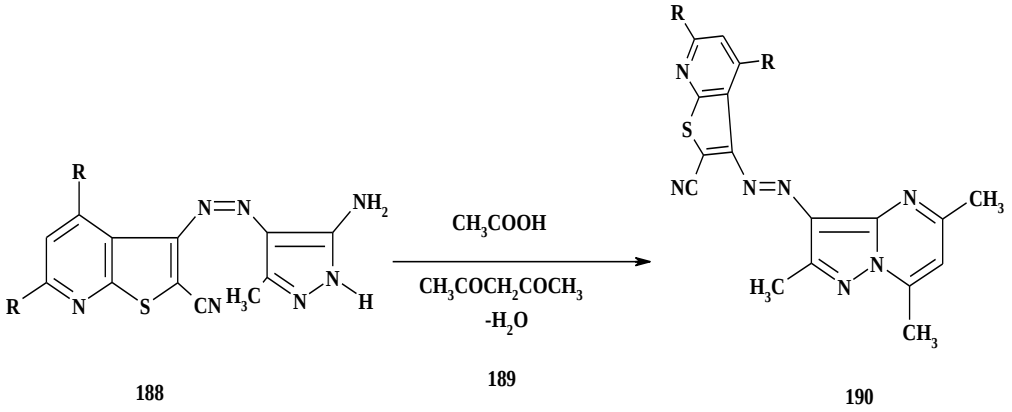
Wu et al[75,76], found that ethyl 2-trifluoromethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate **187** was prepared by reaction of ethyl 5-amino-3-trifluoromethyl(1H)pyrazole 4-carboxylate **185** with pentane-2,4-dione **186** in presence of AcOH and H_2SO_4. (Scheme 43).



185 **187**

(Scheme 43)

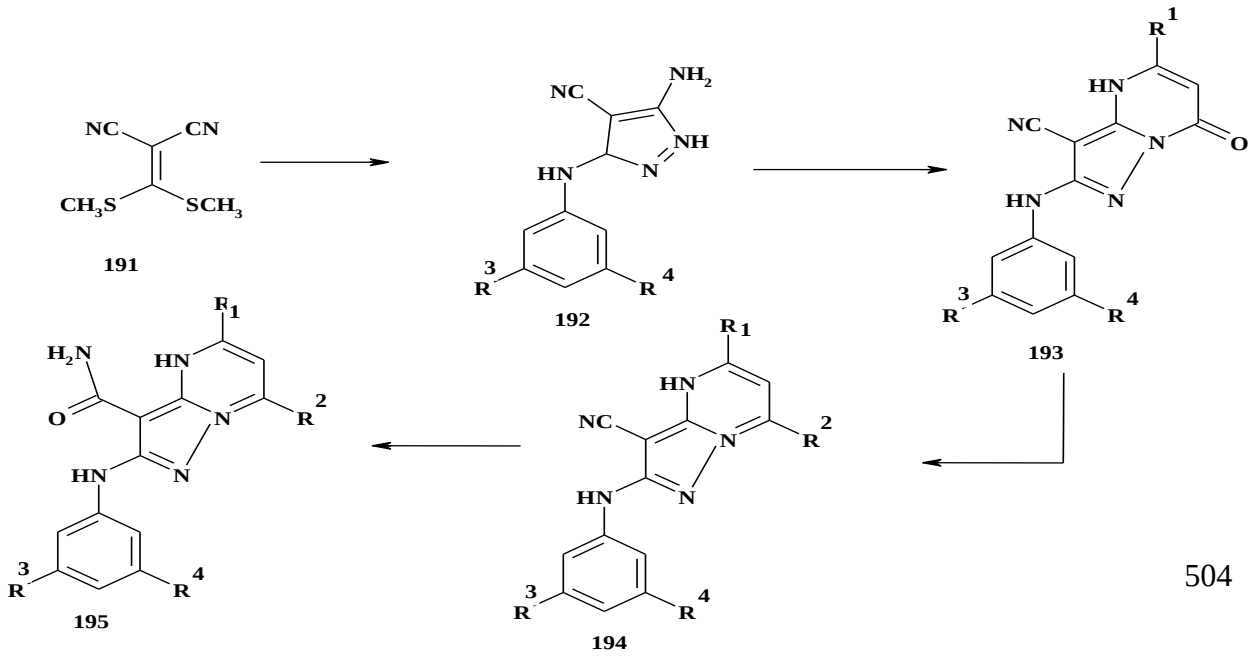
Reaction of 2-cyano-3-(5-amino-3-methyl-pyrazol-4-yl) azo-4,6-disubstituted-thieno[2,3-*b*]pyridine **188** with acetyl acetone **189** in refluxing glacial acetic acid yield 2-cyano-3-(2,5,7)-trimethylpyrazolo[1,5-*a*]pyrimidine-3-yl)-azo-4,6-disubstituted-thieno[2,3-*b*]pyridine dye **190**[77]. (Scheme 44).



188 189 190

(Scheme 44)

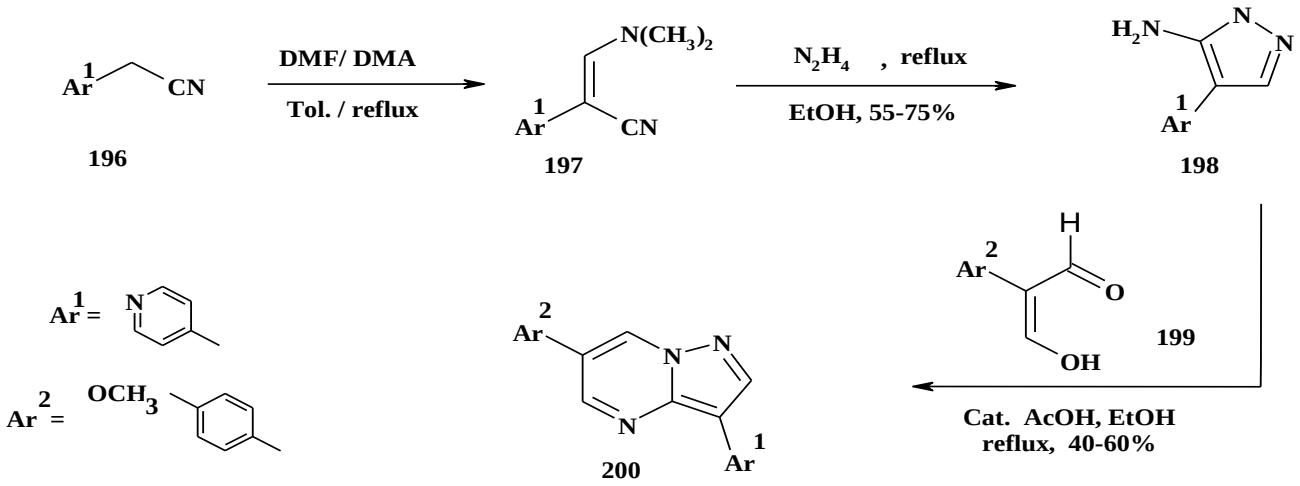
Synthesis of a 5,7-disubstituted-2-anilino pyrazolo[1,5-*a*]pyrimidine **195** was prepared by replacing the corresponding aniline with ketene dithioacetales **191** and then cyclizing with hydrazine monohydrate to yield pyrazolo derivative **192** and cyclized compound **192** by *β*-keto ester derivative generated 2-aniline pyrazolo[1,5-*a*]pyrimidine-7-one-analoge which treatment with phosphorus oxychloride in *N*,*N*-dimethyl aniline provided the corresponding chloro derivative, which were converted to 3-cyanopyrazole[1,5-*a*]pyrimidine **194** by substitution of 7-chlorine with substituted amino alcohol. Finally, the target compound **195** was prepared by hydroxylation of the corresponding nitrile **194** with basic hydrogen peroxide in dimethyl sulfoxide (DMSO)[78]. (Scheme 45).



191 192 193 194 195

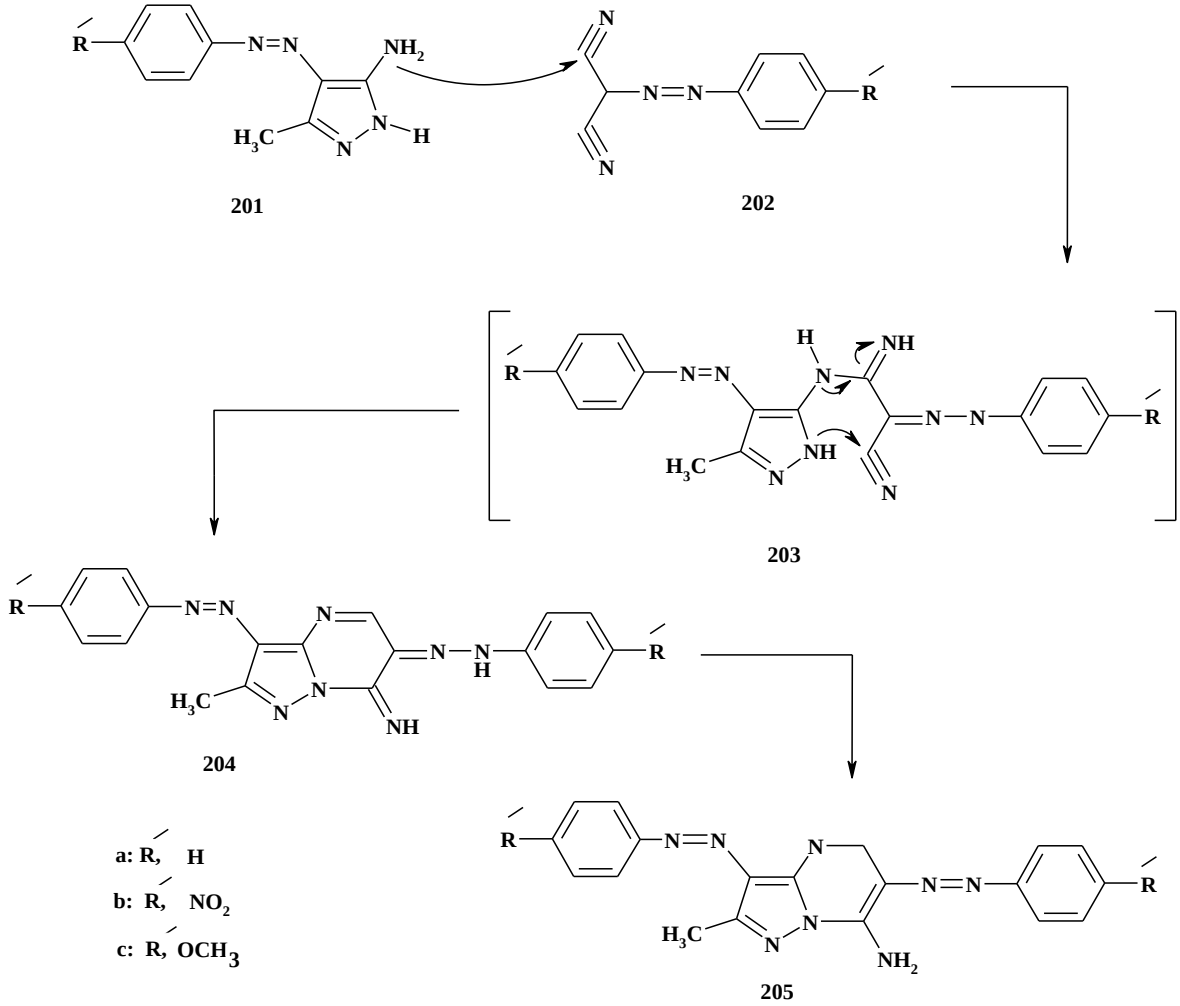
(Scheme 45)

Daniels et al[79-81], found that pyrazolo[1,5-*a*]pyrimidine **200** involve refluxing a 5-amino-4-arylpyrazole **196** with a commercially available 2-arylmalondialdehyde **199** in ethanol with catalytic acetic acid for 24h to deliver pyrazolo[1,5-*a*] pyrimidine. (Scheme 46).



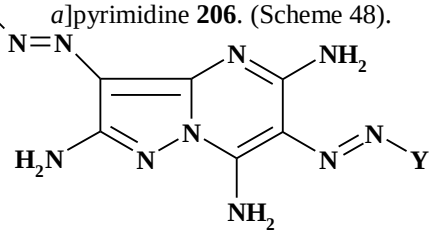
(Scheme 46)

Treatment of 5-amino-4-arylazo-3-methyl-*(1H*)- pyrazole **201a-c** with 2-arylhydrazonomalononitrile **202a-c** in refluxing ethanol-pyridine solutions yielding 3,6-diarylazo-5,7-diamino-2-methyl-pyrazolo[1,5-*a*]pyrimidine **205a-c**[82-85]. (Scheme 47).



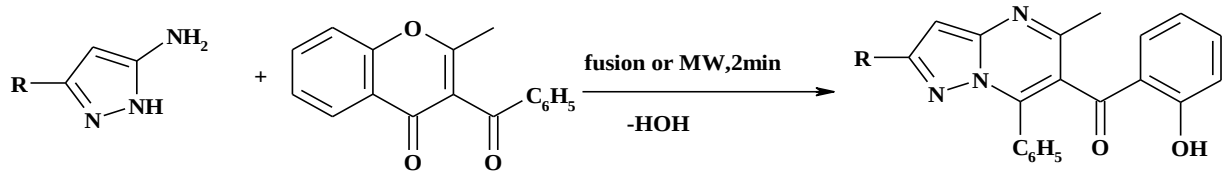
(Scheme 47)

Tasi et al[86], found that 3,6-diaryl-2,5,7-triamino pyrazol[1,5-*a*]pyrimidine diazo, obtained by cyclization of aryl azomalononitrile with 4-arylazo-3,5-diaminopyrazole derivatives which react easily with arylazo-and heteroazomalono nitrile to afford a number of new 3,6-disubstituted-azoyl-2,5,7-triaminopyrazolo[1,5-*a*]pyrimidine **206**. (Scheme 48).



(Scheme 48)

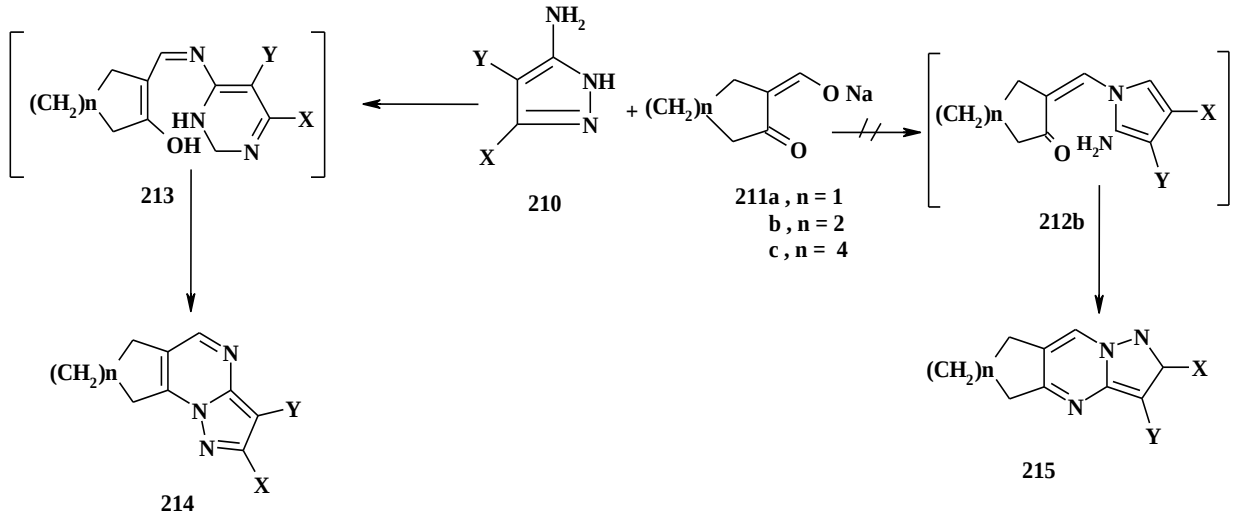
A series of 6-(2-hydroxybenzoyl)-5-methyl-7-phenyl pyrazolo[1,5-*a*] pyrimidines **209** have been synthesized directly by the solvent free reaction between 5-amino-1*H*-pyrazoles **207** and 3-benzoyl-2-methyl-4*H*-chromen-4-one **208**[87]. (Scheme 49).



207 **208** **209**

(Scheme 49)

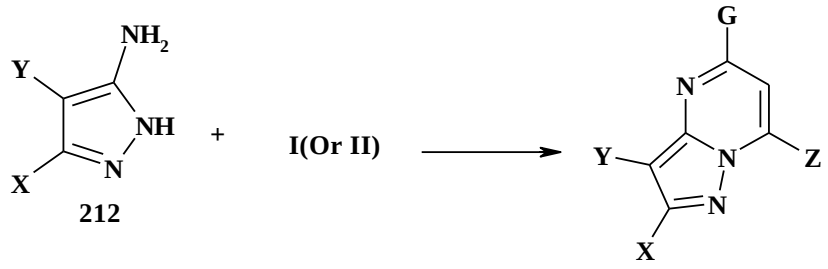
Ahmed et al[88],found that, treatment of 5–amino–3-methylsulfanyl-4-phenyl carbamoyl– *1H*-pyrazole **210a** with sodium (3-oxo cyclo phenyl diene) methanolate **211a** in acetic acid containing piperidine acetate afforded (2-ethylthio (6,7,8,8b-tetrahydrocyclopenta[2,1-*e*]pyrazolo[1,5-*a*]pyrimidin–3-yl)*N* benzamide **214a** or isomeric **215a**. (Scheme 50).



(Scheme 50)

212,214a : y = C_7H_6 NO; X = SCH_3

Reaction of **212a** with 2,4–pentanedione in boiling acetic acid afforded 5,7-dimethyl-2-methylsulfanyl-4-phenylcarbamolypyrazolo[1,5-*a*]pyrimidine **216a** Similarly, 2,4-pentanedione reacted with appropriate **212** in boiling acetic acid, to give pyrazolo[1,5-*a*]pyrimidine **216** respectively[88]. (Scheme 51).



I= CH_3 CO CH_2 CO CH_3

II= $CH_3COCH_2COC_6H_5$

216 ,G = Z= CH_3

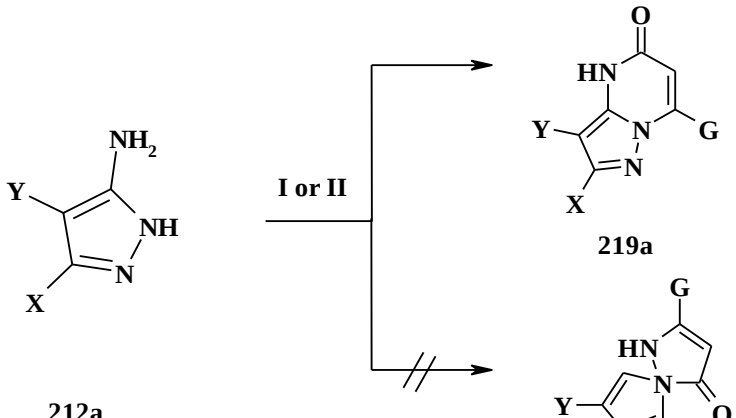
217 ,G=CH_3, Z= C_6H_5

218 , G= C_6H_5 , Z =CH_3

(Scheme 51)

212, 216, 218a: y = C_7H_6 NO ;X = SCH_3 b: y = 4-CH_3.C_7H_5No , X = SCH_3

Treatment of ethyl 3- oxobutanoate with **212a** gave one isolable product 7-methyl 2-methyl sulfonyl -5- oxo-3-phenyl carbamoyl-pyrazolo[1,5-*a*]pyrimidine **219a** or isomeric 5-methyl-2-methyl sulfonyl- 7-oxo–3phenyl-carbamoylpyrazolo[1,5-*a*]pyrimidine **220a**[88]. (Scheme 52).



I = $CH_3COCH_2CO_2C_2H_5$

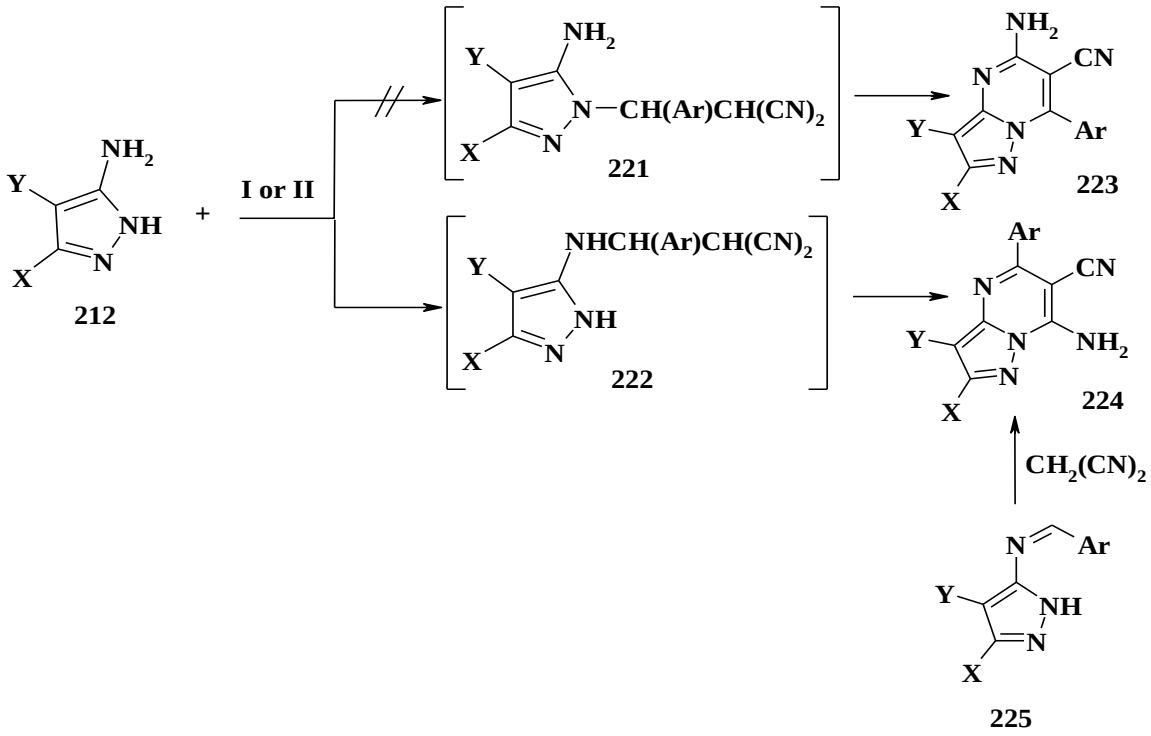
II = $C_6H_5COCH_2COC_2H_5$

(Scheme 52)

212, 219a: y = C_7H_6 NO; X =SCH_3

Also, **212a** reacted with 1-cyano-2-phenyl acrylo nitrile in boiling ethanol under reflux afforded 7-amino-6

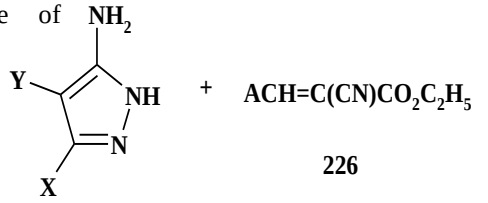
cyano-2-methyl sulfanyl-3-phenyl-carbamoyl-5-phenyl pyrazolo[1,5-*a*]pyrimidine **224a**[88]. (Scheme 53).

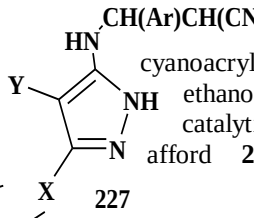


(Scheme 53)

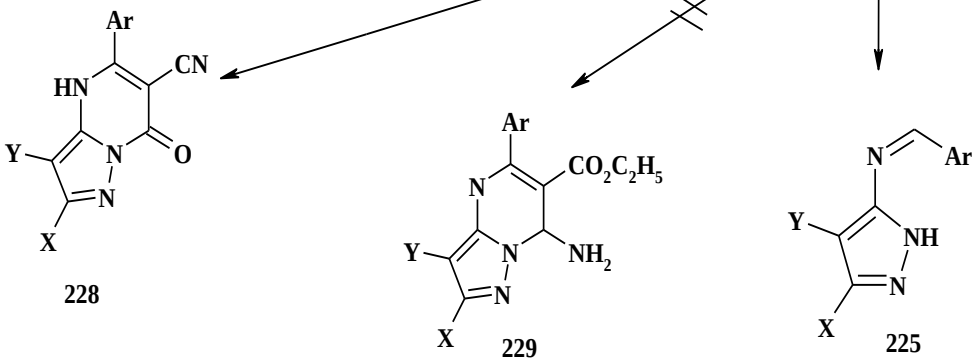
212, 22, 225a: Y = C_7H_6NO, X = SCH_3 ; Ar = C_6H_5

Treatment of **212a** with appropriate of 2-aryl-1-boiling piperidine, 54).



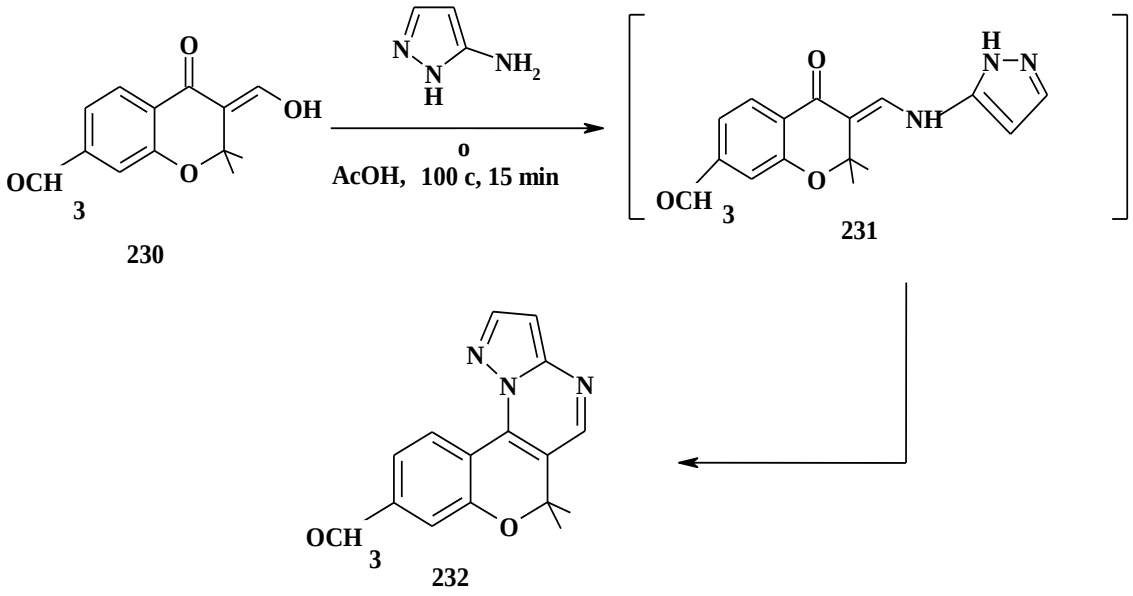


ethyl cyanoacrylate **226a** in ethanol containing catalytical amount of afford **225a**[88]. (Scheme



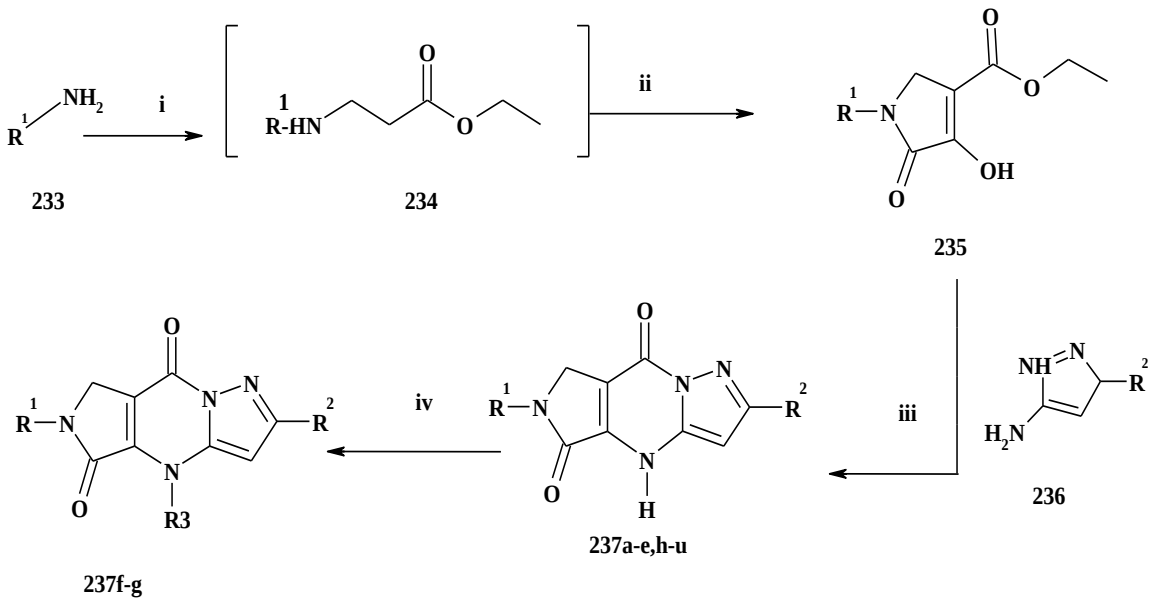
(Scheme 54)

Synthesis of pyrazolo[1,5-*a*]pyrimidine core structures from the hydroxyl– substituted s-cis enone **230** by treatment with 3-aminopyrazolo dervatives, our earlier attemps afforded only an enamine intermediate **231** without any of desired product under reaction conditions similar to those used for the pyrazole formatin. After an extensive screening of the reaction conditions, the desired pyrazolo[1,5-*a*] pyrimidine Fused benzopyran core skeleton **232** was synthesized in excellent yields as single regioisomer under microwave irradiation[89]. (Scheme 55).



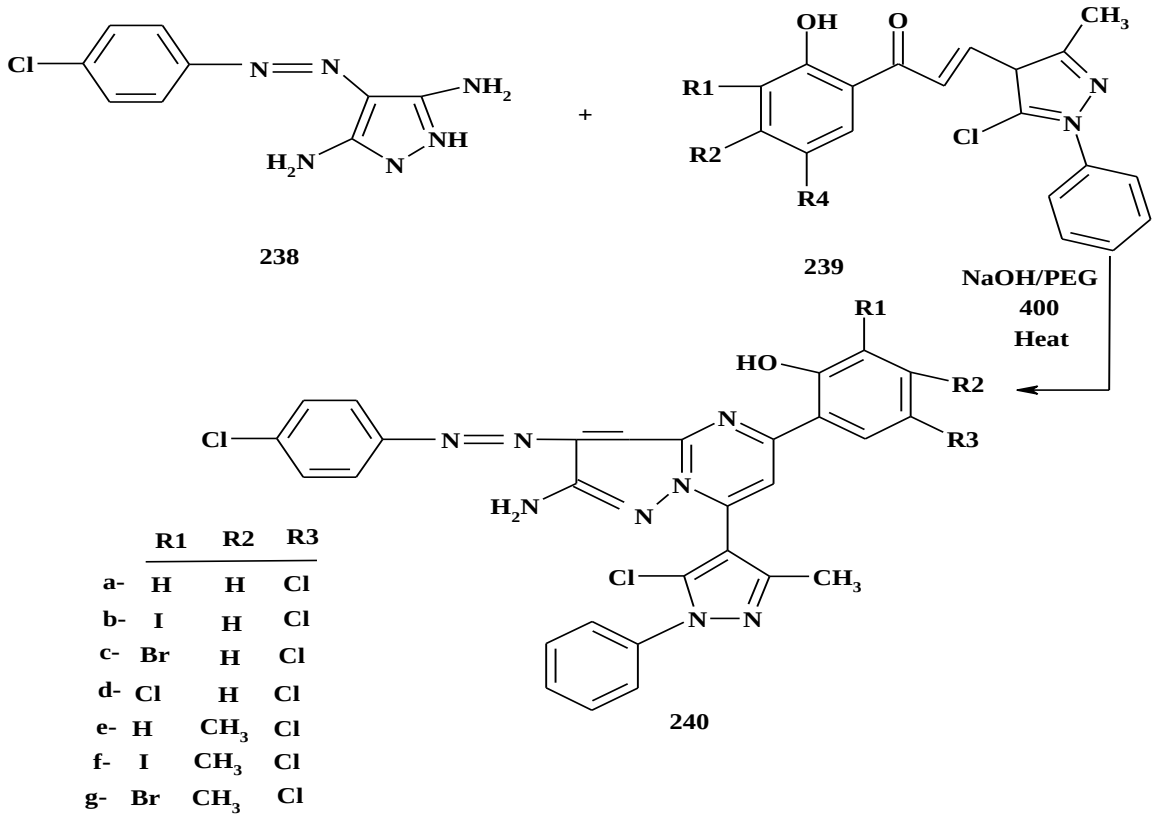
(Scheme 55)

Mohane et al[90], found that the general synthetic method for preparation of fused tricyclic compounds were commercially available amine **233** which were alkylated with ethyl acrylate in absolute ethanol by stirring at room tep. To give **235** . In the case of aniline for **237h,** Refluxing for 24h is required for the completion of the reaction intermediate amines **234** formed which cyclized in situ to the pyrrolidinones **235** using diethyl oxalate and sodium ethoxide in refluxing, Condensation of the latter with various substituted pyrazole **236** in refluxing glacial acetic acid gave the final tricyclic compounds **237a-e** , in 20-25 % overall yields after crystallizating from methanol. Derivitives **237f-g** were synthesized from **236a** by alkylation with methyl iodide or 4-(2-chlororthyl)-morpholing hydrochloride using potassium carbonate. (Scheme 56).



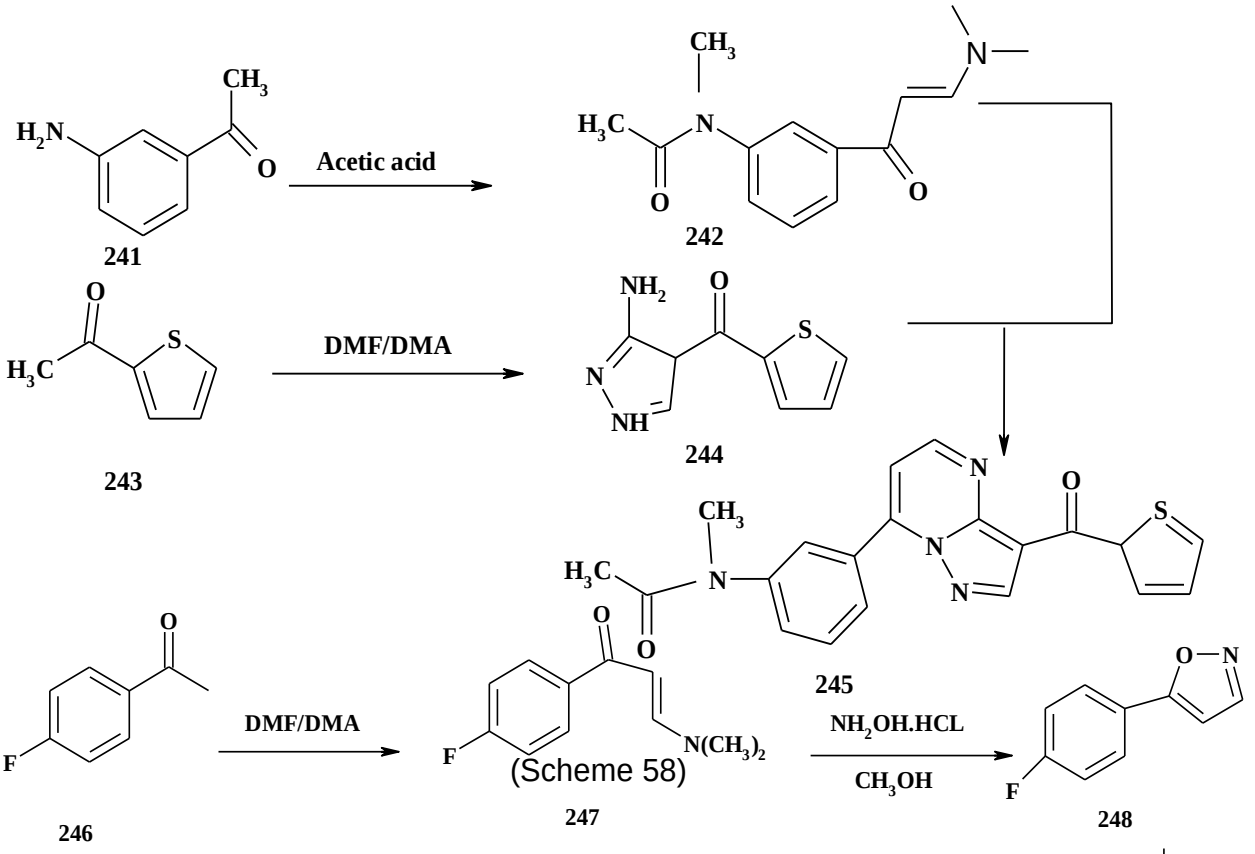
(Scheme 56)

Dawane et al[91], were prepared several pyrazolo[1,5-a]pyrimidine derivative by condensation of chalcones with substituted 5-aminopyrazoloas an alternative polyethylene glycol (PEG-400) as green reaction medium. (Scheme 57).



(Scheme 57)

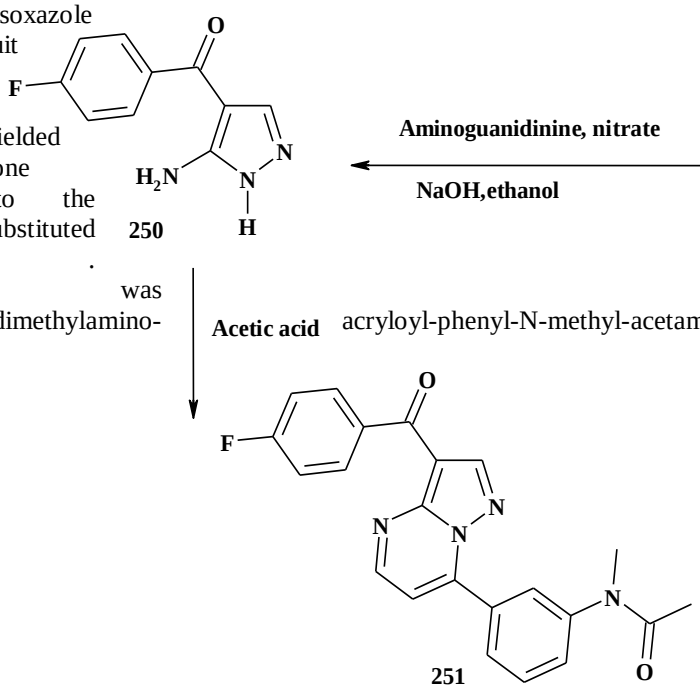
Hoepping et al[92], synthesis of pyrazolo[1,5-a]pyrimidine by reaction of thiophene derivative with aqueous acetic acid. (Scheme 58).



241 242 243 244 245 246 247 248 249

(Scheme 58)

Hoepping et al[93], synthesis of pyrazolo[1,5-a]pyrimidine **251** by conversion of 4-fluoro acetophenone **246** with DMF/DMA to enaminone and futher to the isoxazole proceeded quit smoothly openining of the isoxazole ring yielded cyano-enaminone which was converted to the benzoyl substituted aminopyrazole **250**. aminopyrazole was condensed with N-3-(3-dimethylamino-acryloyl-phenyl-N-methyl-acetamide. (Scheme 59).

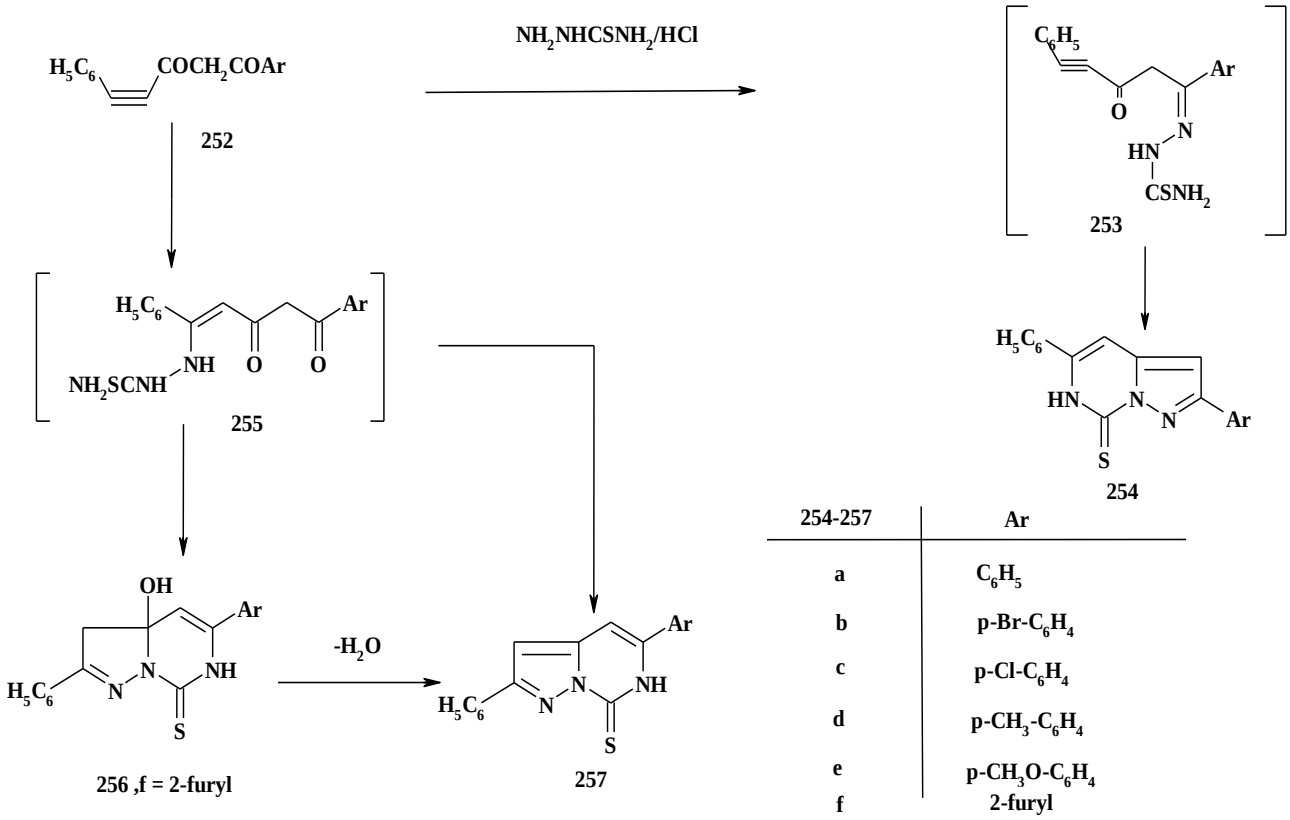


250 251

(Scheme 59)

2.2. Synthesis of Pyrazolo[1,5-c]pyrimidine derivatives.

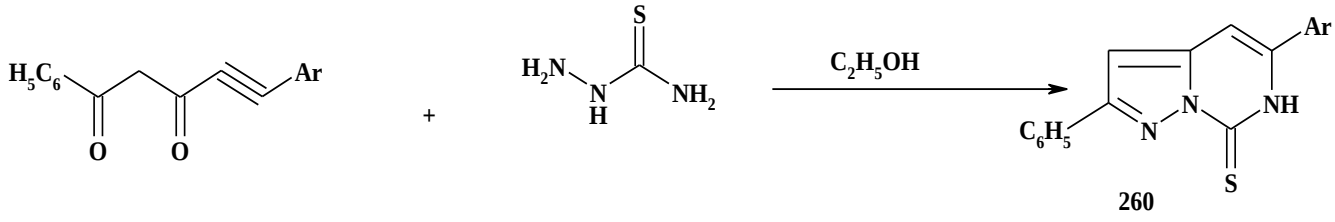
Marei et al[94-96], found that the reaction of 1-phenyl-5-arylpent-l-yne-3,5-diones **252a-c** with thiosemicarbazide or with thiosemicarbazide hydrochloride afforded the respective 2-aryl-5-phenyl-(*6H*)-pyrazolo[l.5-*c*]pyrimidine-7-thiones **254a-c**. However, under identical conditions **252d,e** gave **240d,e**. On the other hand, 5-furyl-9-hydroxy2-phenyl-*(3H,6H)*-pyrazolo[1,5-*c*]pyrimidine-7-thione **256f** was formed from **255f** under the same conditions. The latter could be converted into its thione **257f** on heating in xylene. (Scheme 60).



254-257	Ar
a	C_6H_5
b	p-Br-C_6H_4
c	p-Cl-C_6H_4
d	p-CH_3-C_6H_4
e	p-CH_3O-C_6H_4
f	2-furyl

(Scheme 60)

In a similar manner, the reaction of l-aryl-5-phenylpent-l-yne-3,5-diones **258** with thiosemicarbazide **259** to give 5-aryl-2-phenyl pyrazolo[1,5-*c*] pyrimidin7-thiones **260**[97-99]**.** (Scheme 61).



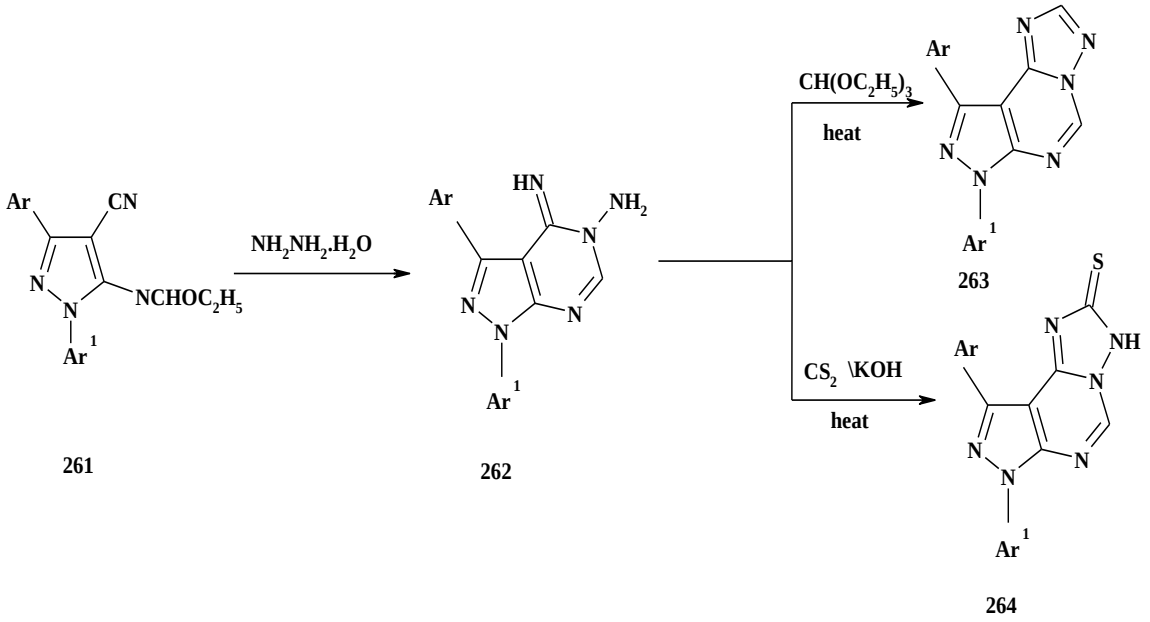
260 ,a,Ar = C_6H_5

b,Ar = C_6H_4-CH_3-p

c,Ar = C_6H_4-OCH_3-p

(Scheme 61)

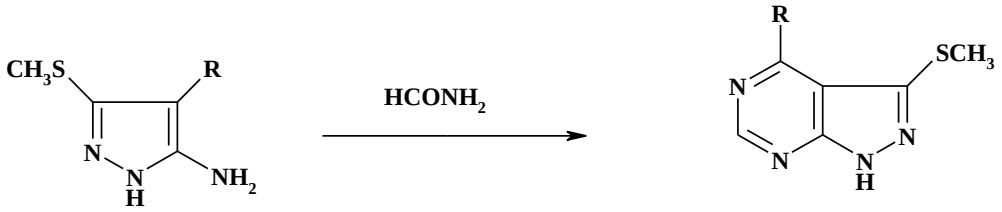
Synthetic development route to pyrazolo[4,3-*e*]1,2,4-trizolo[1,5-*c*] pyrimidines[100]. (Scheme 62).



(Scheme 62)

2.3. Synthesis of Pyrazolo[3,4-d]pyrimidine derivatives.

Cyclization of 5-amino-3-methylthiopyrazole derivatives **265a,b** with formamide afforded 4-amino- or 4-hydroxy-3-methylthiopyrazolo[3,4-*d*] pyrimidines **266a,b**[101,102.] (Scheme 63).

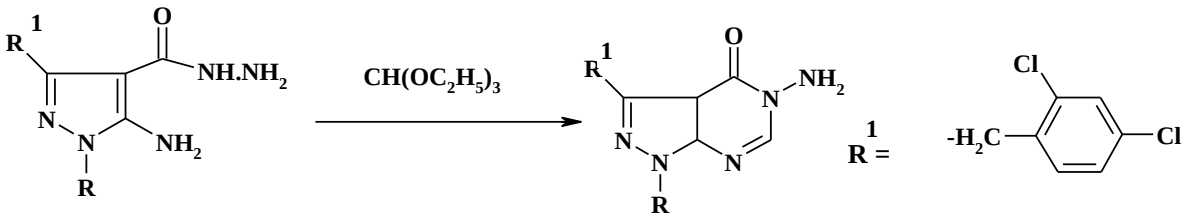


265 ,a, R= CN
b, R=CONH 2

266 a,b

(Scheme 63)

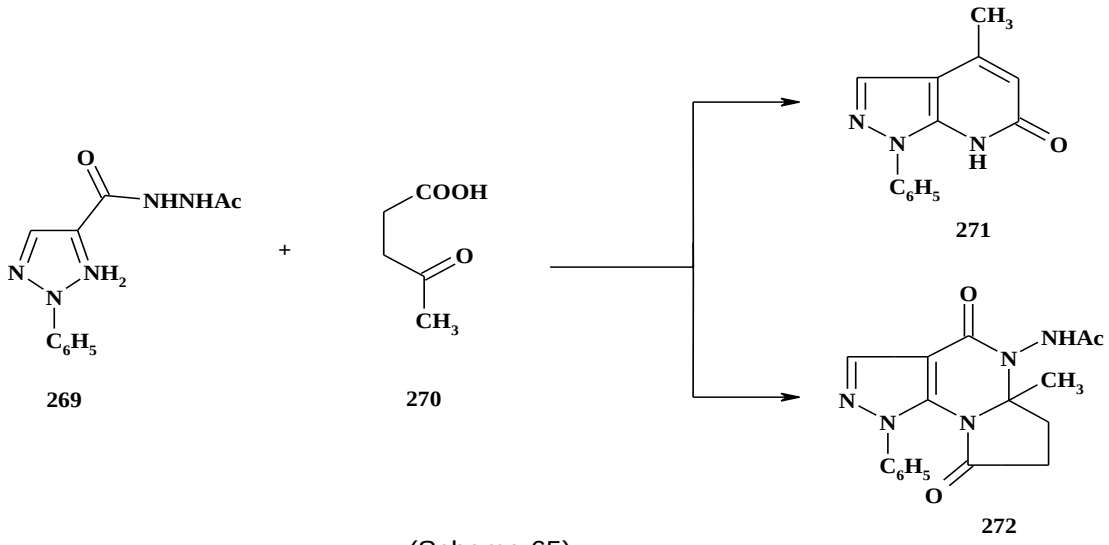
Gatta et al[103-104], described the synthesis of several pyrazolopyrimidines compounds with an imidazole, triazole or tetrazole ring fused to the pyrazolo[3,4-*d*]pyrimidine ring system. Thus the reaction of 5-amino-l-2,4-dichlorobenzyl pyrazole-4-carboxylicacidhydrazides **267** with triethylorthoformate produced 5-amino-l-(2,4- dichlorobenzyl)-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-ones **268.** (Scheme 64).



267 a,b **268 a,b**

(Scheme 64)

The acetyl hydrazide **269** reacted with levulic acid **270** to yield a Pyrazoloazepinone **271** together with pyrrolo pyrazolopyrimidinone **272**[105-113]. (Scheme 65).

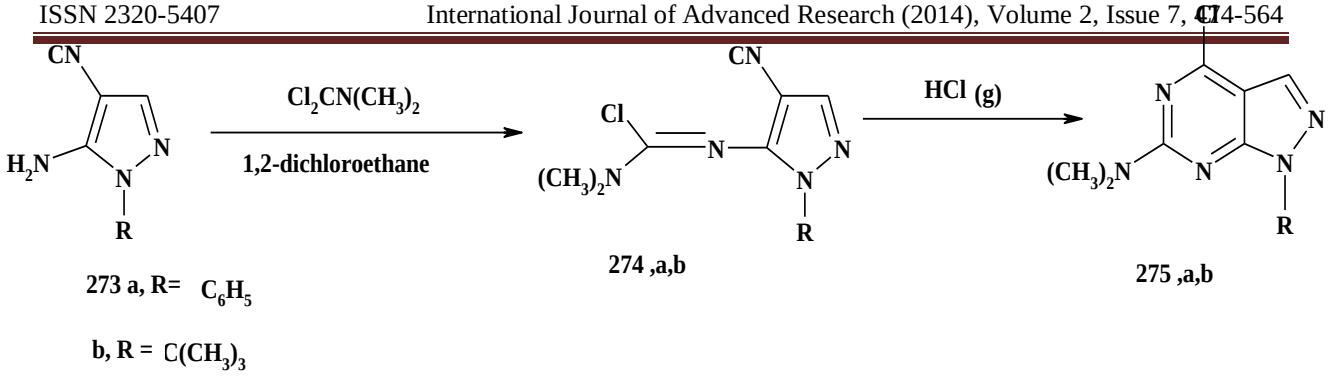


269 **270** **271** **272**

(Scheme 65)

Treatment of *N*-substituted 5-amino-4-cyclopyrazoles

273a,b with phosgene iminium chloride afforded the corresponding chloroamidines **274a,b** which on cyclization yielded the pyrazolo[3,4-*d*]pyrimidines **275a,b**[114-116]. (Scheme 66).



273 a, R= C_6H_5

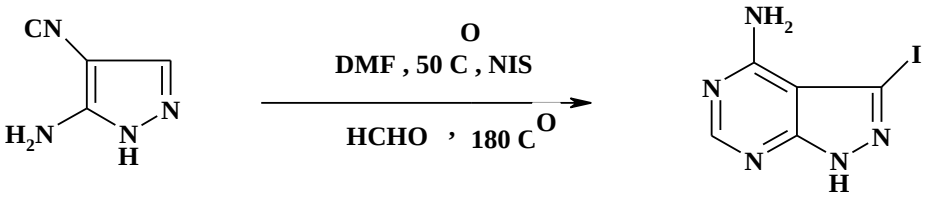
b, R = $C(CH_3)_3$

274 ,a,b

275 ,a,b

(Scheme 66)

Cyclization of the aminopyrazole **1** with formamide followed by iodination at C_3 gave the pyrazolopyrimidine derivative **276**[35,117,118]. (Scheme 67).

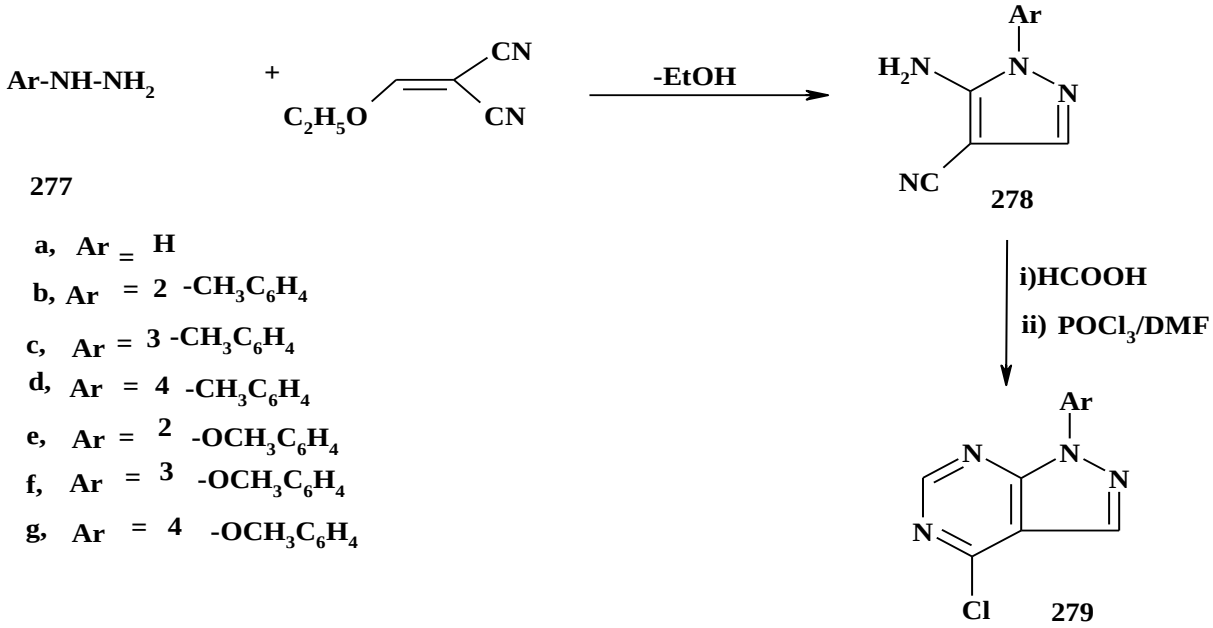


1

276

(Scheme 67)

Treatment of arylhydrazines **277** with ethoxymethylene malononitrile gave 1-aryl-4-cyano-aminopyrazoles **278** which were condensed with aqueous formic acid and treated subsequently with phosphorous oxychloride to give the 4-chloropyrazolo [3,4-*d*]pyrimidines **279**[119]. (Scheme 68).



277

a, Ar = H

b, Ar = 2 -$CH_3C_6H_4$

c, Ar = 3 -$CH_3C_6H_4$

d, Ar = 4 -$CH_3C_6H_4$

e, Ar = 2 -$OCH_3C_6H_4$

f, Ar = 3 -$OCH_3C_6H_4$

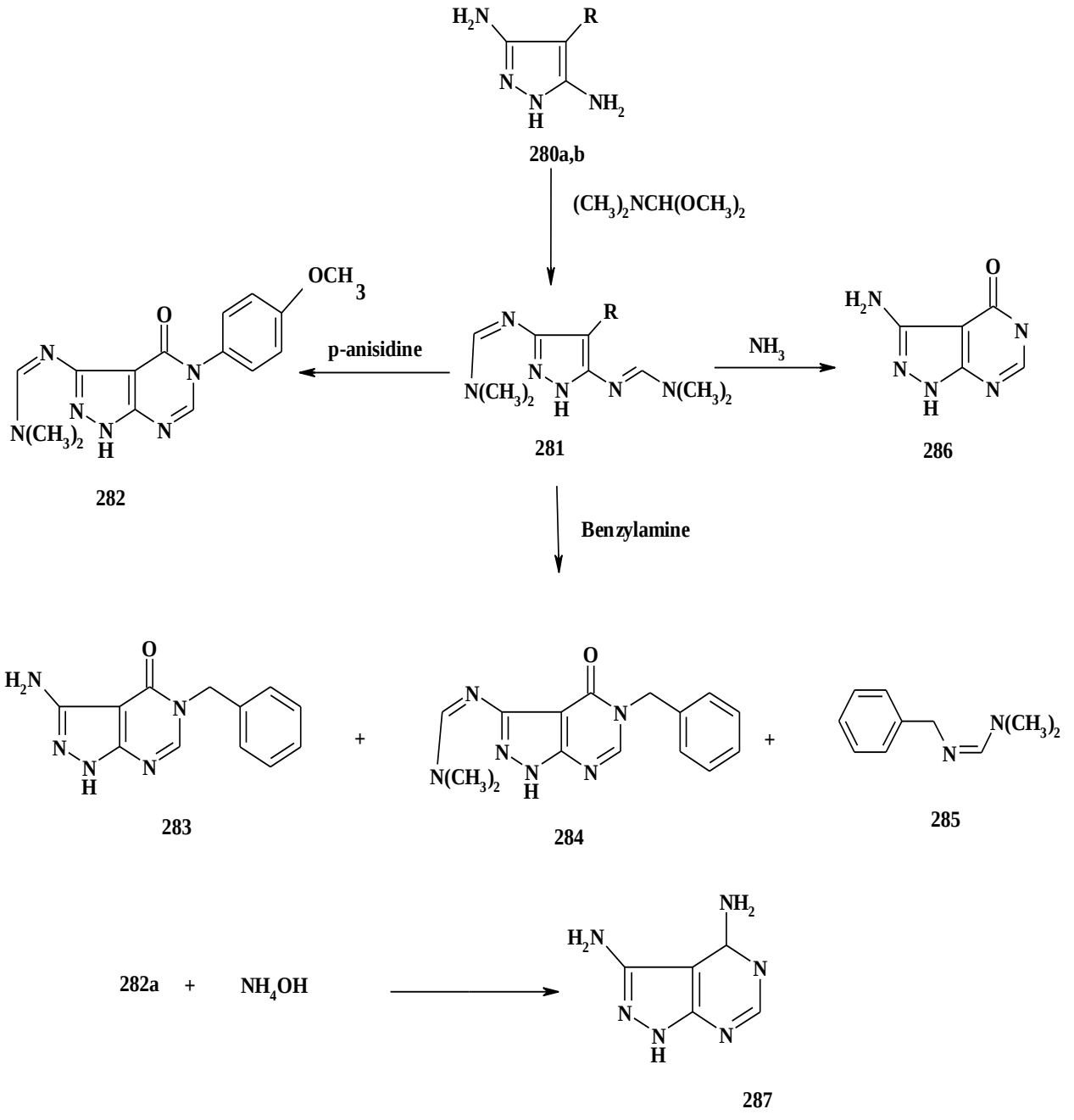
g, Ar = 4 -$OCH_3C_6H_4$

278

279

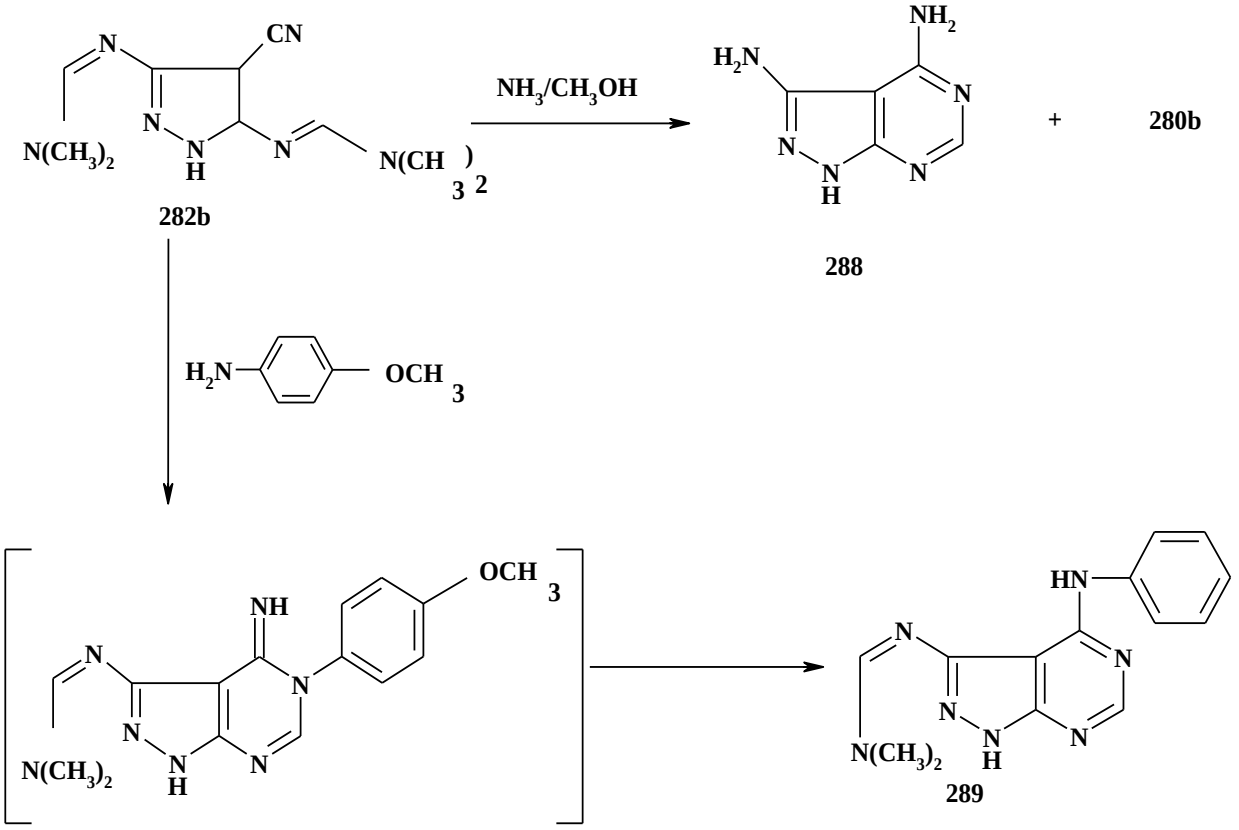
(Scheme 68)

It was reported that, condensation of pyrazoles **280a,b** with DMF/DMA afforded 3,5-bis(dimethylaminomethylene)amino-4-methoxycarbonyl and 4-cyanopyrazoles **281a,b**[38-41]. Heating of diamidino-4-methoxycarbonyl pyrazole **282a** with *p*-anisidine produced 3-amidine derivative **283**, while with more basic benzylamine a mixture of 3-amino,3-amidine derivatives **284, 285** and *N*-dimethyl aminomethyl enebenzyl-formamidine **286** were produced respectively. Also the reaction of pyrazole **282a** with ammonia led to the formation of 3-aminopyrazolo[3,4-*d*]pyrimidine derivative **287**[120-122]. (Scheme 69).



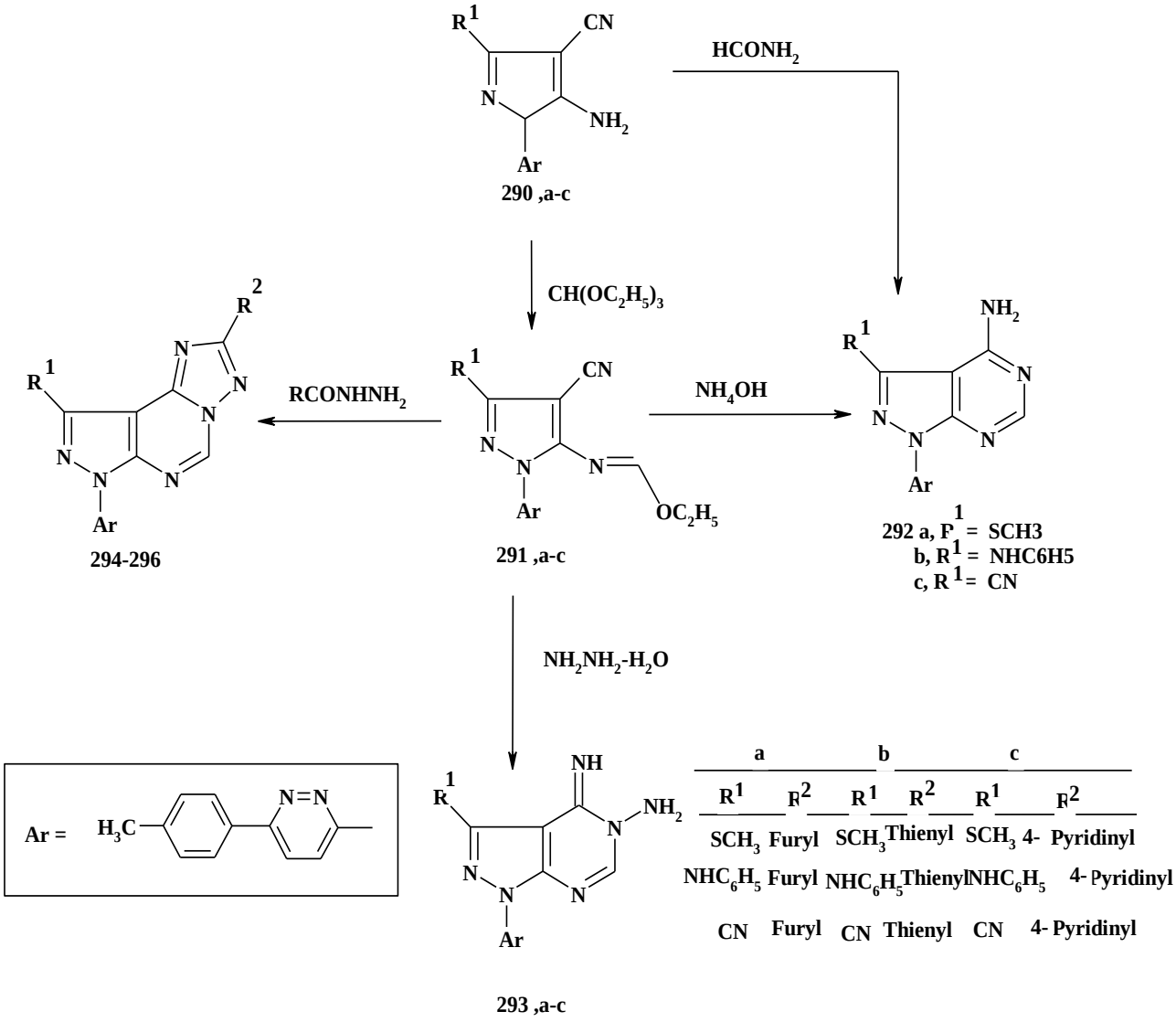
(Scheme 69)

The reaction of diamidine **282b** with ammonia and *p*-anisidine is different, thus, heating of compound **282b** with methanolic ammonia gave a mixture of 3,4-diamino pyrazolo[3,4-*d*]pyrimidine **288** and the diamino derivative **280b** , while with *p*-anisidine -3- dimethyl aminom ethyleneamino-4-*p*-anisidino pyrazolo[3,4-*d*] pyrimidine **289** was formed [120]. (Scheme 70).



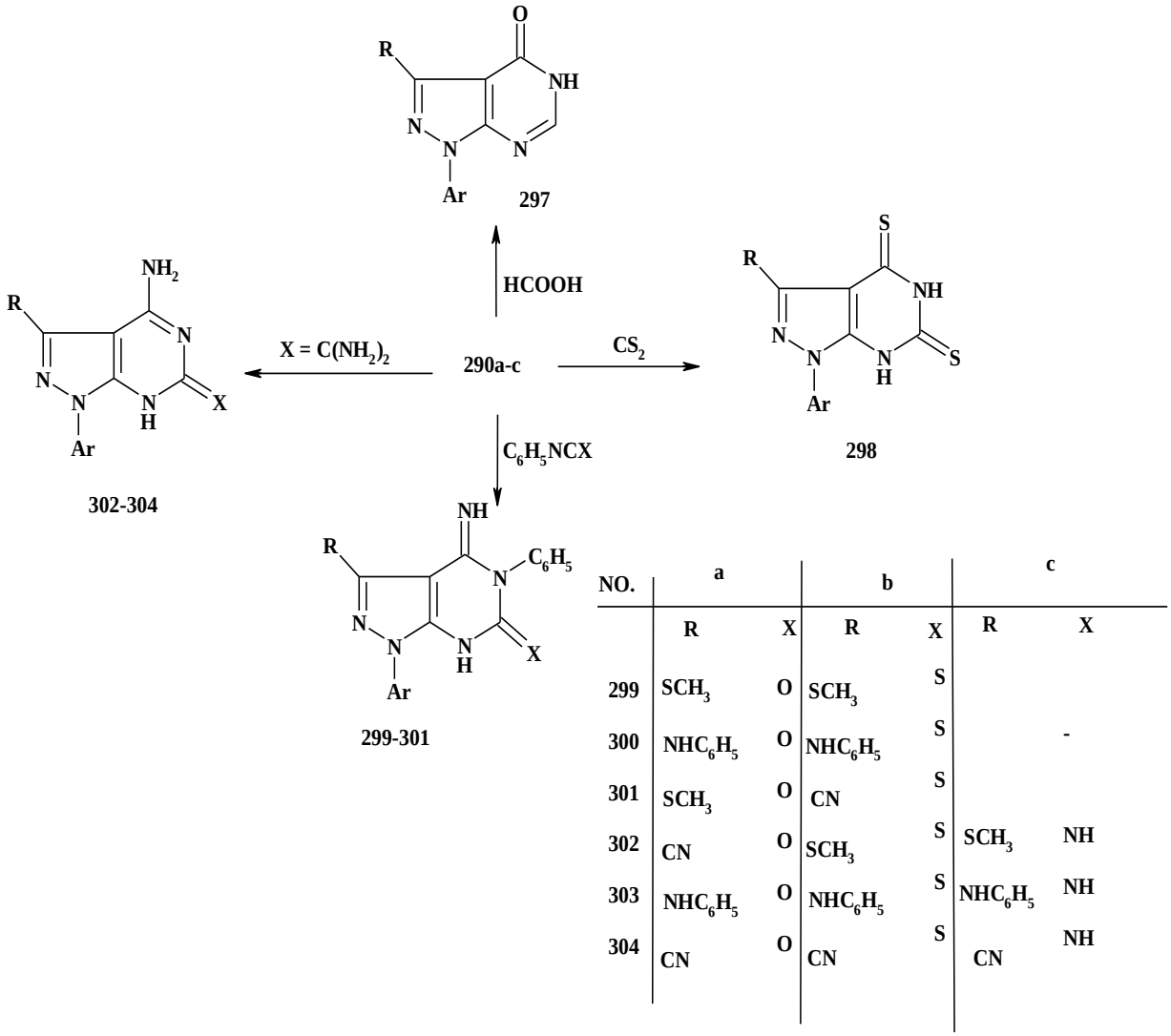
(Scheme 70)

Condensation of 5-aminopyrazole nitriles **290a-c** with diethyl orthoformate afforded the intermediate ethoxymethyleneamino derivatives **291a-c**. The latters on treatment with aqueous alcoholic ammonia yielded 4-aminopyrazolo[3,4-*d*]pyrimidines **292a-c**, which could be synthesized directly by treatment the pyrazoles **290a-c** with formamide . When compounds **290a-c** were stirred with hydrazine hydrate in ethanol , the 5-amino-4-iminopyrazolo[3,4-*d*]pyrimidines **293a-c** were produced in good yield. The intermidiates **290a-c** gave 2-arylpyrazolo[3,4-*d*]1,2,4-trizolo[5,4,*d*]pyrimidine systems **294-296** when reacted with 2-furancarboxylic acidhydrazide, 2-thiophenecarboxylicacidhydrazide and 4-pyridinecarboxylic acidhydrazide respectively[123]. (Scheme 71).



(Scheme 71)

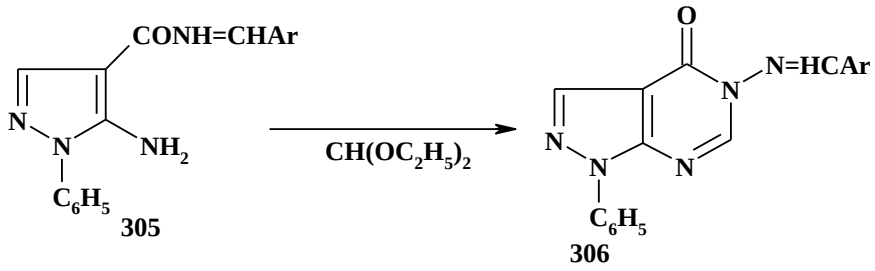
Also, the pyrazole derivatives **290a-c** undergo cyclization to afford several new pyrazolo[3,4-*d*]pyrimidines **297-304** when reacted with each of formic acid, carbon disulfide, phenyl isocyanate, phenyl isothiocyanate, urea, thiourea and guanidine[120]. (Scheme 72).



NO.	a		b		c	
	R	X	R	X	R	X
299	SCH_3	O	SCH_3	S		
300	NHC_6H_5	O	NHC_6H_5	S		-
301	SCH_3	O	CN	S		
302	CN	O	SCH_3	S	SCH_3	NH
303	NHC_6H_5	O	NHC_6H_5	S	NHC_6H_5	NH
304	CN	O	CN	S	CN	NH

(Scheme 72)

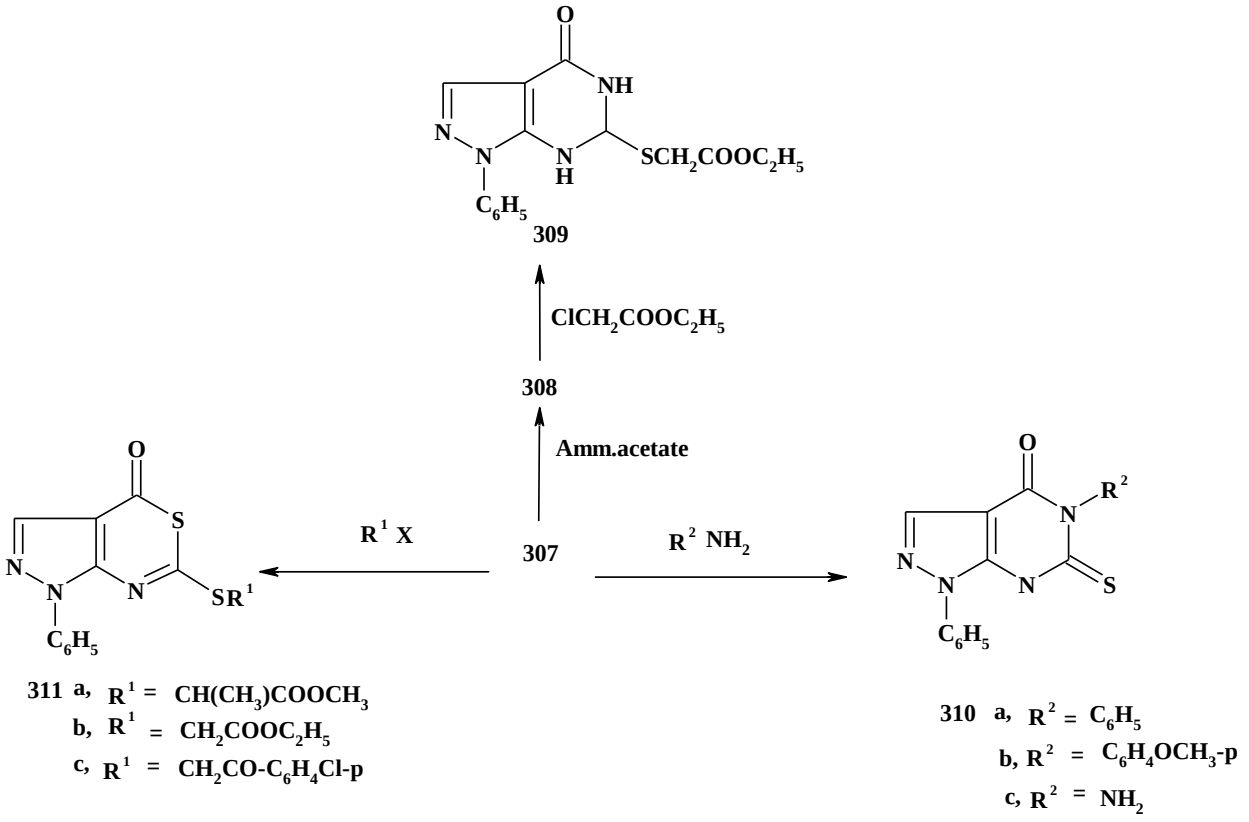
Treatment of arylmethylidenehydrazones **305a-e** with methyl orthoformate gave the pyrazolopyrimidines **306a-e**[124]. (Scheme 73).



a, Ar = C_6H_5
b, Ar = C_6H_4-OCH_3-*P*
c, Ar = C_6H_4-Cl -*P*
d, Ar = C_6H_4-NO_2 -*P*
e, Ar = C_6H_4-OH -*P*

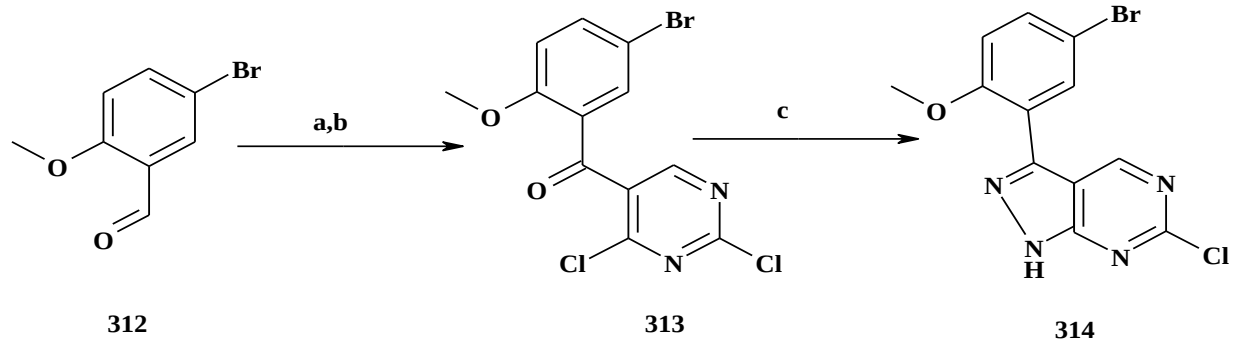
(Scheme 73)

Moreover, the S-ester **309** could be obtained from the reaction of compound **308** with ethyl chloroacetate. Also, compound **307** reacted with aromatic amines and hydrazine hydrate to afford the pyrazolopyrimidine derivatives **310a,c**. The S-alkylated derivatives **311a-c** was produced through the reaction of **307** with haloesters [125,126]. (Scheme 74).



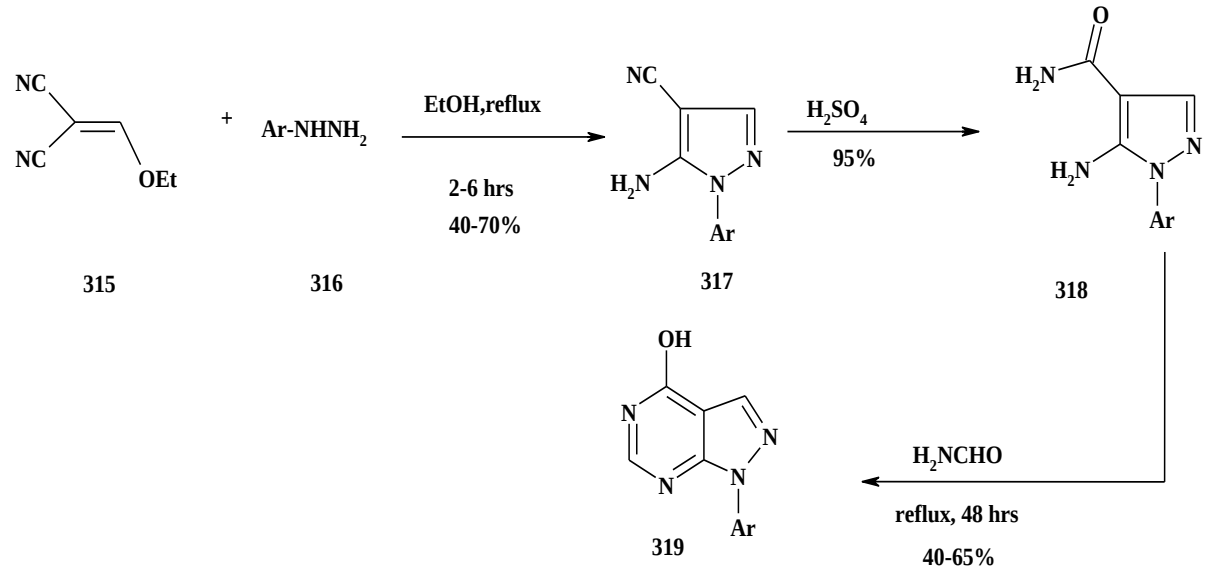
(Scheme 74)

Revesz et al[127,128], found that pyrazolo[3,4-*d*]pyrimidine **314** prepared by reacting 5-lithio-2,4-dichloropyrimidine with 5-bromo-2-methoxybenzaldhyde **312** and oxidizing the resulting alcohol to ketone **313**, followed by addiation hydrazine, at low temperature, to give the prazolo[3,4-*d*]pyrimidine **314**. (Scheme 75).



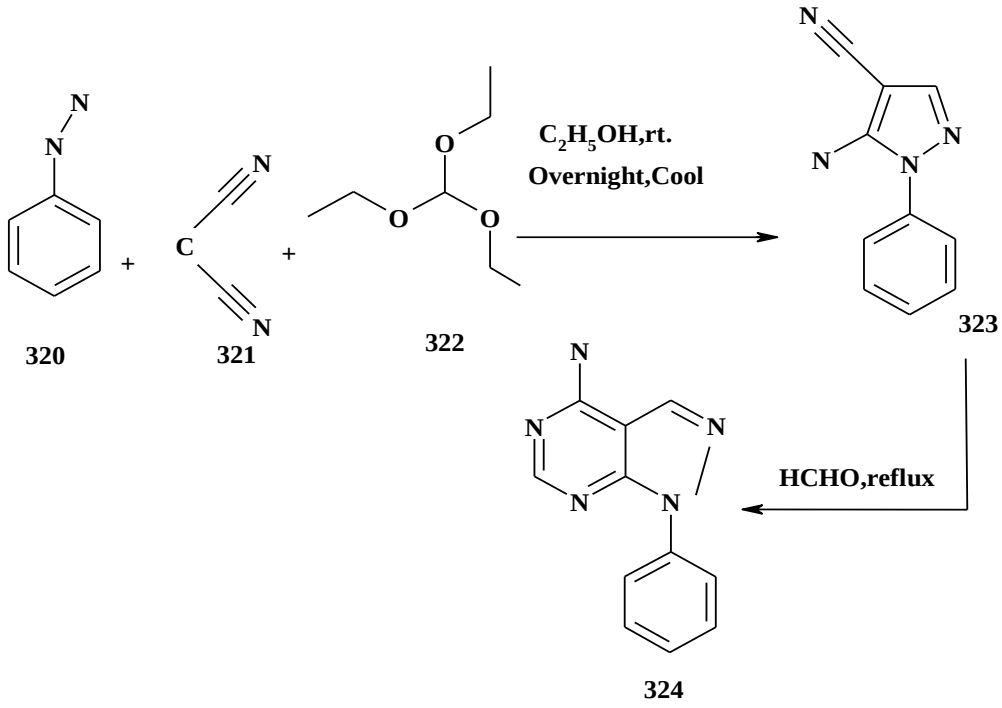
(Scheme 75)

Synthesis of pyrazolo[3,4-*d*] pyrimidine **319** involve the treatment of an aryl hydrazine **316** with ethoxymethylenemalonitrile **315** in refluxing ethanol for 2-6 h to provide 4-cyano-5-amino pyrazole **317** in 50-70% yield. Hydrolysis of the latter with the aqueous H_2SO_4 delivers the corresponding carboxamide **318** which is then heated at reflux for 48h in heat formamide to provide 1-aryl pyrazolo[3,4-*d*] pyrimidine-4-ol **319**[129]. (Scheme 76).



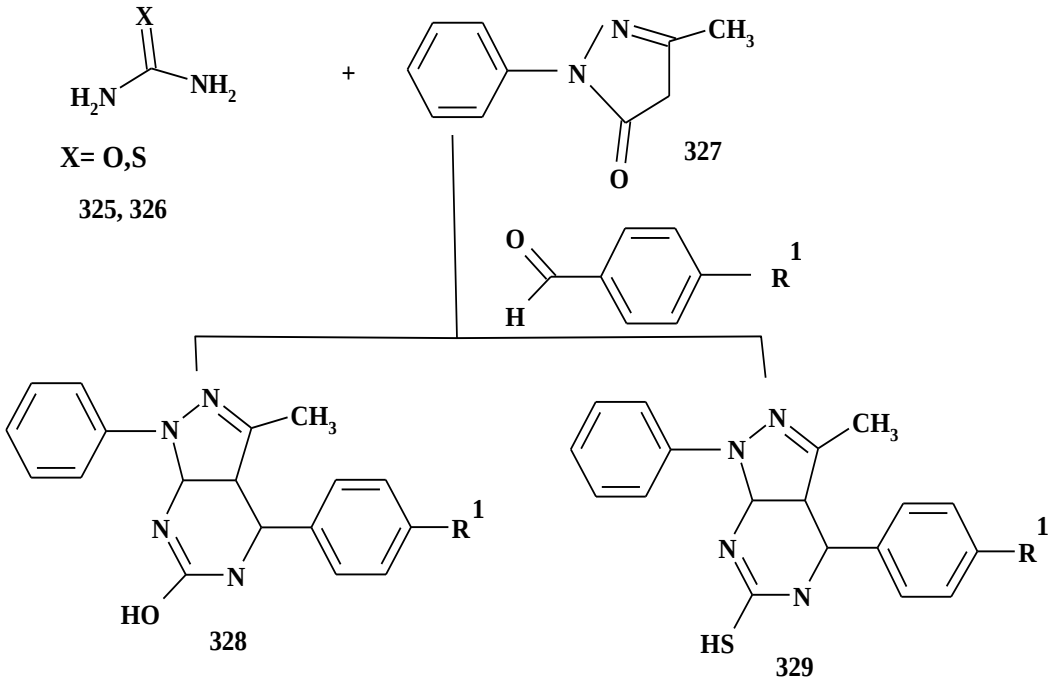
(Scheme 76)

Kota et al[130], synthesized a new 4-4- substitututed benzoyl amino pyrazolo[3,4-d]pyrimidines **324** by reacting with formamide. (Scheme 77).



(Scheme 77)

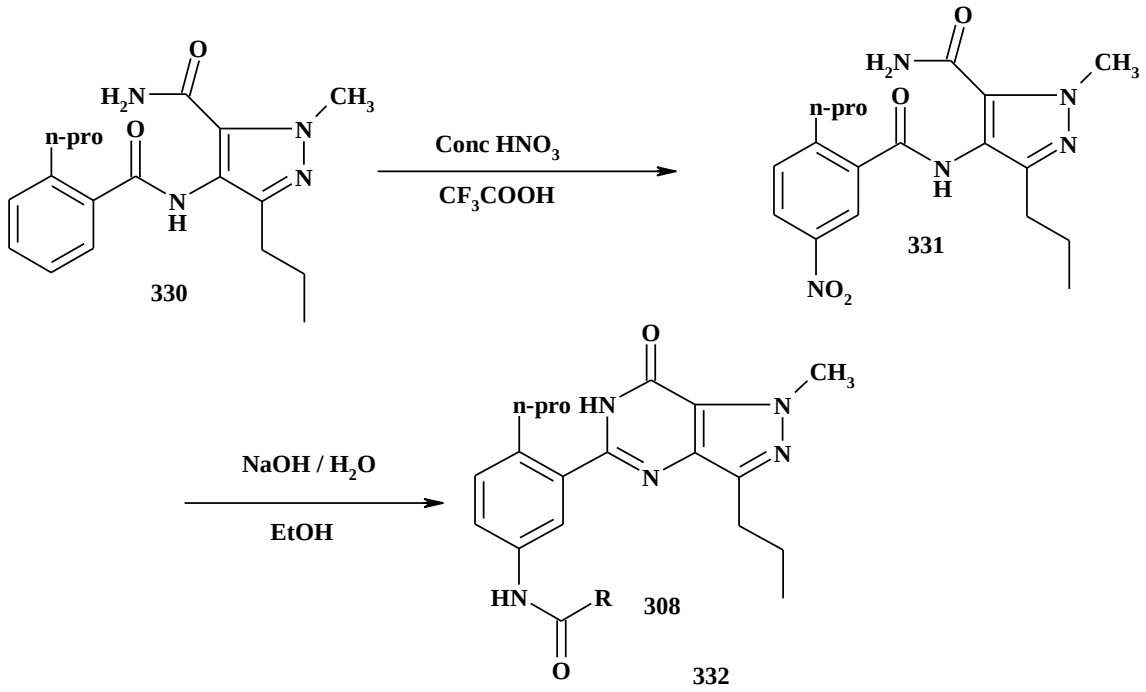
Rajendran et al[131], reported for the synthesis of some pyrazolopyrimidine derivatives **325-326** using 3-methyl-1-phenyl-5-pyrazolone with carbonyl compounds in ionic liquid 2-methyl-3-butyl imidazolium chloride. (Scheme 78).



(Scheme 78)

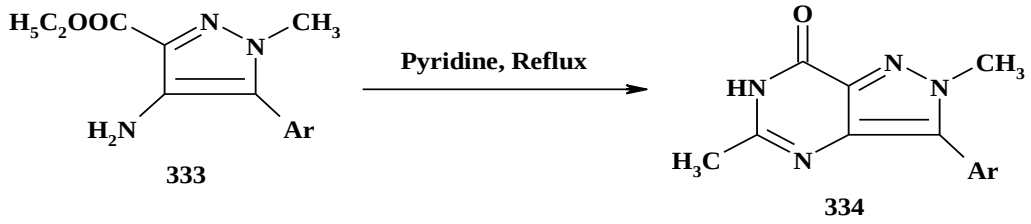
2.4. Synthesis of Pyrazolo[4,3-d]pyrimidine derivatives.

Nitration of 1-methyl-4-(2-n-propoxybenzamido)-3-n-propyl-pyrazole-5-carboxamide **330** afforded mono-nitroproduct **331**. Cyclization of the latter under basic condition afforded the corresponding pyrazo1opyrimidinone **332** [132,133]. (Scheme 79).



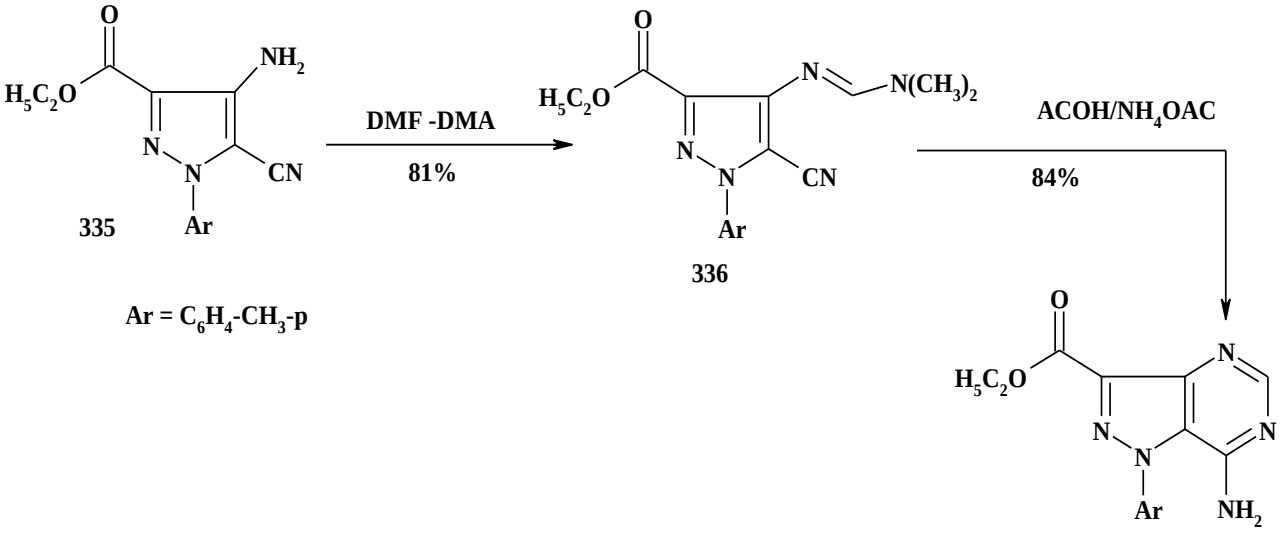
(Scheme 79)

Treatment of aminopyrazoles **333** with benzyl thioacetimidate hydrobromide in refluxing pyridine afforded the pyrazolopyrimidinone **334**[134-137]. (Scheme 80).



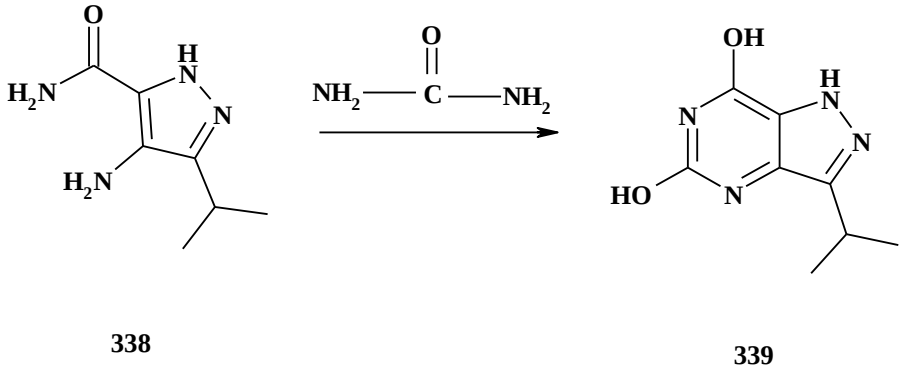
(Scheme 80)

Ghozlan et al [138-143], found that pyrazolo[4,3-*d*]pyrimidine **337** is formed from condensation of 4-amino pyrazole **335** with dimethylformamide dimethylacetal (DMF/DMA) to yield the examine **336** which treated with $AcOH/NH_4$,OAc mixture to convert into pyrazolo[4,3-*d*]pyrimidine **337**. (Scheme 81).



It has been found that, aminoamide **338** , Fusing the amide with urea resulted in the dihydroxy derivative **339**[144]. (Scheme 82).

(Scheme 81)

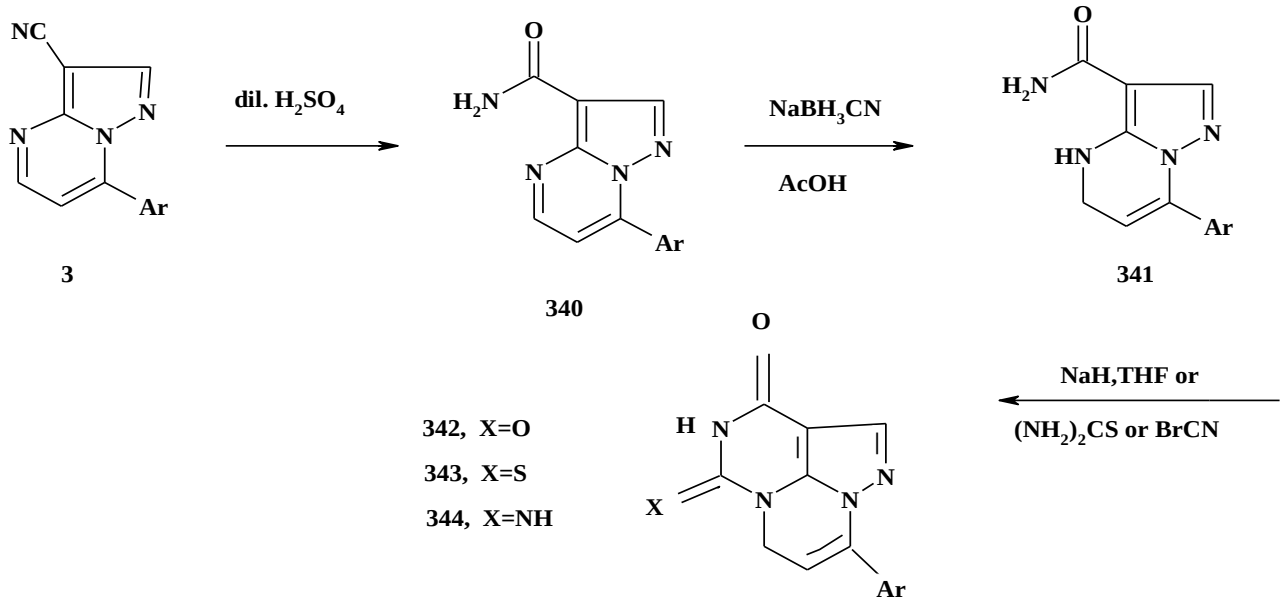


(Scheme 82)

3. Chemical reactivity of Pyrazolopyrimidines derivatives.

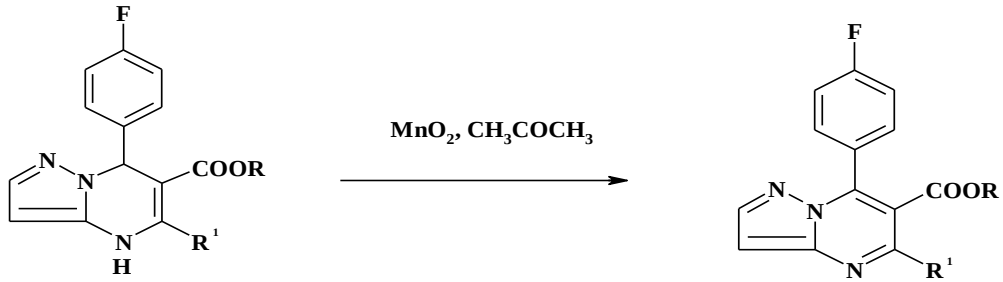
3.1. Chemical reactivity of Pyrazolo[1,5-a]pyrimidine derivatives.

5-Unsubstituted-7-arylpyrazolo[1,5-*a*]pyrimidines **3** could be hydrolyzed to the amide **340**. Sodium cyanoborohydride in acetic acid converted compound **342** into 4,5-dihydropyrazolo[1,5-*a*]pyrimidine **341** which could be reacted with carbonyldi imidazole in refluxing dioxin to give diones **342**. When amide **341** reacted with two equivalents of sodium hydride and followed by addition of thiocarbonyl diimidazole, the cyclic thione **343** could be obtained. Similarly, cyanobromide could be used to provide the exocyclic amines **344** under the same conditions [11-13]. (Scheme 83).



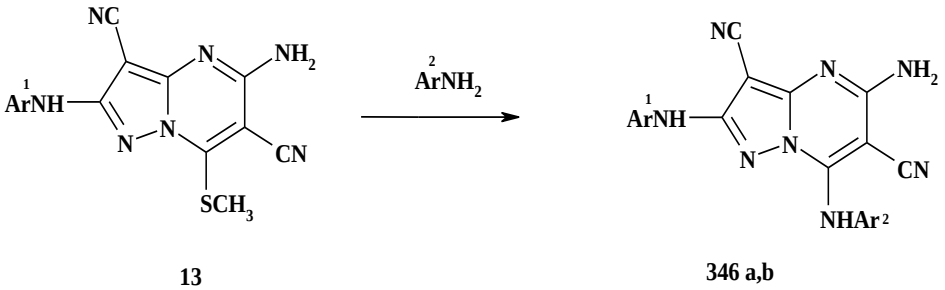
(Scheme 83)

Treatment of Pyrazolo Pyrimidine **6** with MnO_2 , aceton give compound **345**[14]. (Scheme 84).



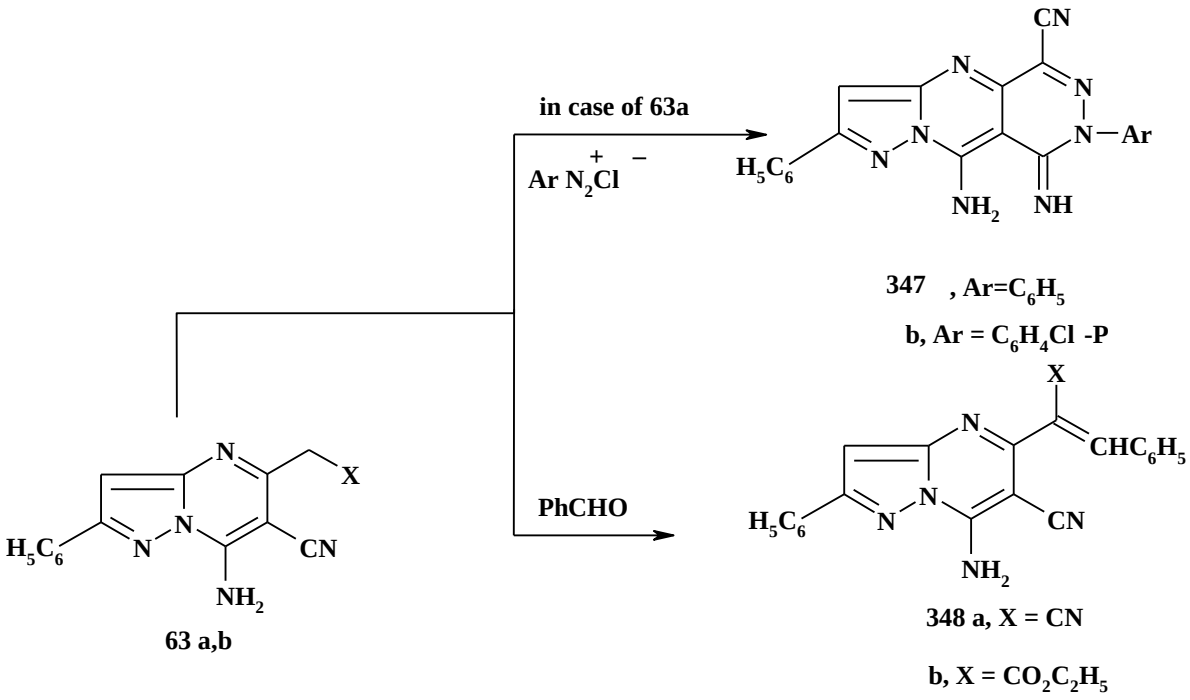
(Scheme 84)

Fusion of **13** with aromatic amines at 140℃, furnished the corresponding aniline derivatives **346a,b**[18-20]. (Scheme 85).



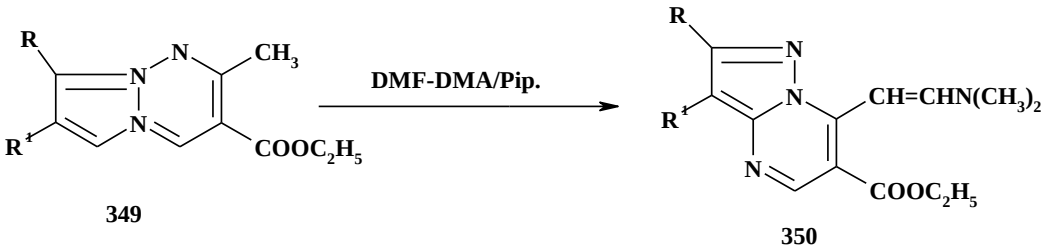
(Scheme 85)

It was found that the reaction of pyrazolo[1,5-*a*]pyrimidine derivatives **63** with aromatic diazonium chlorides or benzaldehydes to give compound **347** or **348** respectively[37-39]. (Scheme 86).



(Scheme 86)

It has been found that , pyrazolo[1,5-*a*]pyrimidine derivatives **349** reacted with DMF-DMA [Di methyl formamide, Di methyl acetal] to give the corresponding 7-(2 dimethylaminovinyl) pyrazolo[1,5-*a*]pyrimidines **350** [145-149]. (Scheme 87).

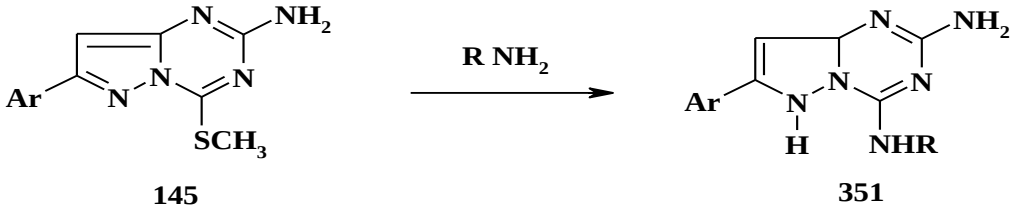


349	R	R 1
a	H	H
b	CH_3	H
c	$CH(CH_3)_2$	H

350	R	R 1
a	H	H
b	CH_3	H
c	$CH(CH_3)_2$	H

(Scheme 87)

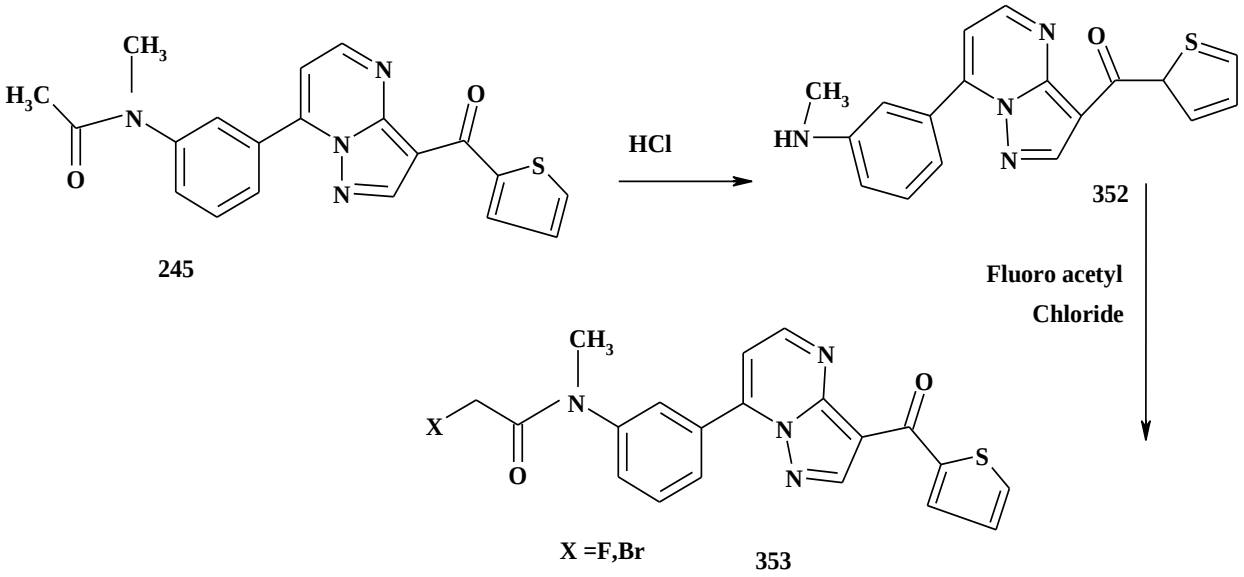
The reaction of 4-methyl thiopyrazolo[1,5-*a*]1,3,5-triazine **145** with hydrazine hydrate and aniline to afford the corresponding hydrazine or aniline derivative **351** [63]**.** (Scheme 88).



145 **351**

(Scheme 88)

Hoepping et al[92], found that pyrazolo pyrimidine **245** react with fluoroacetyl chloride to give indiplon **352-353**. (Scheme 89).

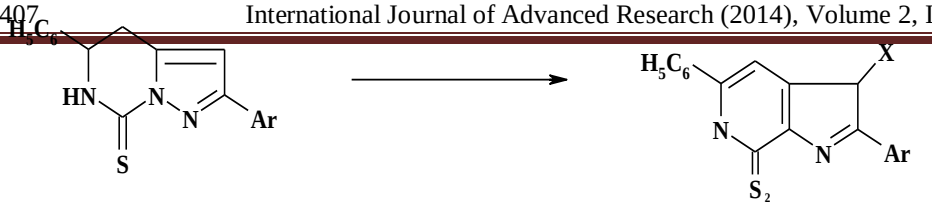


245 **352** **353**

(Scheme 89)

3.2. Chemical reactivity of Pyrazolo[1,5-c]pyrimidine derivatives.

Oxidation of **256** sodium nitrite in glacial acetic acid or with benzene diazonium chloride gave the 7,7-bis-(2-aryl-5- phenylpyrazolo[1,5 *c*]pyrimidinyl) disulfide **354**[94-96]. (Scheme 90).



256

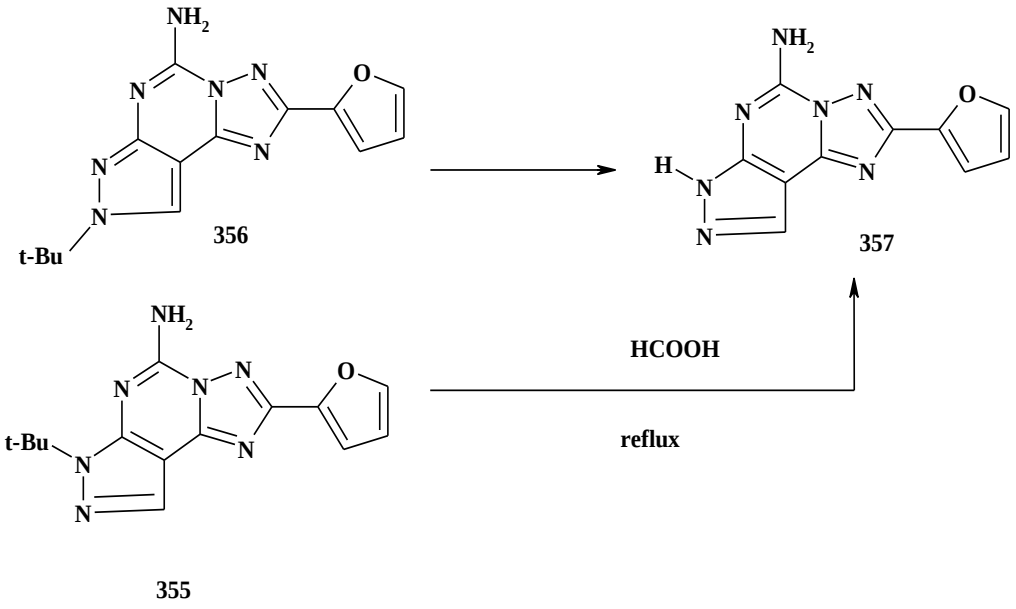
354, a, X=H

b, X=C_6H_5N=N

(Scheme 90)

Baraldi et al[150], found that Medical chemistry approach on the synthesis of pyrazolo[4,3-*e*][1,2,4]Trizolo[1,5-*c*]pyrimidines and related compounds that have permitted us to complete the SAR analyses on this class of Chemical molecules and evaluating their pharmacological profila, Its modification performed to tricyclic nucleus, as introduction at C-position of thioethyl, aminoalkyl and cycloalkylamino radicals and replacement of 2-furyl moiety with substituted aromatic rings which lead to a diminished receptor affinity. Also the replacement of the 2-(2-furyl) triazolo template with new heterocyclic revealed inactive molecules.

Bernard et al[151], found that for preparation of compound **357** , the previously reported method was initially adapted, targeting key intermediate **356** that could be alkylated at position **7** However , this route behaved poorly in our hands with **355** producing primary **357** which describe targets and a critical step in previously synthetic route to pyrazolo[4,3-*e*] -1,2,4-triazolo[1,5-*c*]pyrimidine. (Scheme 91).



356

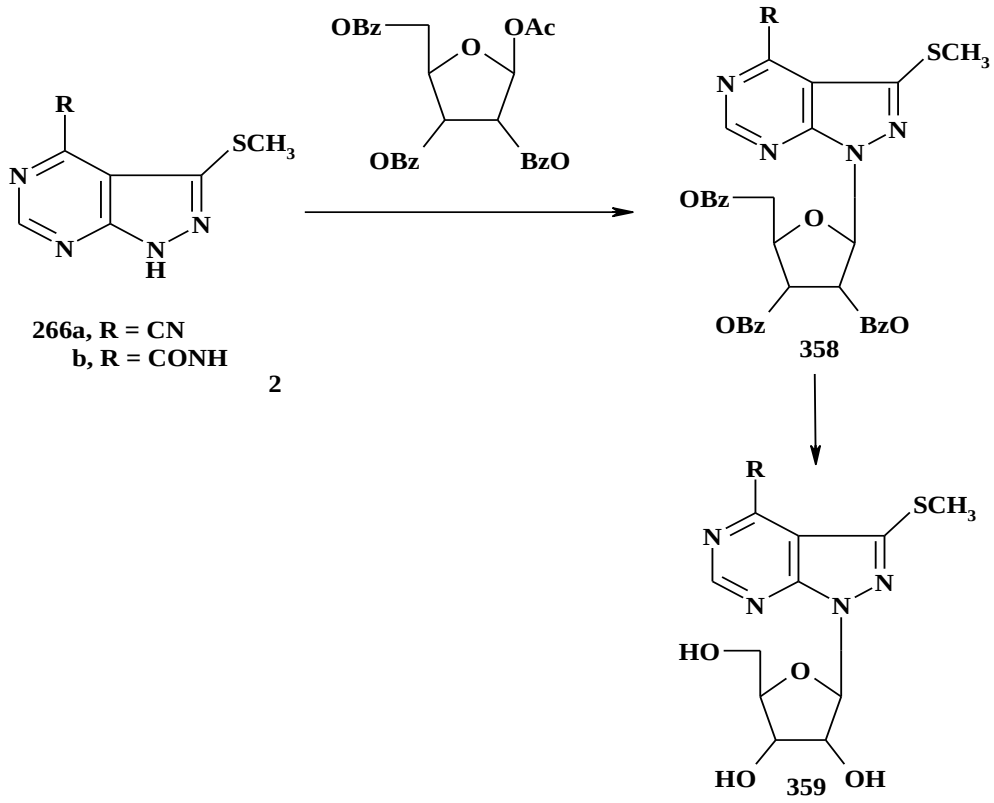
357

355

(Scheme 91)

3.3. Chemical reactivity of Pyrazolo[3,4-d]pyrimidine derivatives.

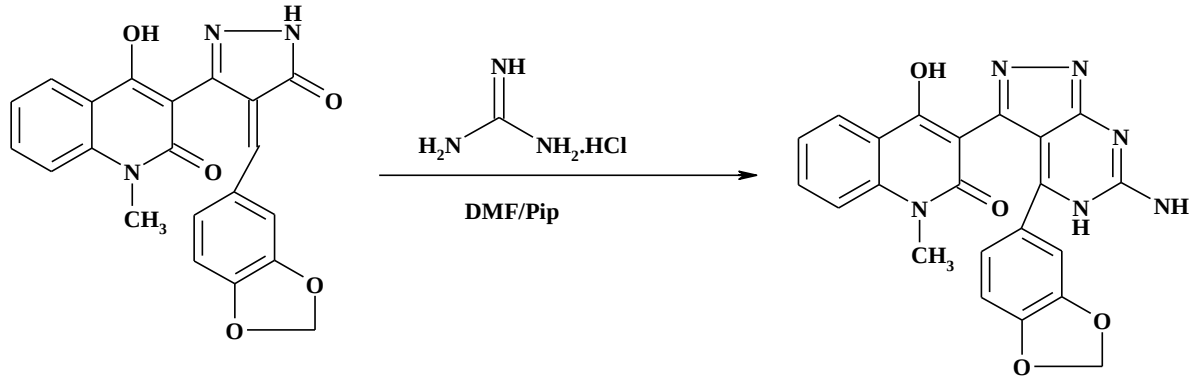
A glycosylation of unsubstituted of 4-amino or 4-hydroxy-3-methyl thiopyrazolo[3,4-*d*]pyrimidines **266a, b** followed by hydrolysis afforded nucleosides **359** [101, 102]. (Scheme 92).



266a, R = CN
b, R = CONH
2

(Scheme 92)

It was reported that, the cyclization of 3-[4-benzo-1,3-dioxolyl methylene-5-oxo-3-pyrazolyl]-4-hydroxy-1-methylquinolin-2(*1H*)-one **360** with guanidine hydrochloride led to the formation of the biologically interested fused pyrazolopyrimidine **361**[151]. (Scheme 93).

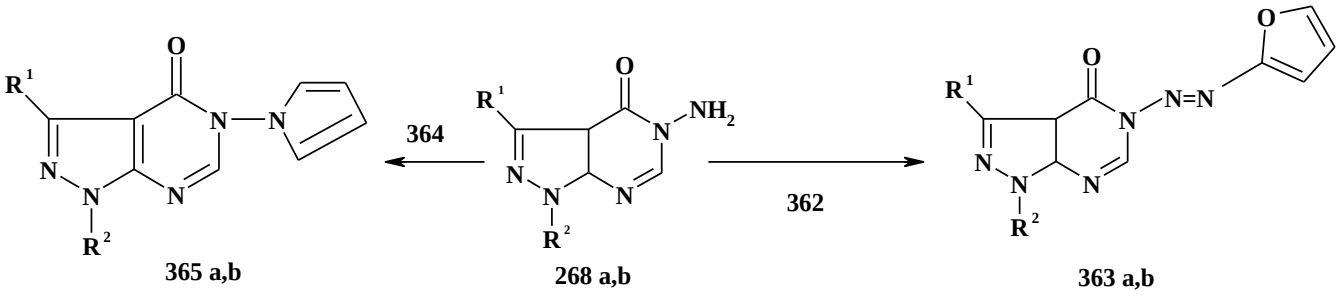


360

361

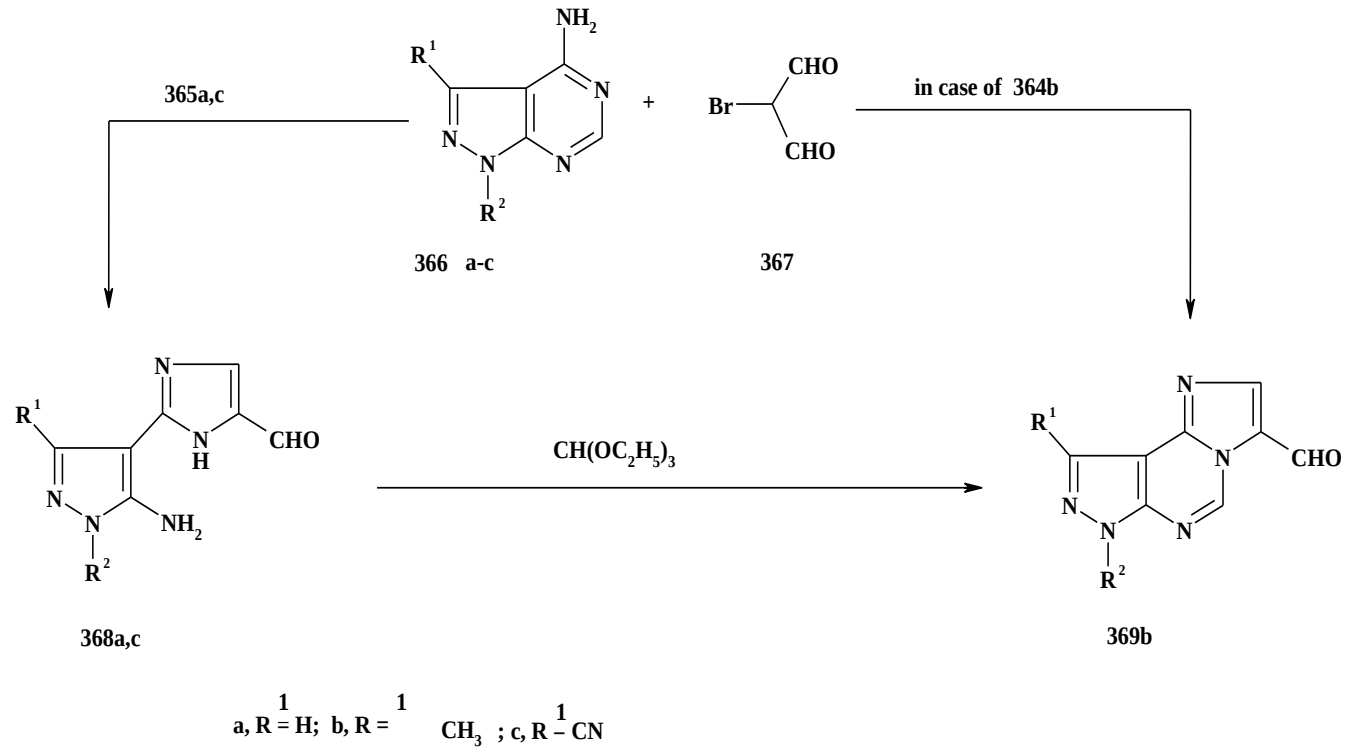
(Scheme 93)

Treatment of 5-amino-l-2,4-dichlorobenzyl-4,5-dihydropyrazolo[3,4-*d*] pyrimidin-4-ones **268** with 5-nitro-2-furfural diacetate **362** gave the Schiff bases **363** and with 2,5-diethoxytetrahydrofuran **364** to produced the pyrrolo derivatives **365**[103-104]**.** (Scheme 94).



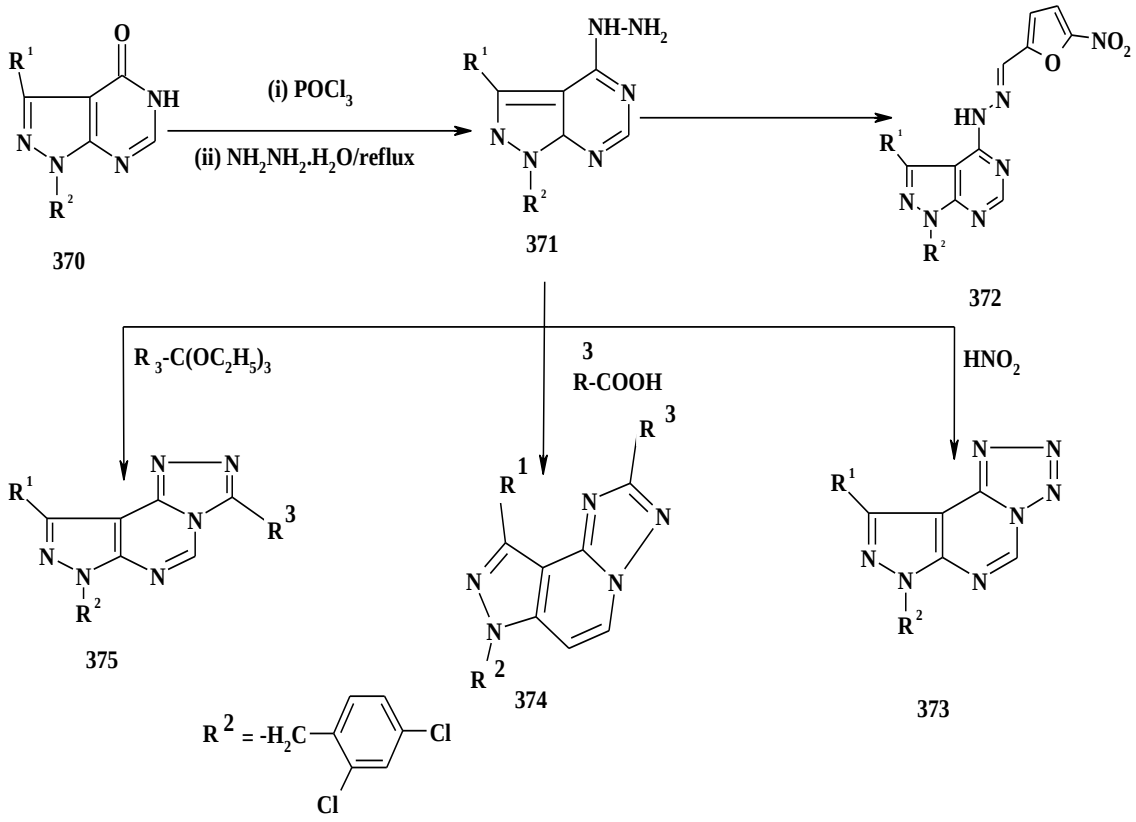
(Scheme 94)

The reaction of 4-aminopyrazolo[3,4-*d*]pyrimidine derivative **366b** with bromomalondialdehyde **367** in aqueous dioxane gave the expected compound **369b** while the reaction of **366a** and **366c** yielded only the corresponding imidazolyl pyrazoles **368a,c**. Compound **356a,c** could be cyclized with triethylorthoformate to give **368, 369a,c**[103-104]. (Scheme 95).



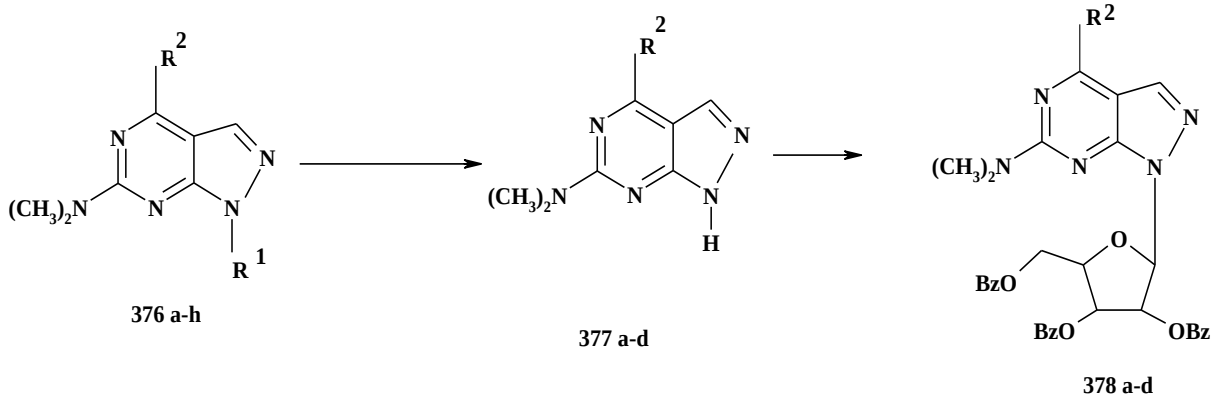
(Scheme 95).

Refluxing of 1-(2,4-dichlorobenzyl)-(*5H*)-Pyrazolo[3,4-*d*]pyrimidin-4-ones **370** with phosphorus oxychloride followed by the reaction with ethanolic hydrazine hydrate gave the 1-2,4-dichlorobenzyl-4-hydrazinopyrazolo[3,4-*d*] pyrimidines **371** which were found to react with 5-nitrofurfuraldiacetate, with triethylorthoformate or orthoacetate, with refluxing formic or acetic acid and with sodium nitrite in hydrochloric acid to give the compounds **371, 372, 373** and **375** respectively [103-104]. (Scheme 96).



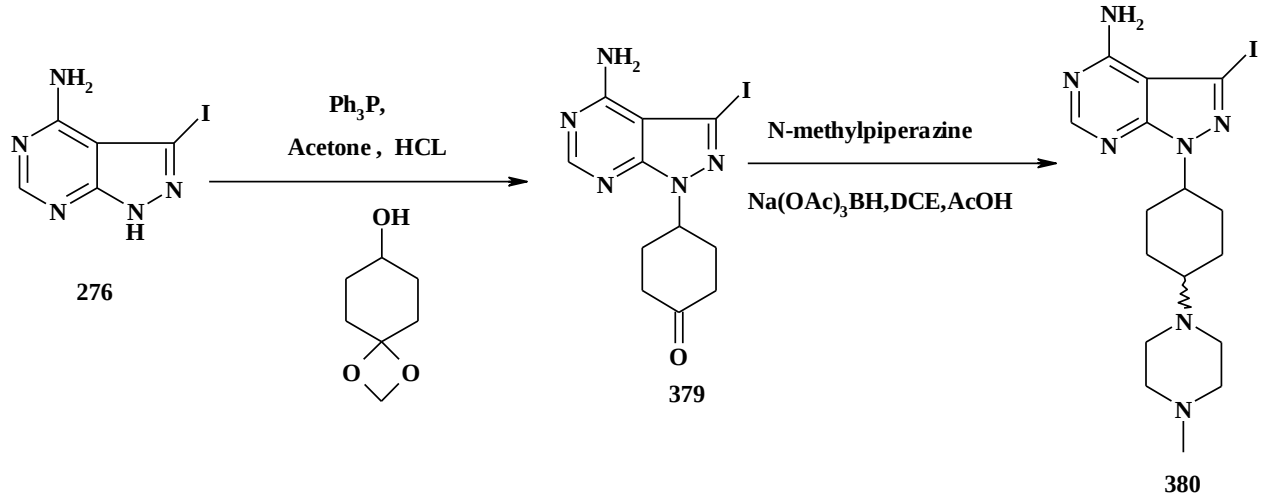
(Scheme 96)

Cleavage of the tert-Bu group of pyrazolo[3,4-*d*]pyrimidines **376** with formic acid gave **377a**,**d** that were subsequently glycosilated by the reaction with 1-*0*-acetyl-1-3,4,5-tri-*0*-benzoyl ribofuranose to give the nucleosides **378a**,**d**[114-116]. (Scheme 97).



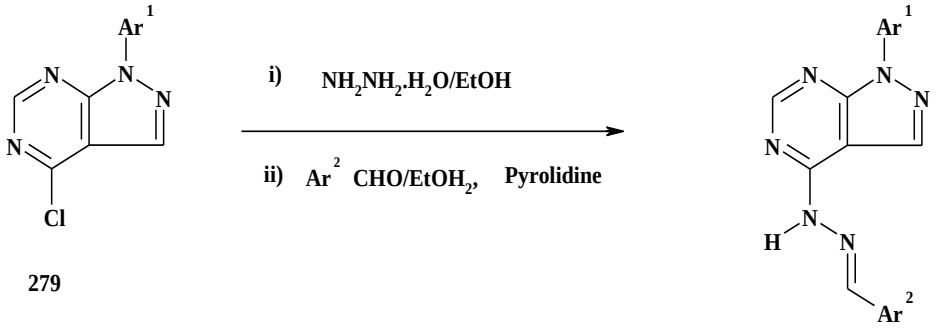
(Scheme 97)

Coupling of Pyrazolopyrimidine derivative **276** with the ketal-alcohol followed by ketone unmasking gave compound **380** [35,117,118]. (Scheme 98).



(Scheme 98)

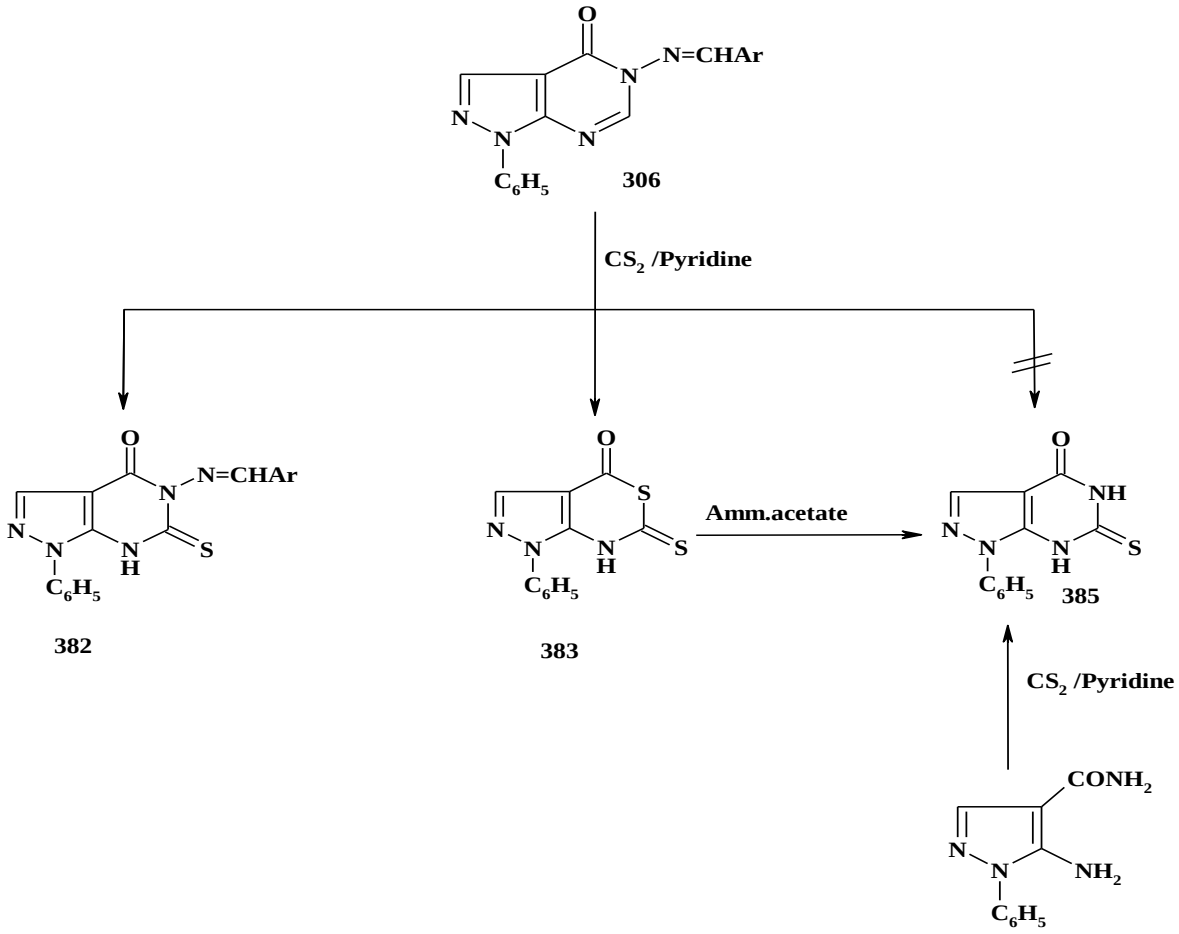
Treatment of 4-chloropyrazolo[3,4-*d*]pyrimidines **265** with hydrazine and final condensation with aromatic aldehydes gave the GSK-3 inhibitor **381**[119]. (Scheme 99).



a, $Ar^1 = H$ **b,** $Ar^1 = 2\text{-}CH_3\text{-}C_6H_4$ **c,** $Ar^1 = 3\text{-}CH_3\text{-}C_6H_4$ $Ar^2 =$ 4-Pyridyl

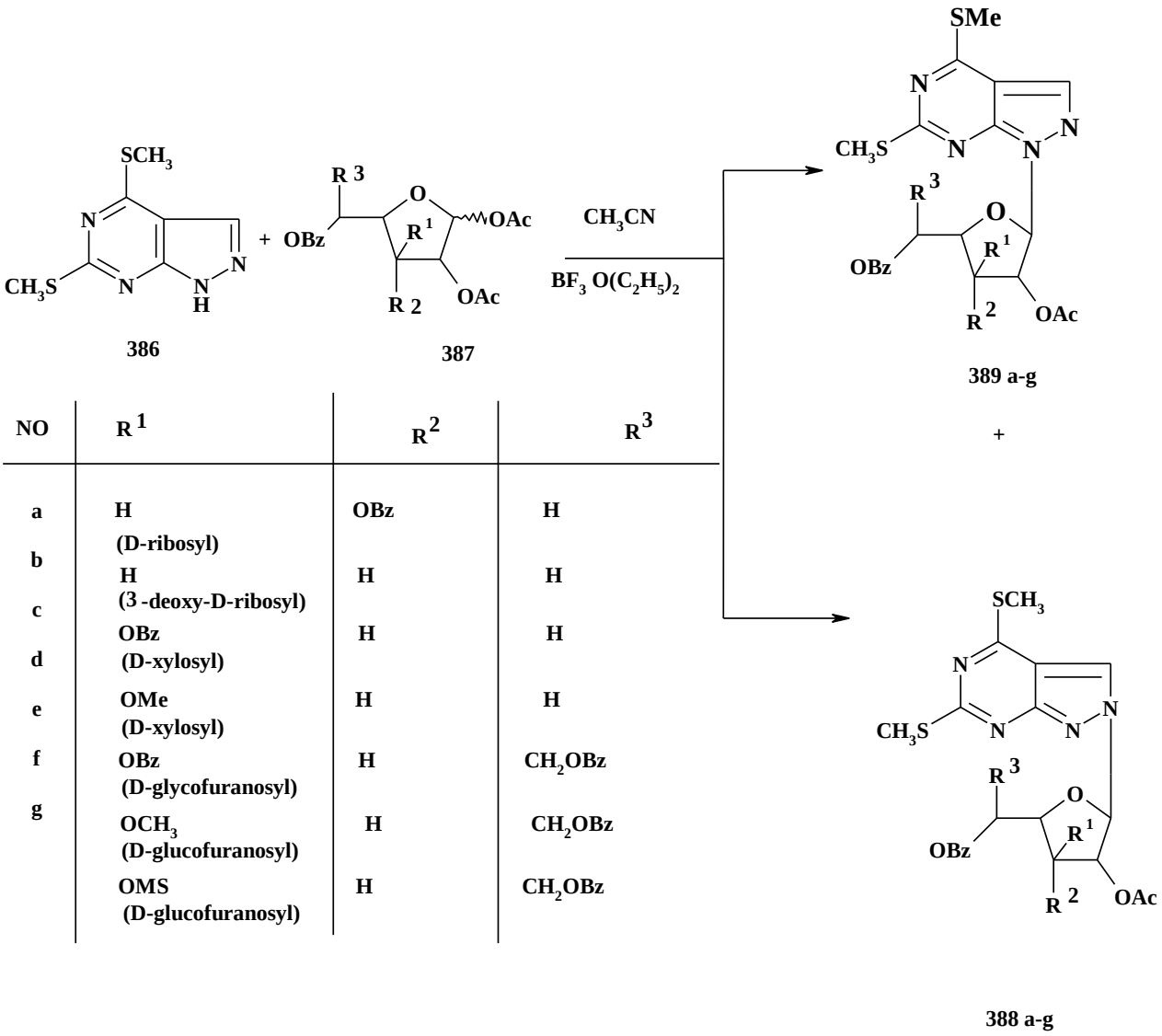
(Scheme 99)

Treatment of pyrazolopyrimidines **306** with carbon disulfide in pyridine gave pyrazolothiazinethione **382** but the pyrazolopyrimidinethione could be obtained from the reaction of aminopyrazole **383** with carbon disulfide or by treatment of **384** with ammonium acetate[124-126]**.** (Scheme 100).



(Scheme 100)

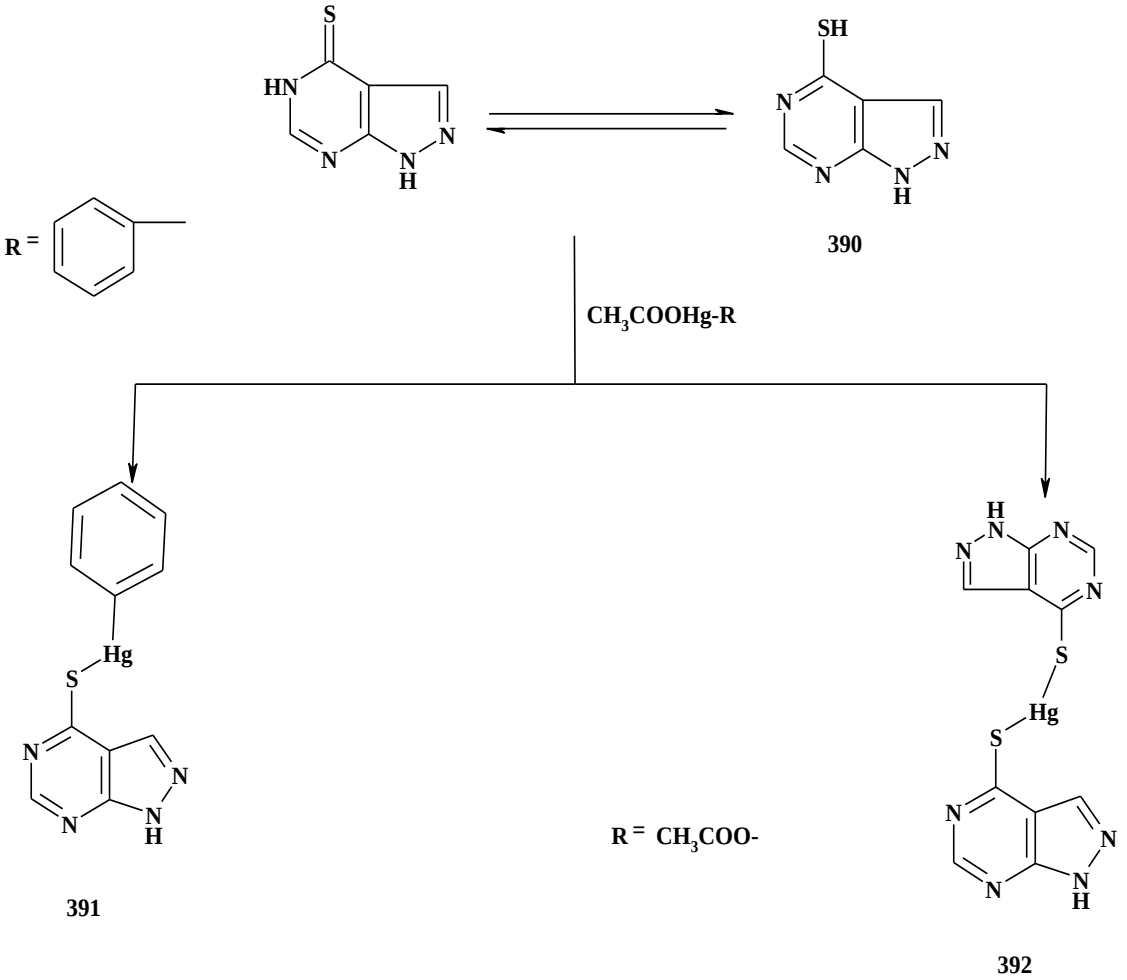
It was reported that, glycosylation of 4,6-bis-methylthio-(*1H*)-pyrazolo[3,4-*d*] pyrimidine **386** with 1,2-di-*o*-acetyl-3,5-di-*o*-benzoyl-D-xylofuranose **387** gave *N*-2-isomer **388** as the major product along with *N*-1-isomer **389** [138-143]. (Scheme 101).



NO	R 1	R 2	R 3
a	H	OBz	H
b	(D-ribosyl) H	H	H
c	(3 -deoxy-D-ribosyl) OBz	H	H
d	(D-xylosyl) OMe	H	H
e	(D-xylosyl) OBz	H	CH_2OBz
f	(D-glycofuranosyl) OCH_3	H	CH_2OBz
g	(D-glucofuranosyl) OMS (D-glucofuranosyl)	H	CH_2OBz

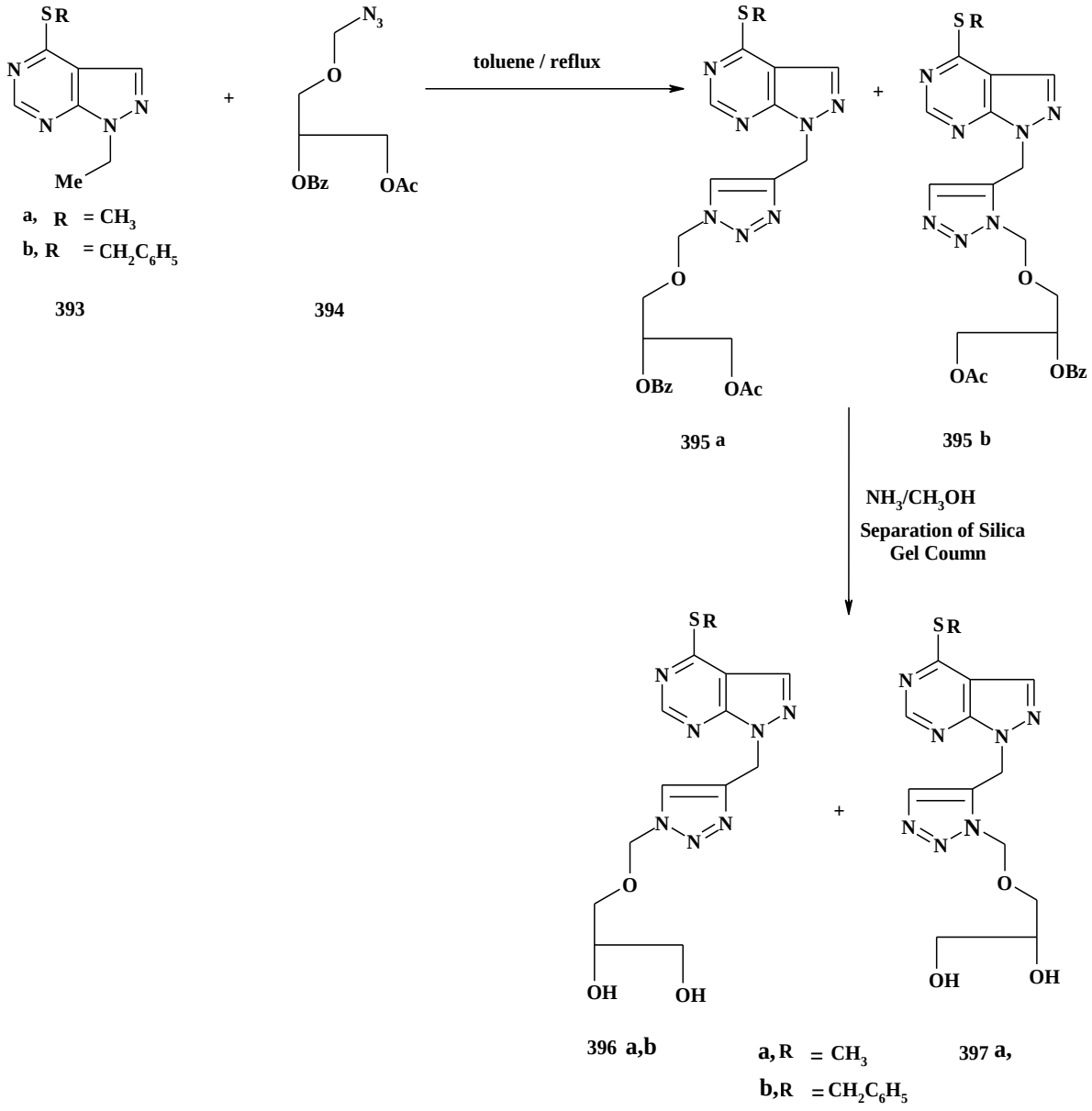
(Scheme 101)

The reaction of 4-mercaptopyrazolo[3,4-*d*]pyrimidine **390** with acetoxyhydrar gyriobenzol afforded 4-(phenylhydrargyriothio) pyrazolo[3,4-*d*] pyrimidine **391** Also, Compound **390** could be treated with mercuric acetate to afford bis(4-pyrazolo[3,4-*d*]pyrimidylthio) hydrargyrium **392**[152-154]. (Scheme 102).



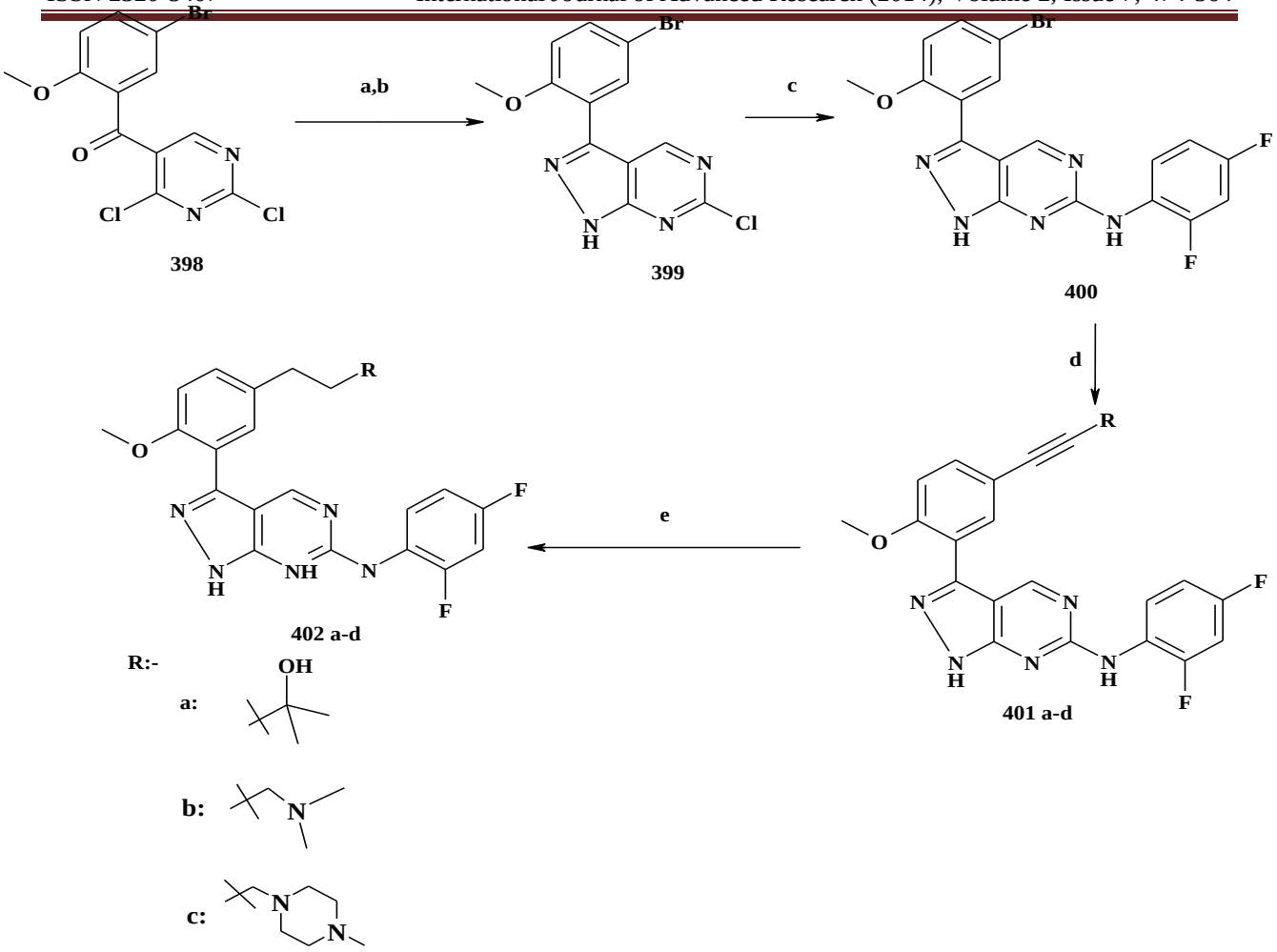
(Scheme 102)

The reaction of 4-(methyl and benzyl)thio-1-propargyl1-(*1H*)-pyrazolo[3,4-*d*] pyrimidines **393a,b** with azidocompound **394** afforded a mixture of two possible regioisomers **395a** and **395b** which by the treatment with a solution of methanol saturated with ammonia to afford a cyclic nucleosides **396a,b** and **397a,b**[155-161] . (Scheme 103).



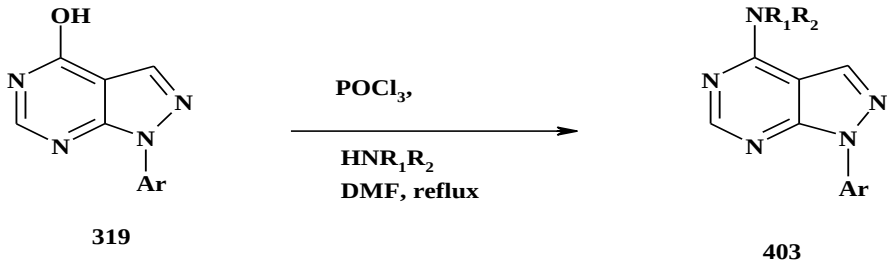
(Scheme 103)

Revez et al[127], found that pyrazolo[3,4-*d*]pyrimidine **401** and **402** were prepared by reacting 5-lithio-2,4-dichloropyrimidine with 5-bromo-2-methoxy benzaldhyde and oxidizing the resulting alcohol to ketone **398**. Hydrazine at low temperature converted **398** into prazolo[3,4-*d*]pyrimidine **399**, which-combined for is min with 2,4-difluoroaniline at 150 ℃ to give **400** in high yield. Then making coupling of **400** with series of alkynes afforded **401a-d** in moderate yield, and hydrogenation gave the saturated analogues **402a-d**[128]. (Scheme 104).



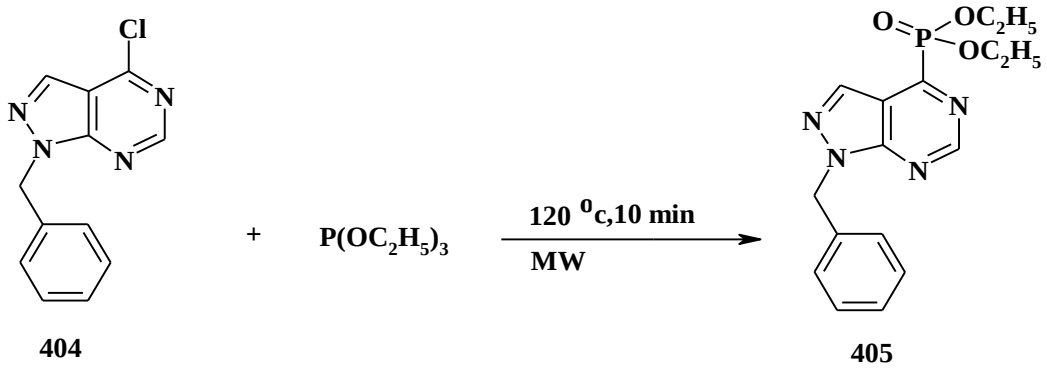
(Scheme 104)

1-aryl pyrazolo[3,4-*d*]pyrimidine-4-ol **319** converted with $POCl_3$ and amine to pyrazolo[3,4-*d*]pyrimidine **403** by treatment[129]. (Scheme 105).



(Scheme 105)

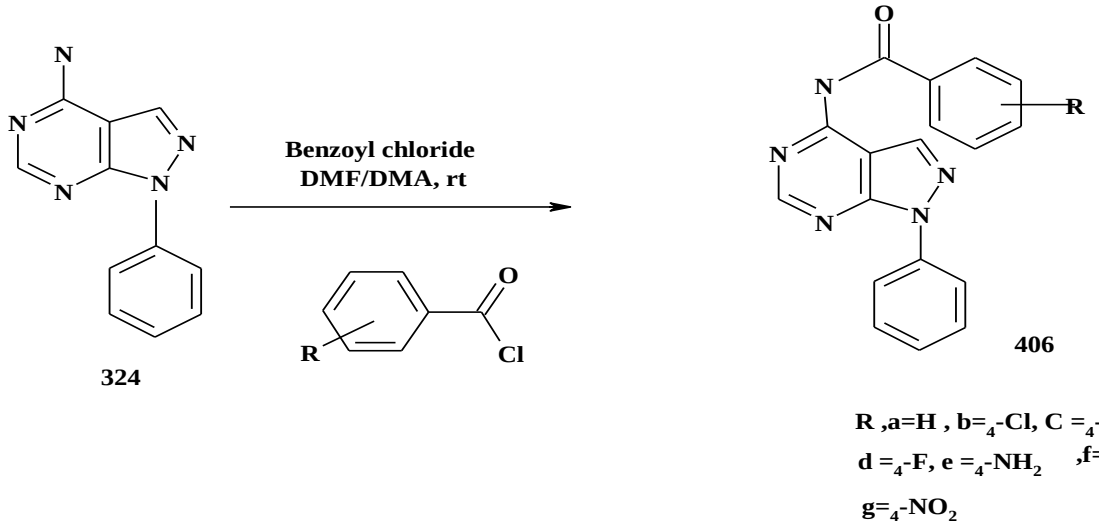
Qu et al [162]' found that, 4-phsphnated pyrozolopyrimidine **405** can be synthesized in good yield from the corresponding 4-chloropyrozolopyrimidine **404** using the same reaction conditions [163]. (Scheme 106).



404 **405**

(Scheme 106)

Kota et al[130], pyrazolo pyrimdine **324** react with benzoyl chloride in DMF and give new pyrazolopyrimidine **406**. (Scheme 107).

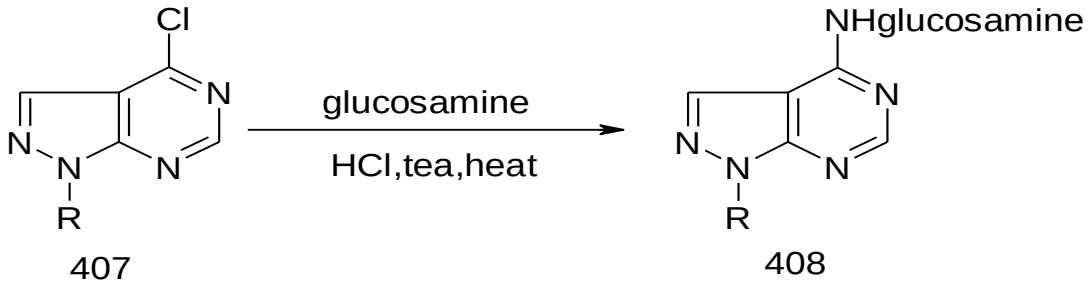


324 **406**

R ,a=H , b=$_4$-Cl, C =$_4$-CH_3
d =$_4$-F, e =$_4$-NH_2 ,f=$_4$-CF_3
g=$_4$-NO_2

(Scheme 107)

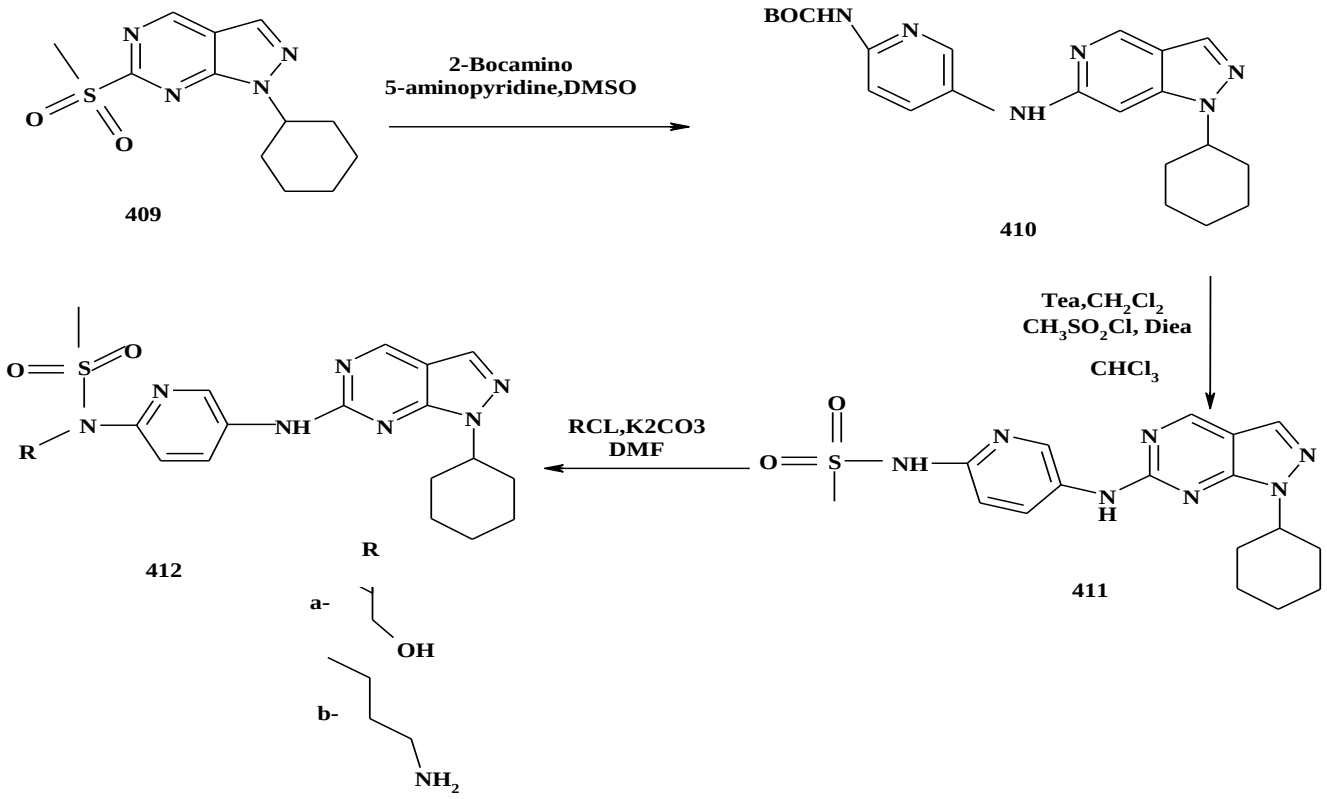
Rashad et al[164], when refluxed novel substituted pyrazolo[3,4-d]pyrimidine **407** with glucosamine hydrochloride in the presence of triethylamine, the reaction afforded pyrazolo pyrimidine **408**. (Scheme 108).



407 408

(Scheme 108)

Zhang et al[165], the preparation of monosulfonamide-pyridyl pyrazolo pyrimidine analogue **412**. (Scheme 109).

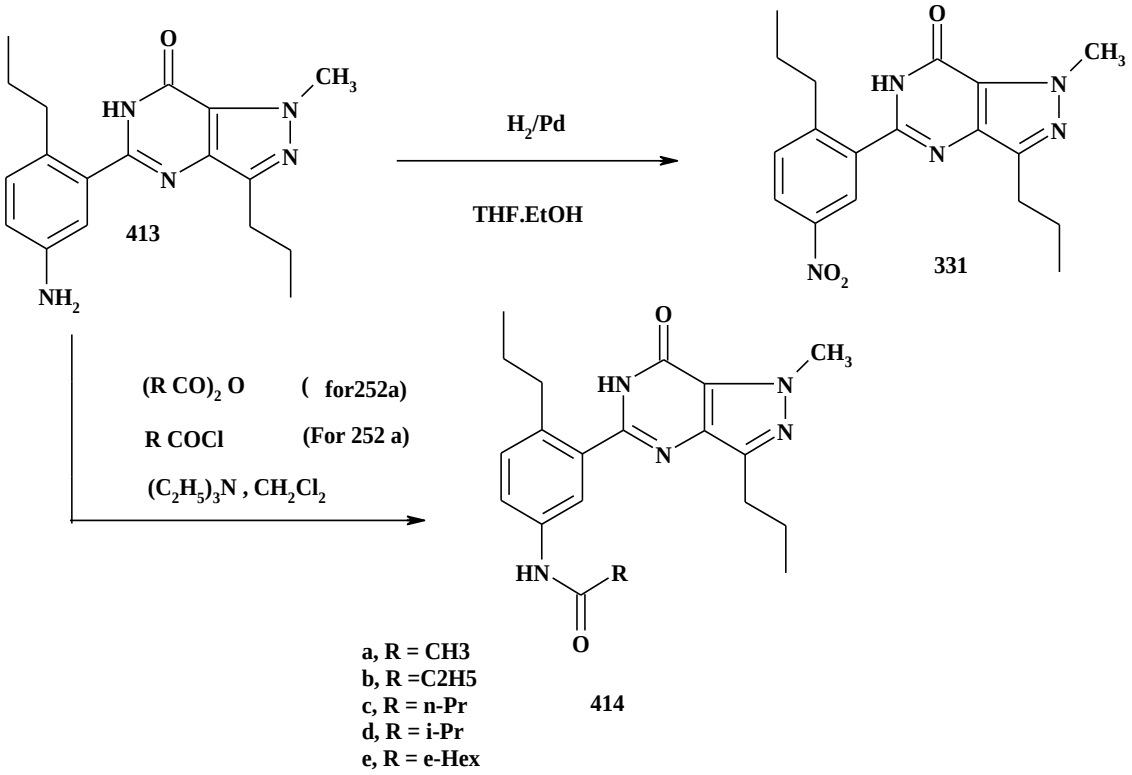


409 410 411 412

(Scheme 109)

3.4. Chemical reactivity of Pyrazolo[4,3-d]pyrimidine derivatives.

Treatment of pyrazolo pyrimidinone **413** , under hydrogenation conditions, afforded the amino derivatives **331**, The latters on acylation, reaction afforded the target phosphodiesterase inhibitors **414a-e**[132,133]. (Scheme 110).

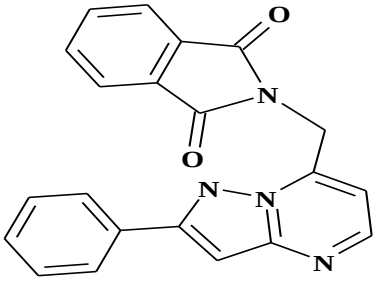


(Scheme 110).

4. Biological activity of Pyrazolopyrimidines derivatives.

4.1. Anti-microbial activity.

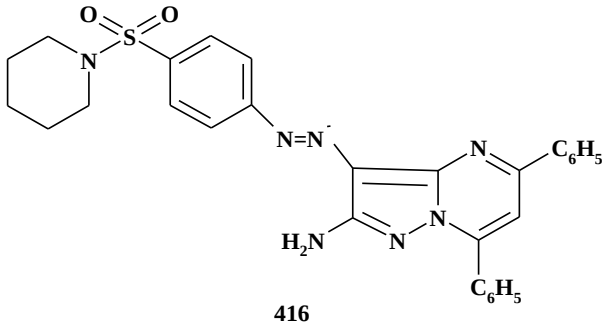
Al Omran et al[166], found that pyrazolo[1,5-*a*]pyrimdine **415** play an important role in antimicrobial and antifungal activity . (Scheme 111).



415

(Scheme 111)

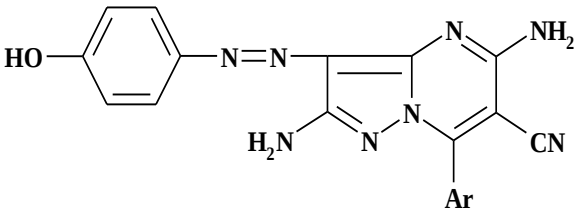
Pyrazolo[1,5-*a*]pyrimidine **416** derives were tested in vitro for their microbial activity[167-168]. (Scheme 112).



416

(Scheme 112)

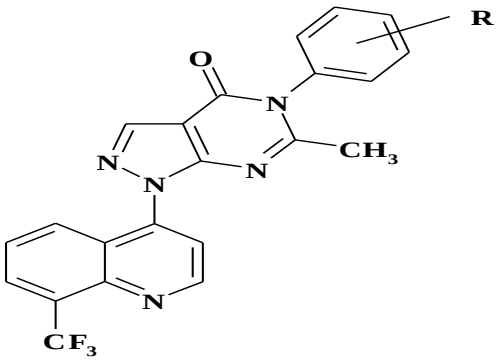
It was found that, 7-aryl-2,5-diamino-3(4-hydroxyphenyazo)[1,5-*a*] pyrimidine-6-carbontriles **417** and effect of their copper (*II*) complex solution were tested for anti- bacterial and anti- fungal activity[169]. (Scheme 113).



417

(Scheme 113)

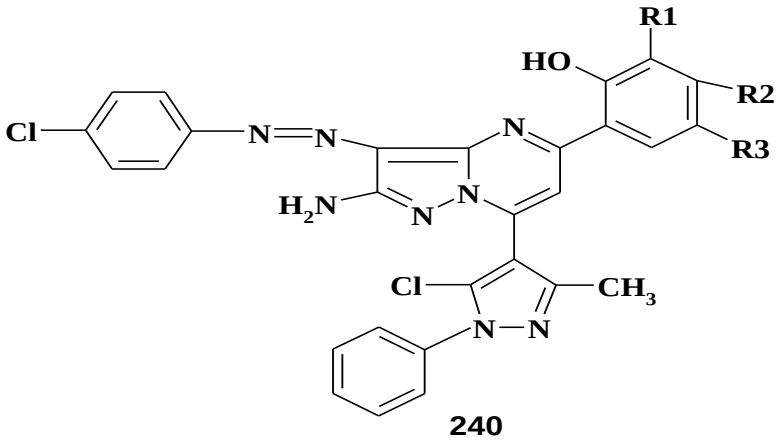
Holla et al [170], found that pyrazolo[3,4-*d*]pyrimidine **418** nucleus contains 8-(trifluoromethyl)quinoline and it has anti-microbial activity. (Scheme 114).



418

(Scheme 114)

Dawane et al[91], these screened newly synthesized compounds **240** were screened for their anti-microbial activity against MTCC443, MTCC441, MTCC96, MTCC98, MTCC96, MTCC227,MTCC160. (Scheme 115).

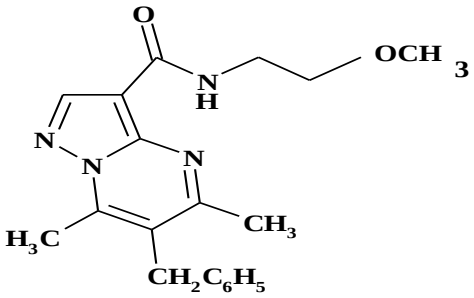


240

(Scheme 115)

4.2. Anti-Cancer activity.

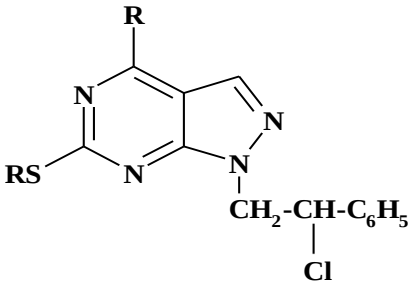
6-benzyl-5,7-dimethyl [pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid **419** used in treatment of cancer [171]. (Scheme 116).



419

(Scheme 116)

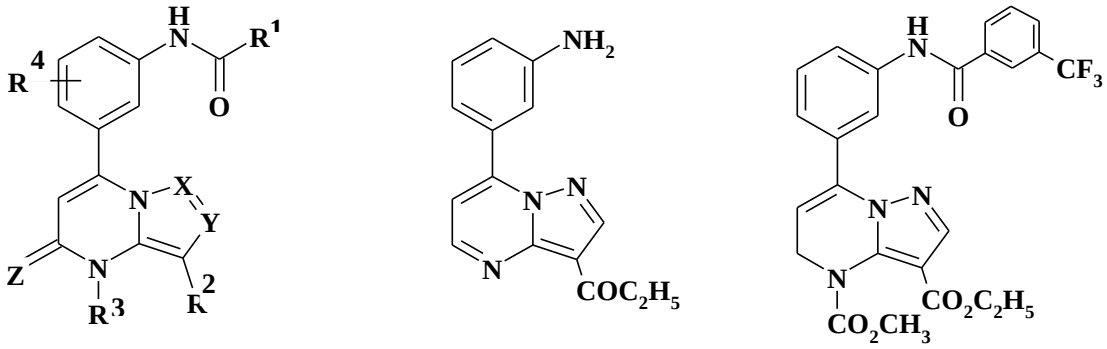
Novel 1,4,6-trisubstituted pyrazolo[3,4-*d*]pyrimidines **420** are used as anti-tumoral agents and able to block Src phosphorylation of breast cancer cells[172]. (Scheme 117).



420

(Scheme 117)

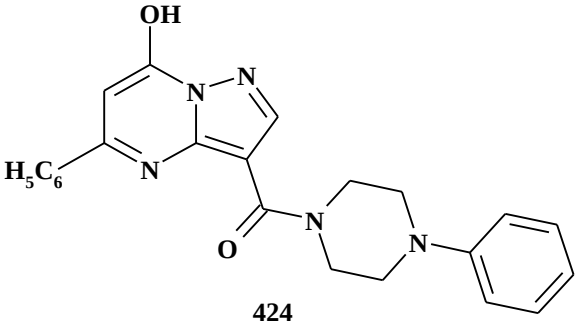
Dihydro pyrazolo[1,5-*a*]pyrimidines **421-423** could be used in treatment of Cancer [173]. (Scheme 118).



421 **422** **423**

(Scheme 118).

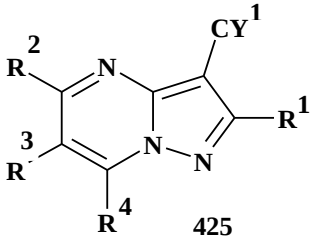
Preparation of pyrazolo[1,5-*a*]pyrimidine-3-carboxamides **424** as casein kinase, (CK2) modulators for the treatment of cancer [174]. (Scheme 119).



424

(Scheme 119)

Finbarr et al [175], study preparation of pyrazolo[1,5-*a*]pyrimidine **425** which used as anti-cancer drug. (Scheme 120).

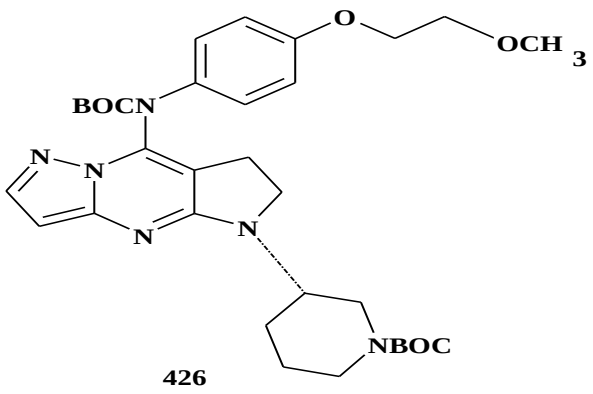


425

(Scheme 120)

R^1- R^3 = H,OH,aryl,alkoxy **R^4= NHCY2, CY2 = substituted cyclic group. CY^1 = Cyclic group.**

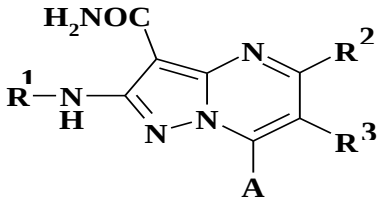
Pyrazolo[1,5-*a*]pyrimidine derivatives **426** which are prepared as MAPKAP K2 inhibitors used in treatment of cancer[176]. (Scheme 121).



426

(Scheme 121)

Harunobu et al[177], found that pyrazolo[1,5-*a*]pyrimidine derivatives **427** are useful for preventation and treatment of cancer. (Scheme 122).



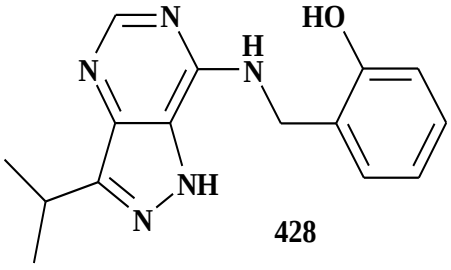
427

(Scheme 122)

R^1 = C_6H_5 , alkyl R^3 = H, alkyl R^2 = H, C_6H_5 A = H

Pyrazolopyrimidine **428** presents as a novel inhibitor of CDK Cyclic B showing as anti-proliferative on cancer cell line K = 562 [178]. (Scheme 123)

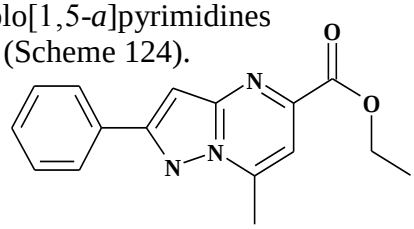
.



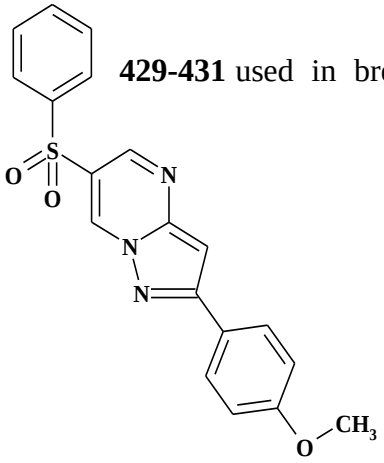
428

(Scheme 123)

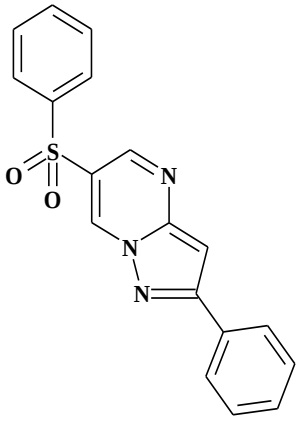
Pyrazolo[1,5-*a*]pyrimidines **429-431** used in breast cancer [179 -185]. (Scheme 124).



429



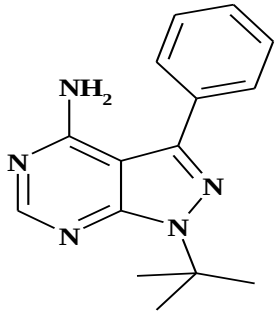
430



431

(Scheme 124)

Rucci1 et al [186], studied the derivatives of pyrazolopyrimidine **432** as anti-cancer agent[187,188]. (Scheme 125).

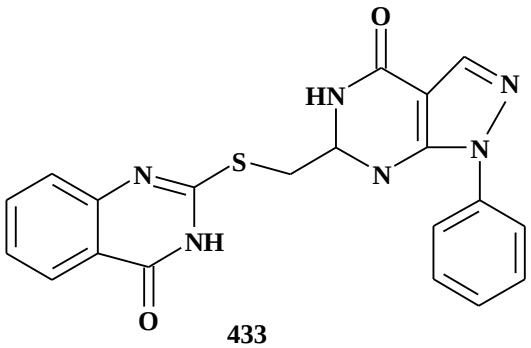


432

(Scheme 125)

The anti-proliferative activity of compound were examined in range of cancer cell lines including human hepomahep G2, breast cancer cell line MCF7, LUNG CANCER CELL

LINE a549, and prostate cancer cell line PC.3 using the MTT assay with doxorubiain as positive control[189]. (Scheme 126).

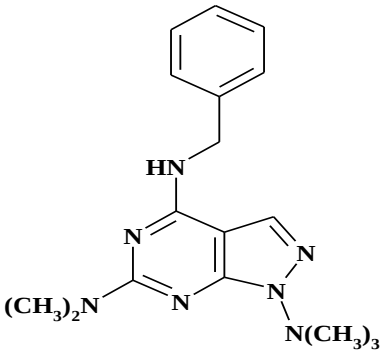


433

(Scheme 126)

4.3. Anti-inflammatory activity.

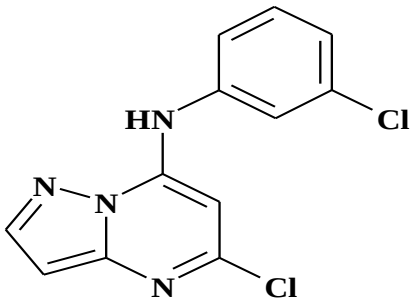
It was found that, N^4-benzyl-N^6, N^6-dimethyl-1-1(*tert*-butyl)-1*H*-pyrazolo[3,4-*d*] pyrimidine-6,4-diamine **434** (DPP) used as Pro-inflammatory agent[190]. (Scheme 127).



434

(Scheme 127)

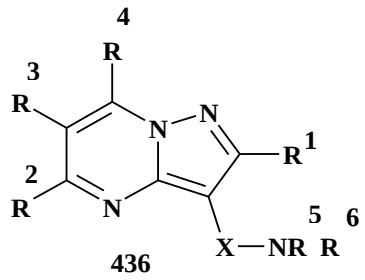
It was found that, 5,7-dichloropyrazolo[1,5-*a*] pyrimidine **435** with 3-chloro aniline are useful as JNK inhibitors for treatment of metabolic diseases as inflammatory diseases[191]. (Scheme 128).



435

(Scheme 128)

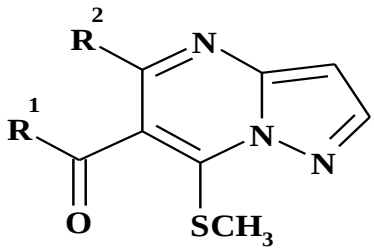
Horiuchi et al[192], study the preparation of pyrazolo[1,5-*a*]pyrimidine derivatives **436** as asteoclast differentiation inhibitors which are used as anti-inflammatory agent. (Scheme 129).



436

(Scheme 129)

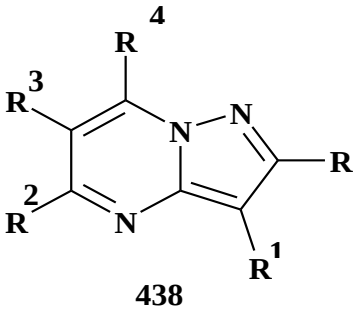
Pyrazolo[1,5-*a*]pyrimidine **437** are useful for treatment of kinase mediated disorder such as inflammation[193]. (Scheme 130).



437

(Scheme 130)

Griffith et al[194], found that, 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl) pyrazolo[1,5-*a*] pyrimidine-7-yl]-4-ethylaminopiperidine-4-carboxylic acid amide **438** as useful for treating diseases as sclizophrina , parinson's diseases and inflammation. (Scheme 131).

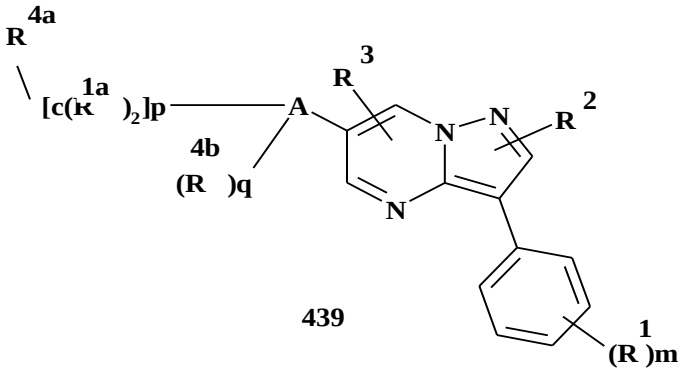


438

(Scheme 131)

R,R^1 = unsubstituted Aryl , R^2,R^3 = H,halo-cl-4-alkyl,halo,cl-4-alkyl ,R4 = Q , Q^1,OR^5

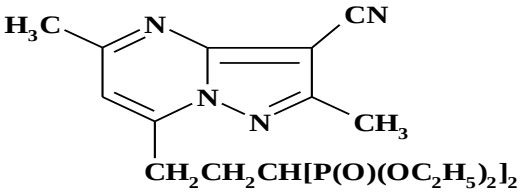
1-phenyl-N[y-(3-phenyl pyrazolo [1,5-*a*] pyrimidine-6-yl)benzyl] ethanamine **439** used in treatment of tryrosine kinase dependent diseases and condition such as inflammatory diseases, Cancer and Tumor growth [195]. (Scheme 132).



439

(Scheme 132)

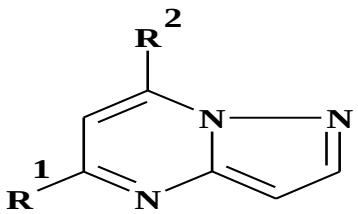
New pyrazolo[1,5-*a*]pyrimidine **440** is potent inhibitors of amurine modle of chronic and cutaneous inflammation[196]. (Scheme 133).



440

(Scheme 133)

Inoue et al[197], found that 5-alkyl pyrazolo[1,5-*a*]pyrimidine -7-yl **441** is useful as anti-inflammatory, antiasthmatic , antipyretic , antirheumatic and antiallergy agents. (Scheme 134).



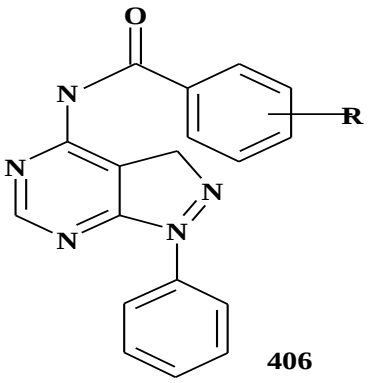
441

R^1 = alkyl **R^2 = NRR^3**

(Scheme 134)

Kota et al[130], these compouds were screened for anti-inflammatory activity by carrageenan induced edemamodel. (Scheme 135)

.



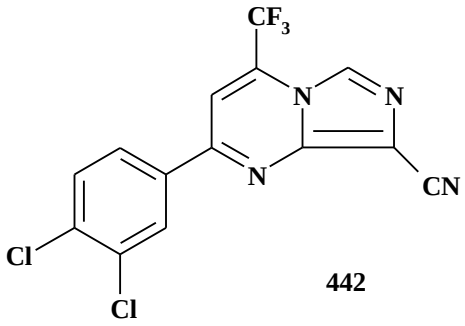
406

R:a=H, b=4-cl, c=4-CH3
d=4-F, e=4-NH2, f=4-CF3, g=4-NO2

(Scheme 135)

4.4. Al Zheimer's diseases.

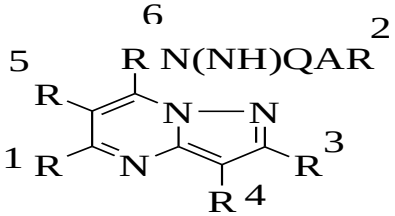
Wichmann et al[198], found that preparation of pyrazolo pyrimidine derivative **442** as metabotropic glutamate receptor antagonist is useful for preparation and treatment of Alzheimer's diseases and schizophrenia. (Scheme 136).



442

(Scheme 136)

Pyrazolo[1,5-*a*]pyrimidine derivatives **443** are useful for treatment of Alzheimer's diseases, cerebral injury, Huntinatones diseases and Parkin son's diseases [199].(Scheme 137).

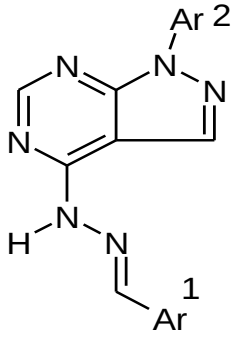


443

(Scheme 137)

R^1 = H,furyl , thienyl ,R^2 = naphthyl , cycloalkyl ,R^3 = H,Ph
R^4 = H R^5 = H R^6 = H,benzoyl
Q = Carbonyl , sulfonyl A = Single bond

It was found that , aseries of 1-aryl-pyrazolo[3,4-*d*]pyrimidine-4-aryl hydrazones **444** is important in treatment of Al Zheimer's dieases[199]. (Scheme 138).

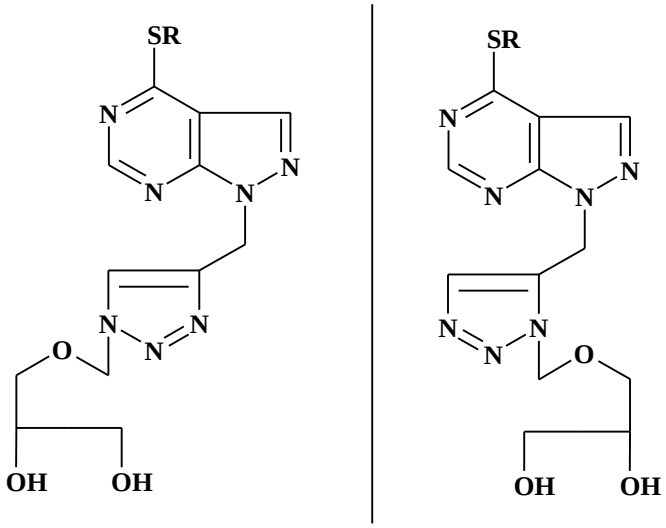


444

(Scheme 138)

4.5. Anti HIV.

Moukha et al[155], studied that pyrazolo[3,4-*d*]pyrimidine nueleosides **396-397** were evaluated for their inhibitory effects on HIV-1 (IIIB) and HIV-2 (ROD) replication MT-4 cell .



396 **397**

a, R = CH_3
b, R = CH_2 C_6H_5

(Scheme 139)

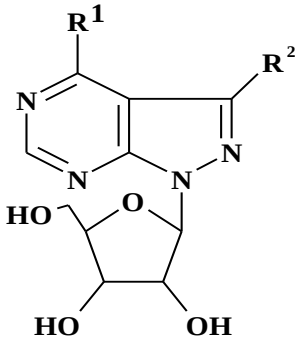
4.6. Antiviral activity.

Pyrazolo[3,4-*d*]pyrimidine **359** was select to be tested for anti-viral activity against helps simplex virus [HSV-1] [101,102,200] (table 1).

Antiviral activity of Mercapto pyrazolopyrimidines Table (1) :-

compd	R^1	R^2	Toxic level	Virus rating			
				Para	VSV	VV	HSV1
359a	OH	SMe	$5x10^{-3}$	0.11	Not tested	0	0.16
359b	SH	CN	Non toxic	1.10	0.56	1.24	1.00
359c	OH	$CSNH_2$	$5x10^{-3}$	1.15	0	0.40	0

Compounds of pyrazolo[3,4-*d*]pyrimidine-4(SH)-selone ribonucleosides exhibited significant activity against HSV-2 in vitro, whereas pyrazolo[3,4-*d*] pyrimidine-4(SH)-thione ribonucleosides exhibited the most potent activity against measls and had a very low toxicity. Also, the sulfur compounds were tested against herpes simplex type 2 (HSV-2, 359), Vaccinia (VV) and Parainfluenza type 3 (Para 3) viruses in vitro as in table (2**) .** (Scheme 140).



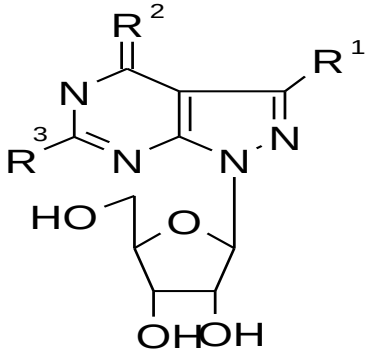
359

(Scheme 140)

In vitro antiviral activity Table (2).

R^1	R^2	R^3	ED_{50} M				
			Para 3	measles	VV	HSV-2	Toxic level, M
H	Se	H	> 5 x 10^{-3}	1.2 x 10^{-6}	9.6 x 10^{-6}	5 x 10^{-6}	1.6 x 10^{-4}
H	Se	CH_3	1.3 x 10^{-5}	1.3 x 10^{-6}	1.6 x 10^{-5}	5 x 10^{-6}	5 x 10^{-4}
H	S	CH_3	> 5 x 10^{-3}	1.4 x 10^{-9}	1.2 x 10^{-3}	3.2 x 10^{-4}	5 x 10^{-3}
H	S	H	> 5 x 10^{-3}	1.2 x 10^{-5}	2.9 x 10^{-4}	1.6 x 10^{-4}	none

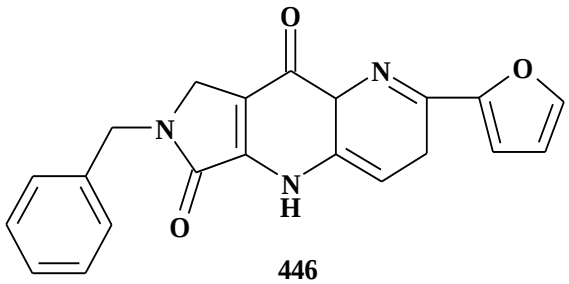
4,6-Dimethylthiopyrazolo[3,4-d]pyrimidine **445** and their derivatives showed anti-viral against RDV and EMCV. (Scheme 141).



445

(Scheme 141)

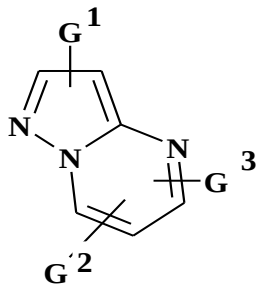
Naruganawli et al[201], found that tricycles 6,7dihydro-*4H*- pyrazolo[1,5-*a*] pyrol[3,4-*d*] pyrimidine -5,8–dione **446** was used as anti-viral activity [203,203]. (Scheme 142).



446

(Scheme 142)

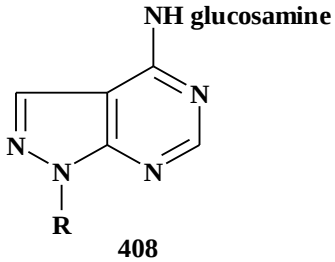
It was found that , pyrazolo[1,5-*a*]pyrimidine **447** used as anti-viral agents against hepatitis C virus (HCV) infection [204,205]. (Scheme 143).



447

(Scheme 143)

Rashad et al[164], showed that compound **408** have promising anti-viral activity against hepatitis-virus (HAV) and herpes simplex virus type (HSV-1). (Scheme 144).

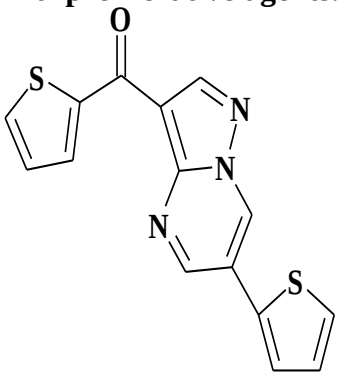


408

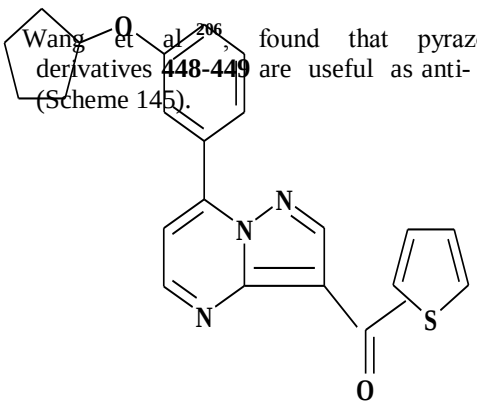
(Scheme 144)

4.7. Anti-proliferative agents.

Wang et al [206], found that pyrazolo[1,5-*a*]pyrimidine derivatives **448-449** are useful as anti- proliferative agents. (Scheme 145).



448

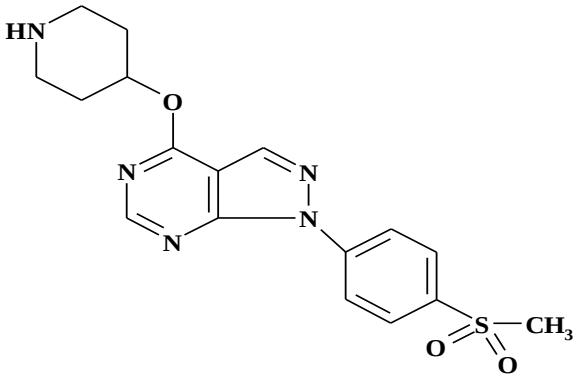


449

(Scheme 145)

4.8. Anti-metabolized.

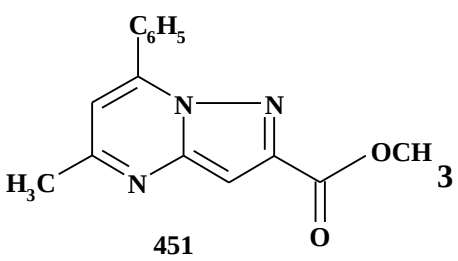
Preparation of pyrazolo[3,4-*d*]pyrimidine **450** as modulators of G.coupled protein receptor are useful in the prophylaxis or treatment of metabolic disorder[207]. (Scheme 146).



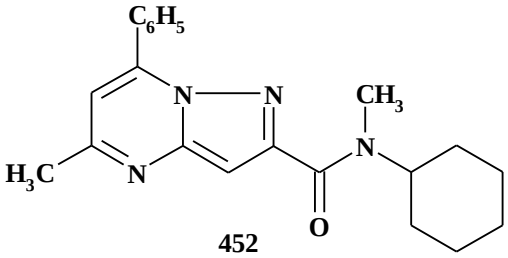
450

(Scheme 146)

Pyrozolo[1,5-*a*]pyrimidine **451-452** as *ß*–hydroxyl steroid dehydrogenase type1 modulator especially inhibitors for metabolic disorders [208].(Scheme 147).



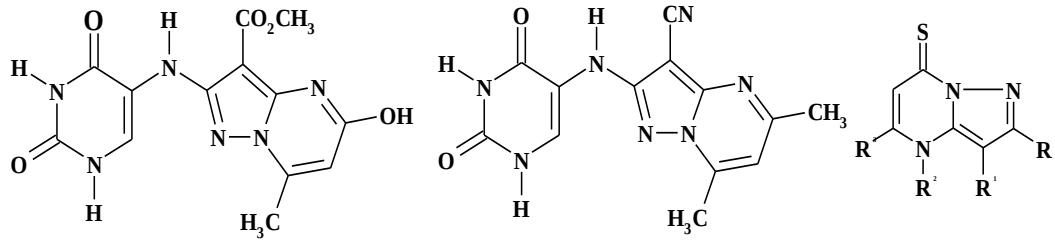
451



452

(Scheme 147)

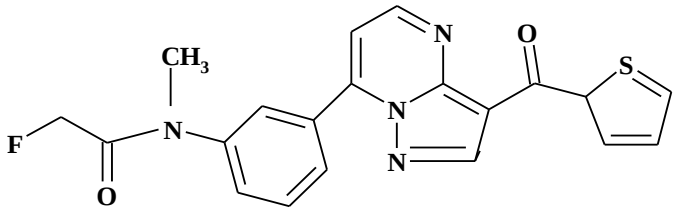
Fathalla et al [209], found that Novel 3–cyano–2-(3-uracilyl-5-amino) pyrozolo[1,5-*a*]pyrimidine **453-455** were studied as cytotoxic anti-metabolities of Biom phalaria alexandrina snails. (Scheme 148).



453 **454** **455**

(Scheme 148)

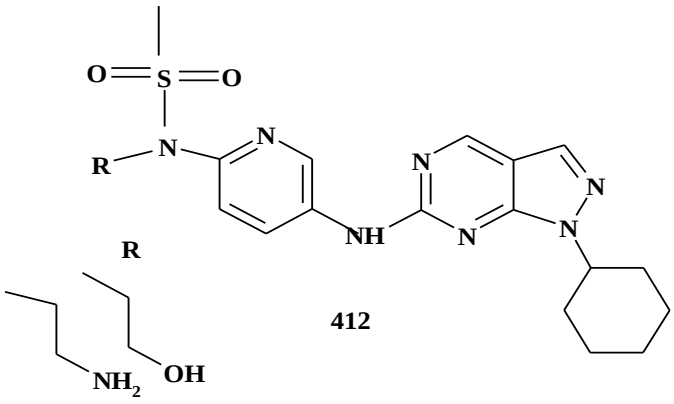
Hoepping et al[92], found that [f[18]]fluoro-indiplon **353** shows good in vitro features, it is not suitable for in vivo imaging studies because of its metabolism . (Scheme 149).



353

(Scheme 149)

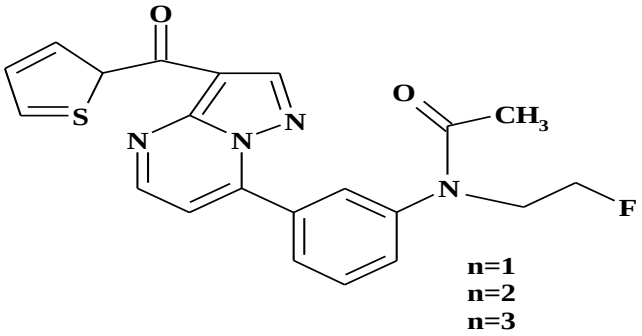
Zhang et al[165], showed compound **412** dual inhibition of aurora kinase A(AKA) and cylin-dependent kinase (CDKI). (Scheme 150).



412

(Scheme 150)

wengner et al[210], show that the fluorinated indiplon **456** derivatives have high affinity, specificity and potency at neuronal and recombinant α1 containing $GABA_a$ receptors comparable to indiplon. (scheme 151).



456

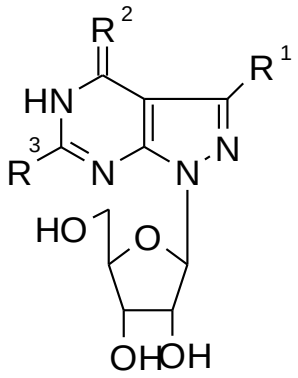
(Scheme 151)

4.9. Antischistosomal.

Several pyrazolo[3,4-d]pyrimidines **445** are tested for anti-schistosomal activity against *Schistosoma mansoni* and the greatest degree of activity in vitro was found pyrazolo[3,4-d]pyrimidines. In particular some of pyrazolo[3,4-d] pyrimidines proved Lethal at 100 Mg/ml after an exposure for only 1h . On the other hand different pyrazolo[3,4-d]pyrimidines could be used as analgesics [101,102] (table 3). (Scheme 152).

Table (3)

R^1	R^2	R^3	Antischistosomal act.MAC, μg/mL
H	H	H	1.0
H	H	CH_3	3.2
H	H	C_6H_5	1.0
H	H	H	1.0
H	H	CH_3	1.0
C_6H_5	H	C_6H_5	1.0
4-ClC_6H_5	H	CH_3	100
3-$CH_3C_6H_4$	H	CH_3	100
$COOC_2H_5$	H	CH_3	10

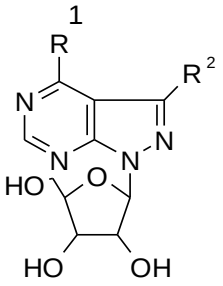


445

(Scheme 152)

4.10. Anticoccidial.

4-Alkylthiopyrazolo[3,4-*d*]pyrimidines **359** have been shown to be useful anticoccidial agents and the unsaturated 4-alkylthio and 4-crotylthio derivatives were shown to be more active in vivo against *Eimeria tenella* than their saturated congeners other compounds were effective in vitro against E. tenella, E. necatrix, E. maxima, and E. brunette [101,102]. (Scheme 153).

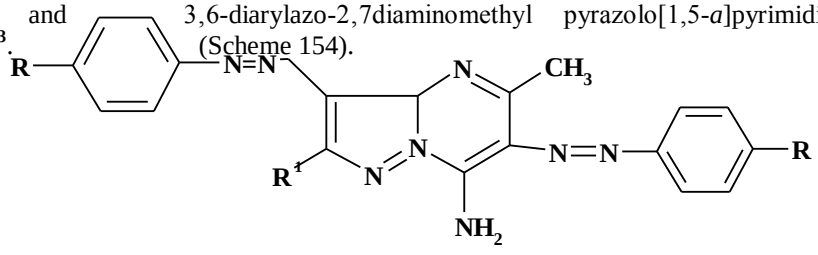


359

(scheme 153)

4.11. Dye industry.

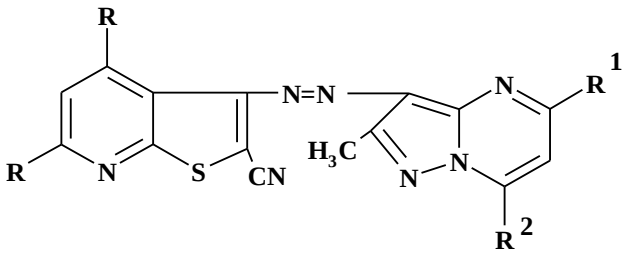
It was found that, diazopyrazolo[1,5-*a*]pyrimidine derivatives **457** as 3,6-diaryl azo-7-amino-2,5-dimethyl[1,5-*a*]pyrimidine and 3,6-diarylazo-2,7diaminomethyl pyrazolo[1,5-*a*]pyrimidine is used in dyes industry[211-213]. (Scheme 154).



457

(Scheme 154)

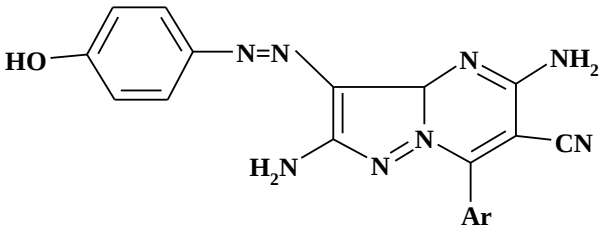
Synthesis of some new azopyrazolo[*1*,5–*a*]pyrimidine derivatives **458** used in dye industry[214 ,215]. (Scheme 155).



458

(Scheme 155)

Elgemeie et al [216], found that pyrazolo[1,5-*a*]pyrymidine derivatives **459** were useful for hair dyes . (Scheme 156).



459

(Scheme 156)

5. Conclusion.

we have described some recent advances in the synthesis of Pyrazolopyrimidines derivatives from heterocyclic compounds, Chemical reactions of Pyrazolopyrimidines derivatives and biological activity of Pyrazolopyrimidines derivatives. This review showed the significant development in Pyrazolopyrimidines derivatives synthetic methods, and its reactivity however, these derivatives are now being more popular because of its efficiency, and its importance in biological field and its pharmaceutical effect.

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