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# The chemistry of pyrazolopyrimidines and their applications

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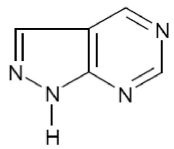
## INTRODUCTION

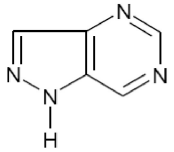
The heterocyclic fusion of pyrimidine and pyrazole rings resulted in formation of pyrazolopyrimidines, the structural analogs of biogenic purine class. Pyrazolopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. Also, due to the presence of pyrazolopyrimidine moiety in some important drugs, interest in the construction of such molecules has been aroused. In the last few decades, an enormous number of papers and reviews have been reported dealing with the chemistry and applications of this class of compounds[1-6].

## STRUCTURE OF PYRAZOLOPYRIMIDINES

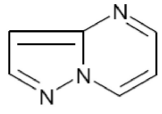
The four fundamental structures of pyrazolopyrimidine are:



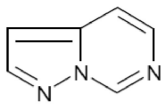
Pyrazolo[3,4-*d*]pyrimidine



Pyrazolo[4,3-*d*]pyrimidine



Pyrazolo[1,5-*a*]pyrimidine



Pyrazolo[1,5-*c*]pyrimidine

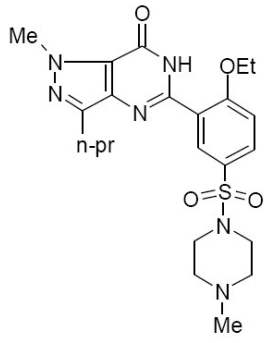
## IMPORTANCE OF PYRAZOLOPYRIMIDINES

Undoubtly, pyrazolopyrimidines have high significance in the field of pharmaceutical and biotechnological sciences with wide spectrum of biological activities and several applications were reported for these four types as:

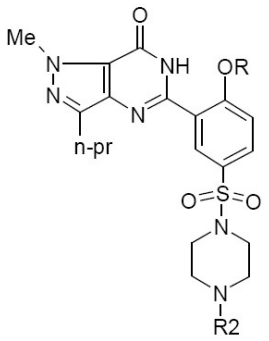
1- Numerous pyrazolo[3,4-*d*]pyrimidine derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. They have a high significance in the field of pharmaceutical and biotechnological sciences with wide spectrum of biological activities.

2- One of the most important pharmacological applications of pyrazolo[4,3-*d*]pyrimidine derivatives are the use of Sildenafil (Viagra®), a selective phosphodiesterase 5 (PDE5), as oral agent for the treatment of male erectile dysfunction. Recently, a series of Sildenafil analogs (R = Me, Et; $R_2$ = Me, Et, -$CH_2CH_2OH$) was prepared and their *in vitro* PDE5 inhibitory activities were evaluated and the results revealed improved activity and selectivity[7].

Moreover, Yuan *et al*[8], described the synthesis of 3-arylpyrazolo[4,3-*d*]pyrimidines as potential corticotropin-releasing factor (CRF-1) antagonists and the effects of substitution on CRF-1 receptor binding were investigated. In addition, a series of novel pyrazolo[4,3-*d*]pyrimidin-7-ones were synthesized and their *in vitro*

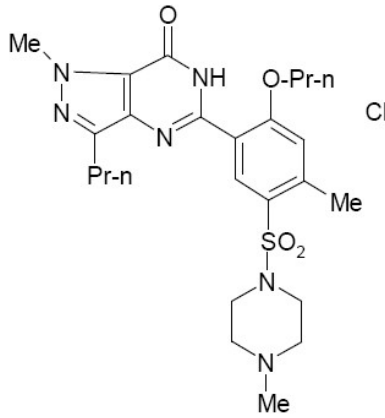



sildenafil structure




sildenafil analogs

bronchodilatory activities were tested in guinea-pigs and it was found that compound **(1)** has more potent activity than aminophylline[9]. Also, pyrazolo[4,3-*d*]pyrimidines demonstrated potential anticancer properties, where 6-arylcarboxamidopyrazolo[4,3-*d*]pyrimidin-7-one derivative **(2)** was synthesized and showed activity against colon cancer cell lines (HT-29) and human prostate cell lines (DU-145)[10]. Moreover, a new potent CDK2 inhibitor with pyrazolo[4,3-*d*]pyrimidine scaffold has been synthesized, characterized, and evaluated in cellular and biochemical assays as a bioisostere of the well-known CDK inhibitor Roscovitine. Importantly, as the anticancer activities of the pyrazolo[4,3-*d*]pyrimidine derivatives exceed those of its bioisostere Roscovitine and may be preferable for cancer therapy[11].

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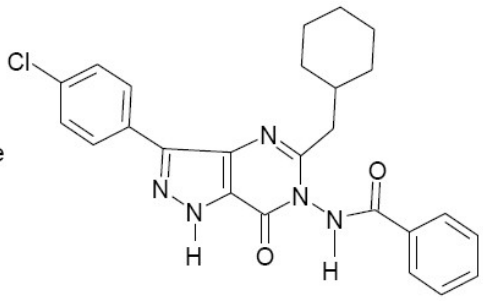


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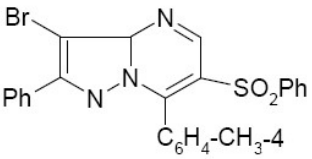



3

3- Recently, the chemistry of pyrazolo[1,5-*a*]pyrimidines attracted great attention as synthetically important class of compounds[12]. They represent a biologically important compounds of purine analogs and this class have attracted wide pharmaceutical interest as inhibitors of lymphocyte-specific kinase (Lck) with enzymatic, cellular and *in vivo* potency[13]. Also, they considered as novel PDE-4 inhibitors[14], selective Peripheral Benzodiazepine Receptor (PBR) ligands[15], COX-2 selective inhibitors[16], AMP phosphodiesterase inhibitors[17], and as antianxiety agents[18]. In 2003, a research group from NRC synthesized some pyrazolo[1,5-*a*]pyrimidines and studied their biological effects as anti-inflammatory, analgesic and antipyretic drugs in comparison to Novalgin[19]. Other pharmaceutical activity has been reported as some novel pyrazolo[1,5-*a*]pyrimidine derivatives were screened for their antimicrobial properties and showed significant activity when compared with known standard drugs[20].

Also, a novel series of pyrazolo[1,5-*a*]pyrimidines bearing a 3-hydroxyphenyl group at C(3) and substituted tropanes at C(7) has been identified as high potent B-Raf inhibitors[21]. In addition, Shaaban *et al*[22], prepared pyrazolo[1,5-*a*] pyrimidine systems incorporating phenylsulfonyl moiety and analgesic, anti-inflammatory activities were investigated *in vivo*. The studies revealed that 3-bromo-2-phenyl-6-(phenylsulfonyl)-7-(4-methylphenyl)-pyrazolo [1,5-*a*] pyrimidine **(3)** was found to have an excellent analgesic activity in comparison with indomethacin as a reference drug.

4- Pyrazolo[1,5-*c*]pyrimidines known to possess significant hypnotic, tranquilizing, fungicidal, insecticidal and antibacterial activities[23-25]. Also, the coordination of pyrazolo[1,5-*c*]pyrimidines to transition metal ions such as $Cu^{+2}$ and $Ni^{+2}$ enhances their biological activities[26,27]. Moreover, Gudmundsson *et al*[28], studied the antiviral activity of some sub-

stituted pyrazolo[1,5-*c*]pyrimidine derivatives and the tested compounds demonstrated potent activity against herpes simplex viruses (HSV-1, 2).

However, it is not feasible to discuss the chemistry and applications of all these types in this report, since each type needs and deserves a separate treatment and presentation. So, the scope of the present work will be confined to the first type: pyrazolo[3,4-*d*]pyrimidine derivatives.

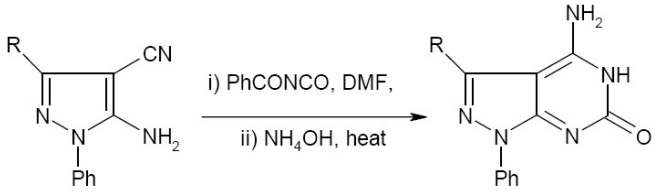
## SYNTHESIS OF SOME PYRAZOLO[3,4-*d*]PYRIMIDINE RING SYSTEMS

Synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives was performed according to the following general strategies:

(i) Annulations of the pyrimidine on a pyrazole ring system
(ii) Annulations of the pyrazole on a pyrimidine ring system
(iii) From acyclic intermediates

### i- Annulations of pyrimidine on pyrazole ring system

Paulsen *et al*[29], synthesized 4-amino-1-phenylpyrazolo[3,4-*d*]pyrimidinone derivative **(5)** *via* the reaction of *β*-enaminonitrile **(4)** with benzoyl isocyanate in the presence of ammonium hydroxide as a base.




4 5

R = $CH_2CN$

Also, treatment of 5-amino-3-cyanomethyl-1-phenyl-1*H*-pyrazole-4-carbonitrile **(4)** with triethyl orthoformate in acetic anhydride afforded the methanimidate **(6)** which was converted to the pyrazolo[3,4-*d*]pyrimidin-4-ylamine derivative **(7)** upon treatment with ammonia[30].

5-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidine derivative **(9)** could be obtained directly by treatment of the 5-aminopyrazole-4-carbonitrile **(8)** for mamidine in acetic acid[31].

*N*-Methylformamide converted 5-amino-1-methyl-1*H*-pyrazole-3,4-dicarbonitrile **(10)** to the imine intermediate **(11)**. The latter intermediate underwent ring opening by a typical Dimroth rearrangement and recyclized to furnish the pyrazolo[3,4-*d*]pyrimidine **(12)** carrying a methylamino group at 4-position[32].

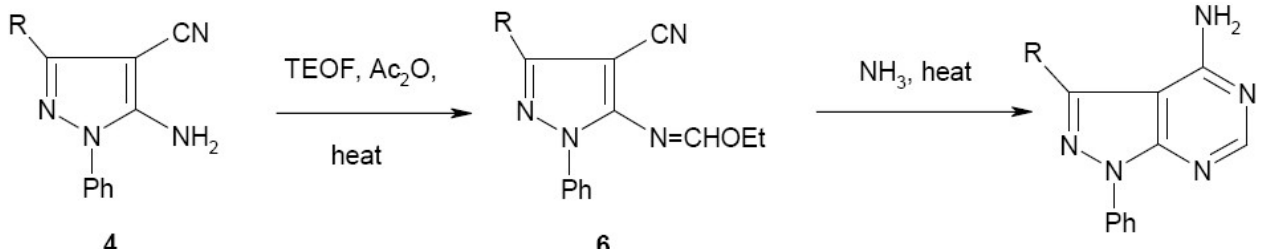
Compound **(8)** was converted to the corresponding carboxylic acid amide derivative **(13)** by hydrolysis of the nitrile group with sulphuric acid. Subsequent fusion of **(13)** with thiourea provided 4-hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine **(14)**[33].

Moreover, 5-amino-1*H*-pyrazole-4-carbonitrile **(8)** was fused with urea or thiourea to give the corresponding 4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives **(15)** and **(16)**, respectively[34].

Also, 5-amino-1*H*-pyrazol-4-carbonitrile derivative **(17)** was refluxed with carbon disulfide in pyridine to give the corresponding 4,6-dithioxopyrazolo[3,4-*d*]pyrimidine derivative **(18)** through subsequent rearrangement of the thiazine intermediate by the action of alkali[35].

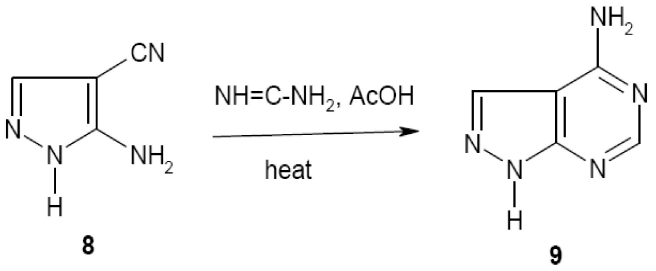
5-Amino-1*H*-pyrazole-4-carbonitrile **(8)** was reacted with phenyl isothiocyanate in dimethylformamide to furnish pyrazolo[3,4-*d*]pyrimidine-6-thione **(19)**[36].

Recently, Kandeel *et al*[37], have prepared pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivative **(21)** by treatment of 5-amino-3-methyl-1*H*-phenylpyrazole-4-carbonitrile **(20)** with formic acid.



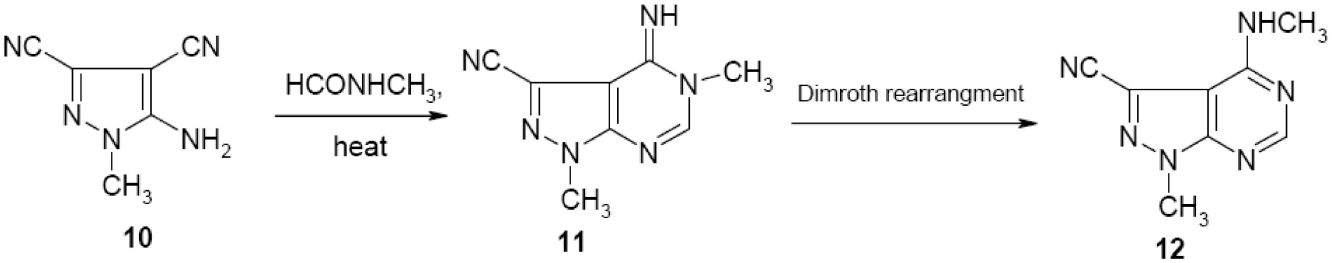

4 6 7

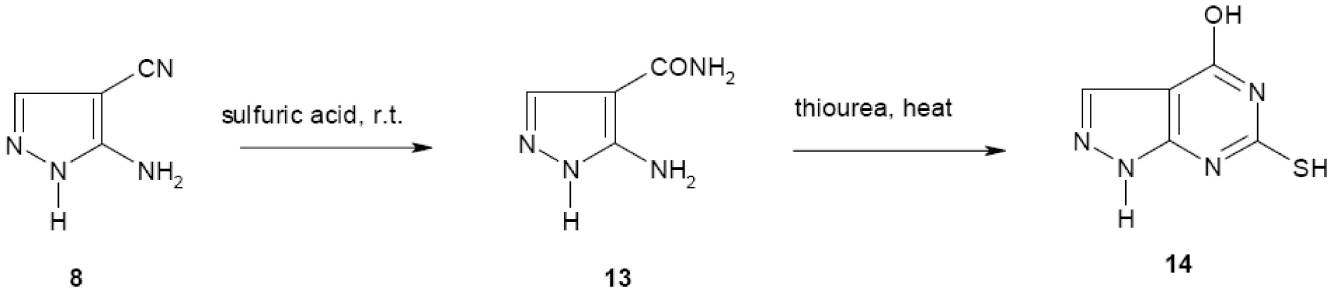
R = $CH_2CN$

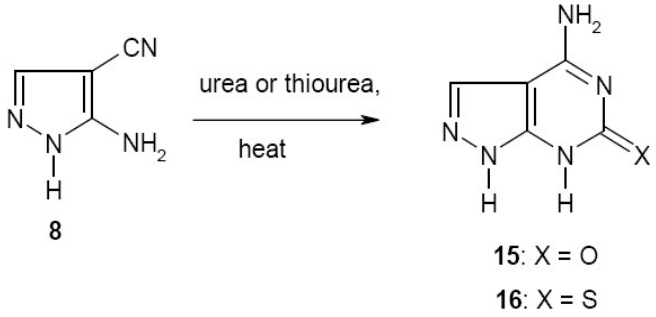



Compound **(4)** (R =H) was easily converted to the corresponding chloroamidine **(22)** on treatment with phosgene methyliminium chloride. Compound **(22)** was cyclized, in the presence of hydrochloric acid, to pyrazolo[3,4-*d*]pyrimidine **(23)**[38].

Moreover, when pyrazolylcarbothiohydrazide **(24)** was treated with formic acid or triethyl orthoformate, it



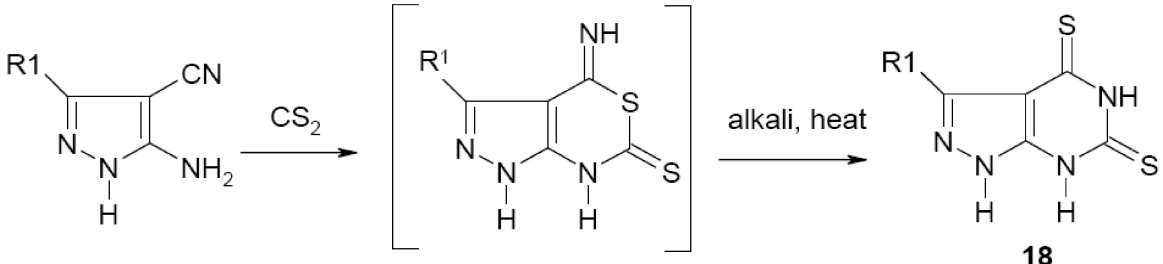



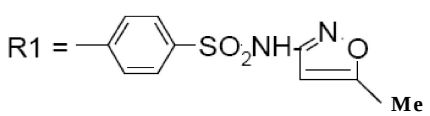

gave 3-methylsulfanyl-1-(1,3,4-thiadiazolyl-2-yl)pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **(25)**[39].

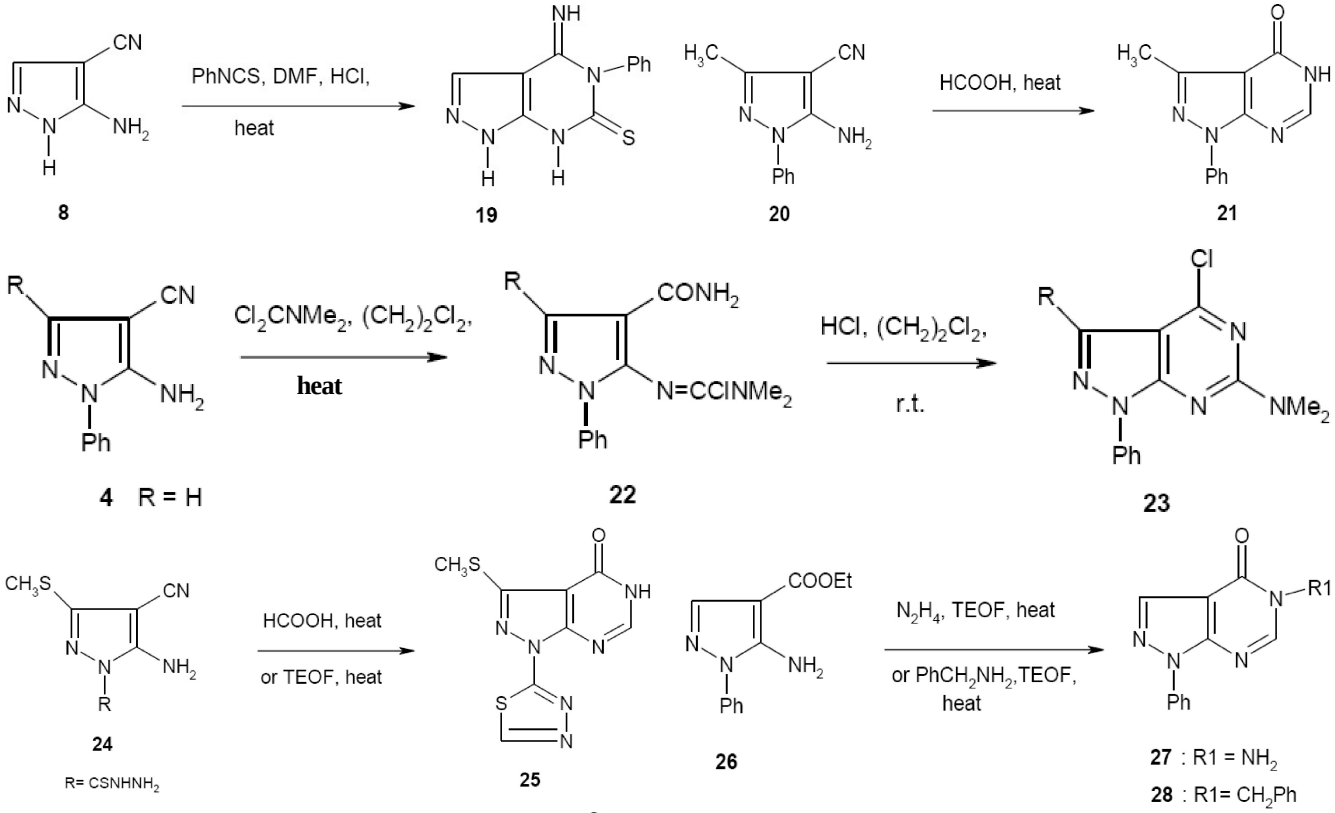
Ghorab *et al*[40], treated ethyl 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate **(26)** with hydrazine hydrate or with benzyl amine in the presence of triethyl orthoformate to produce the 5-substituted derivatives **(27)** and **(28)**, respectively.

In addition, reaction of derivative **(29)** with formamide at 200 °C for 8 h afforded the pyrazolo[3,4-*d*]pyrimidin-4-one **(30)**[41].

Moreover, El-Enany *et al*[42], treated 5-amino-3-methylsulphanyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid amide **(31)** with propionic anhydride, chloroacetyl chloride or 3-chloropropionyl chloride to furnish the 6-substituted pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivatives **(32a-c)**, respectively.



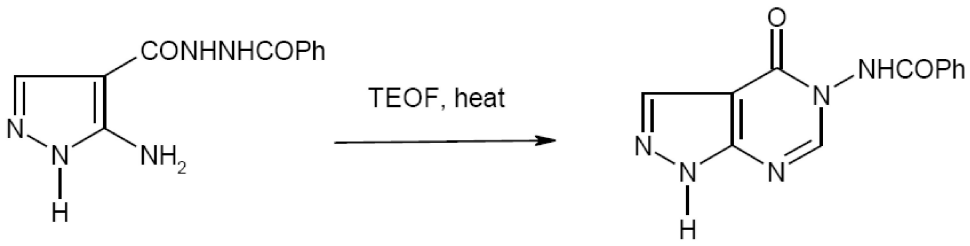


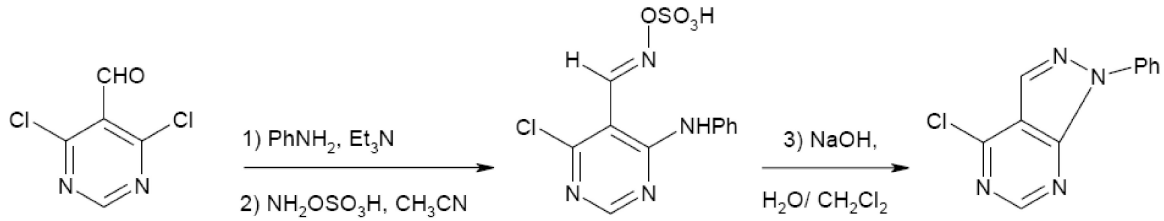

Also, pyrazolo[3,4-*d*]pyrimidine-4,6-dione derivative **(34)** was synthesized from the reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid hydrazide **(33)** with urea in decaline[40].

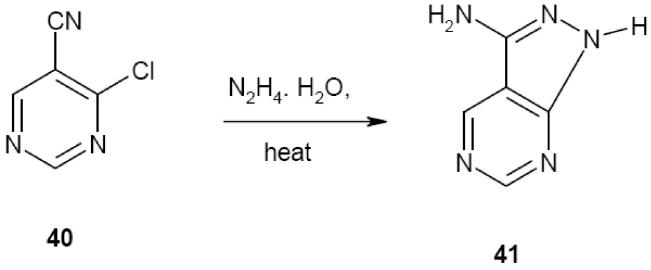
On the other hand, 5-benzamido-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one **(36)** has been prepared by reacting 5-amino-1*H*-pyrazole-4(*N*-benzoyl)carbohydrazide **(35)** and triethyl orthoformate[43].

## ii- From annulations of pyrazole on pyrimidine ring system

In 2012, Evanes *et al*[44], have described an efficient synthesis of 1-phenylpyrazolo[3,4-*d*]pyrimidine

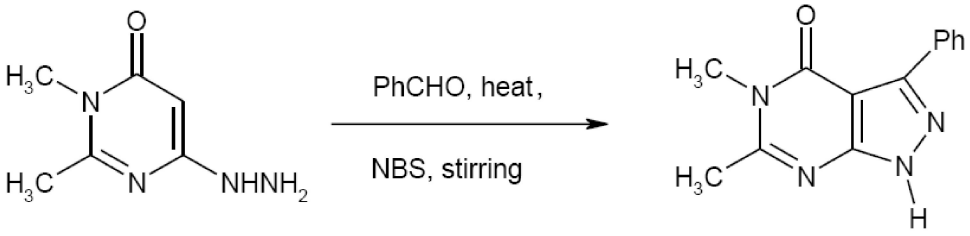


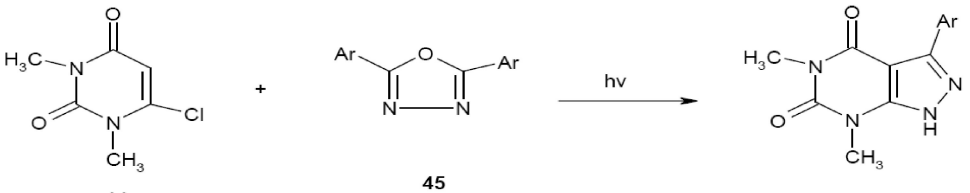



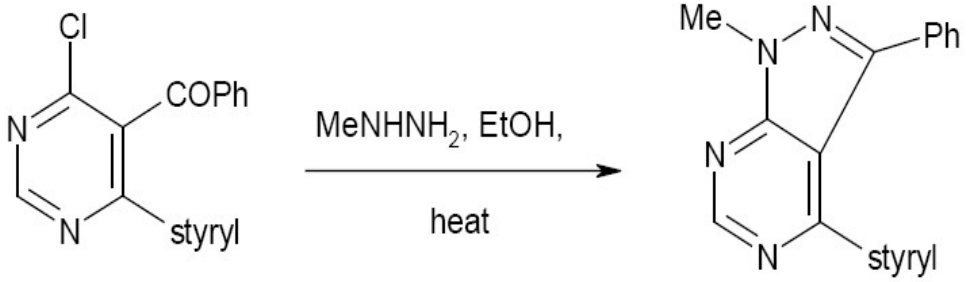

**(39)** starting with 4,6-dichloropyrimidine-5-carbaldehyde **(37)**, aniline and hydroxylamine-*O*-sulfonic acid. The key step was a cyclization reaction of the oxime **(38)** to form the N–N bond of the product.

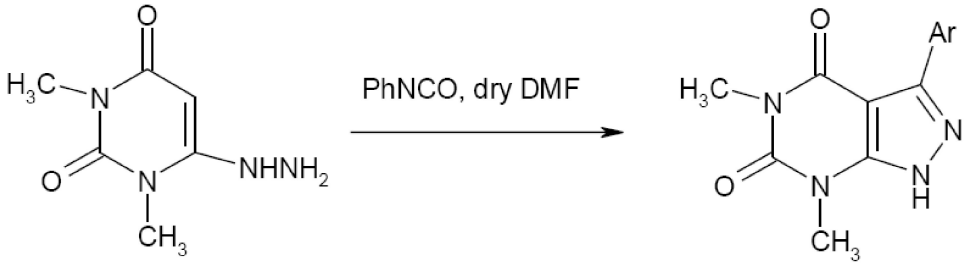
In general, 3-aminopyrazolo[3,4-*d*]pyrimidine **(41)** was prepared by heating of 4-chloropyrimidine-5-carbonitrile **(40)** with hydrazine hydrate[45].



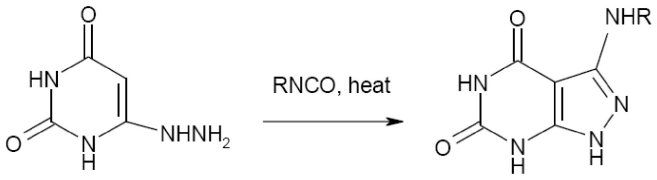

Ar = Ph






**49** **46**

Ar = NHPh




**50** **51a-c**

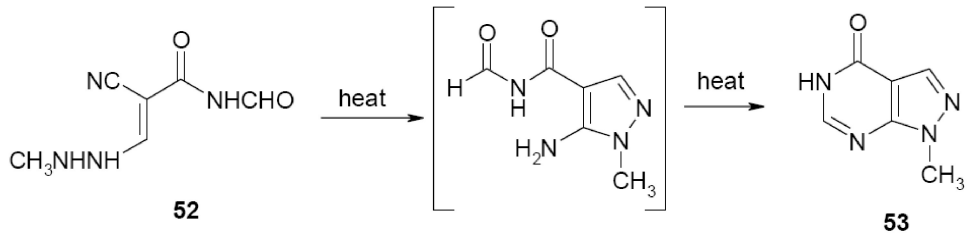
**a**; R = Me

**b**; R = Ph

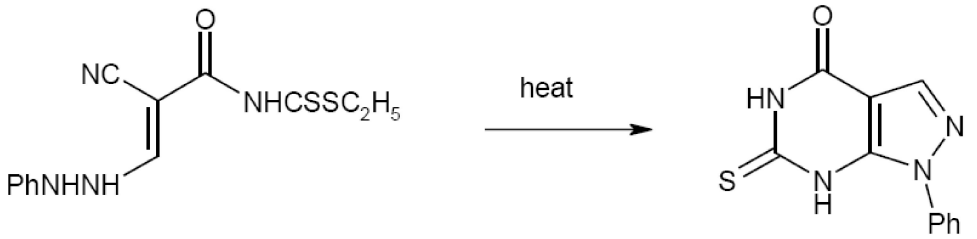
**c**; R = $CH_2Ph$

4-Hydrazinopyrimidine **(42)** (having an adjacent activated hydrogen in position 5) is readily converted to the corresponding substituted pyrazolo[3,4-*d*]pyrimidine **(43)** *via* condensation with benzaldehyde in the presence of *N*-bromosuccinamide (NBS)[46].

Photolysis of 6-chloro-1,3-dimethyluracil **(44)** with 1,3,4-oxadiazole **(45)** afforded pyrazolo[3,4-*d*]pyrimidine derivative **(46)** (Ar = Ph), with photoelimination of benzoyl chloride[47].

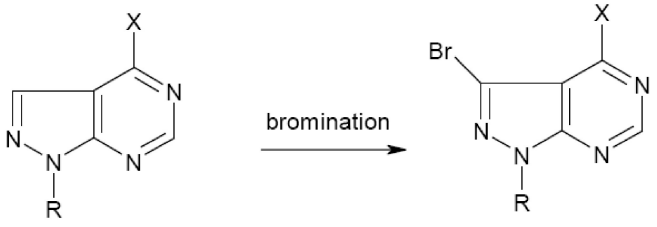



**52** **53**




**54** **55**

Gomtsyan *et al*[48], reported that when compound **(47)** was treated with methyl hydrazine in ethanol, it gave the desired pyrazolo[3,4-*d*]pyrimidine derivative **(48)**.




**56** **57**

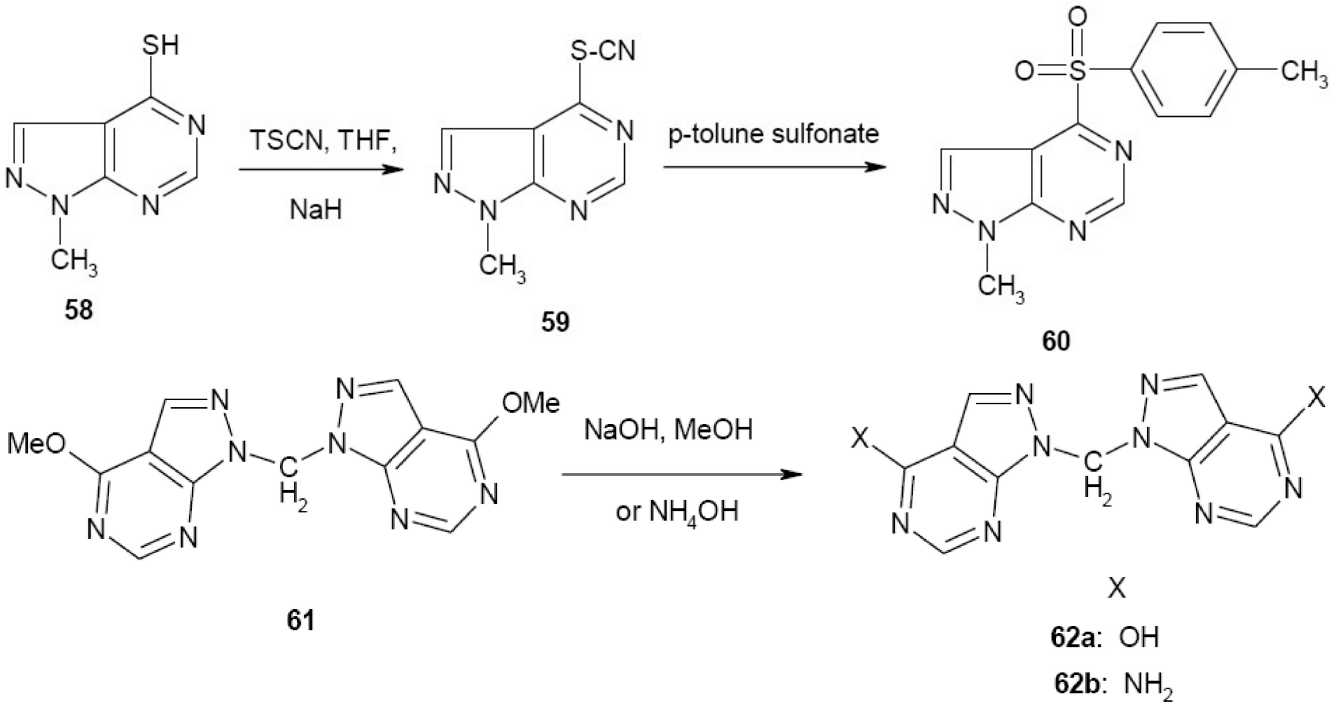
X = H or $NH_2$

Also, an efficient one-pot synthesis of pyrazolo[3,4-*d*]pyrimidine-4,6-dione **(46)** (Ar = NHPh) in excellent yield was achieved by the reaction of 6-hydrazino uracil **(49)** with phenyl isocyanate[49].

Similarly, Abu Elmaati[50], reported that the reaction of 6-hydrazinopyrimidine-2,4-dione derivative **(50)** with alkyl or aryl isocyanates resulted in a novel and facile synthesis of pyrazolo[3,4-*d*]pyrimidine-4,6-diones **(51a-c)** in good yields.

### iii- From acyclic intermediates

The vinyl hydrazine derivative **(52)** was cyclized on

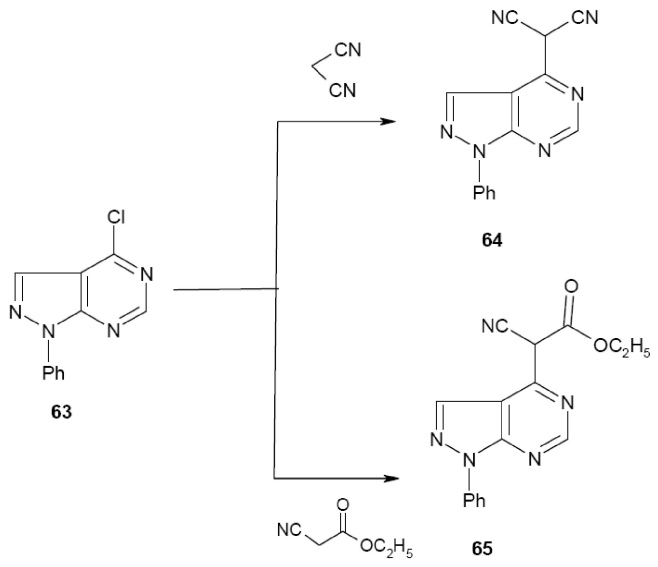



heating to pyrazole carboxylic acid amide intermediate; which was not isolated and underwent intramolecular cyclization on further heating to give pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one derivative **(53)**[51].

Similarly, heating of the dithioester **(54)** resulted in intramolecular cyclization giving pyrazolo[3,4-*d*]pyrimidinone derivative **(55)**[51].

## REACTIONS OF PYRAZOLO[3,4-*d*]PYRIMIDINES

### i- Electrophilic substitution reactions

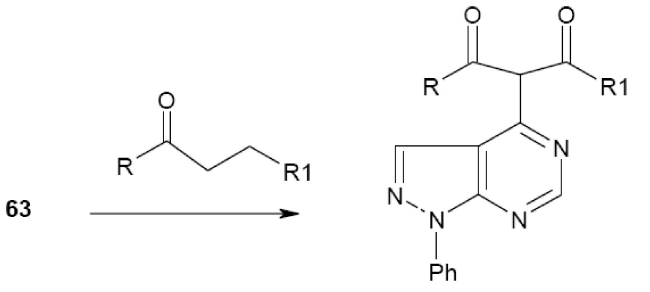



It was noticed that, the electrophilic substitution reactions of pyrazolo[3,4-*d*] pyrimidines occur mainly at C-3. Thus, bromination of 4-substituted pyrazolo[3,4-*d*] pyrimidine **(56)** (X = H or $NH_2$) afforded 3-bromo-1-*H*-pyrazolo[3,4-*d*]pyrimidine derivative **(57)**[52].

Meanwhile, electrophilic cyanation of pyrazolo[3,4-*d*]pyrimidine-4-thiol **(58)** with *p*-toluene sulfonyl cyanide (TSCN) in THF in the presence of sodium hydride, gave the corresponding thiocyanate derivative **(59)**, which reacts through nucleophilic displacement with *p*-toluene sulfonate to afford the 4-*p*-tosylpyrazolo[3,4-*d*]pyrimidine **(60)**[53].

### ii- Nucleophilic substitution reactions

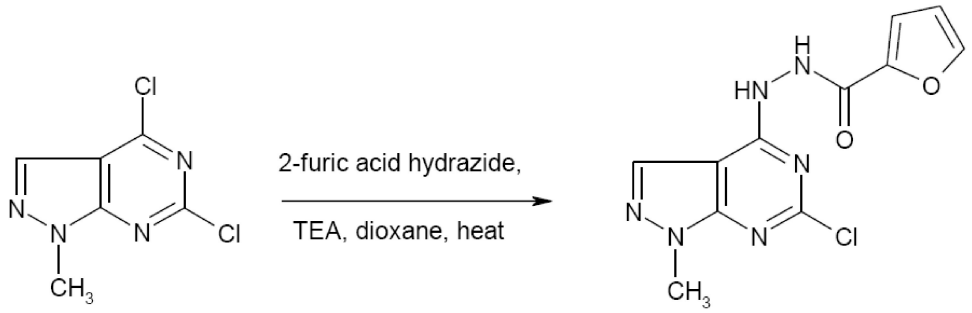
Nucleophilic displacement of the 4-methoxy group



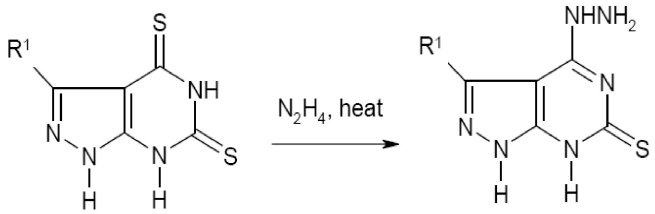

a, R = R1 = $CH_3$

b, R = $CH_3$ , R1 = $OC_2H_5$

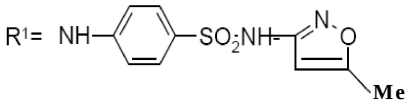
c, R= R1 = $OC_2H_5$




67 68

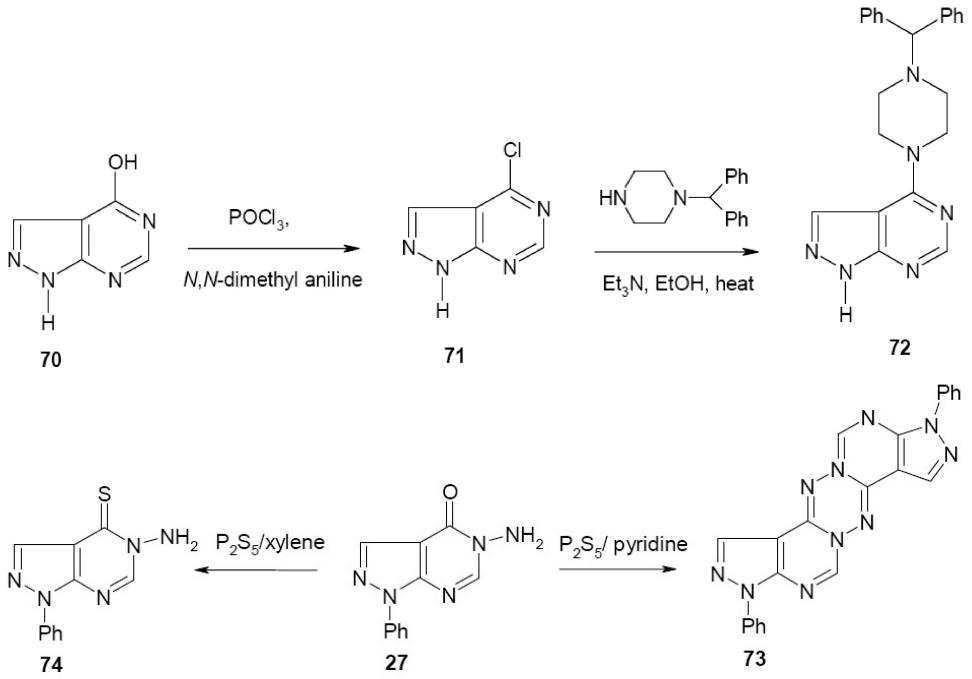



18 69




of the methylenebis(4-methoxy-pyrazolo[3,4-*d*]pyrimidines) **(61)** by 1*N* NaOH/MeOH (1:1) gave the corresponding methylenebis-(allopurinol) **(62a)** (X = OH). Even a weaker nucleophile such as ammonia (25 % aq. $NH_3$) is able to substitute the 4-methoxy group of compound **(61)**, yielding compound **(62b)** (X = $NH_2$)[54].

Compound **(63)** was reacted with active methylene compounds like: malononitrile and ethyl cyanoacetate to afford pyrazolo[3,4-*d*]pyrimidine derivatives **(64)** and **(65)**, respectively[55].




70 71 72

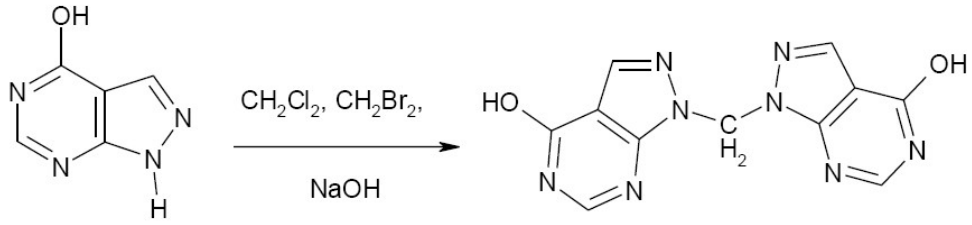
74 27 73

While treatment of **(63)** with acetyl acetone, ethyl acetoacetate or diethyl malonate yielded pyrazolo[3,4-*d*]pyrimidine derivatives **(66a-c)**, respectively[55].

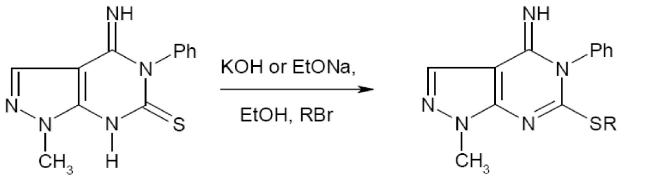
Recently, Baraldi *et al*[56], have reported that nucleophilic displacement of chlorine atom in 4-chloropyrazolopyrimidine derivative **(67)** with 2-furoic acid hydrazide afforded pyrazolo[3,4-*d*]pyrimidine **(68)**.

Pyrazolo[3,4-*d*]pyrimidine-4,6-dithione derivative **(18)** was converted to the 4-hydrazinyl derivative **(69)** by refluxing with hydrazine hydrate[35].

Meanwhile, chlorination of allopurinol **(70)** with phosphorous oxychloride in *N*,*N*-dimethyl aniline under reflux gave the 4-chloroderivative **(71)**. Nucleo-




70 62a




74

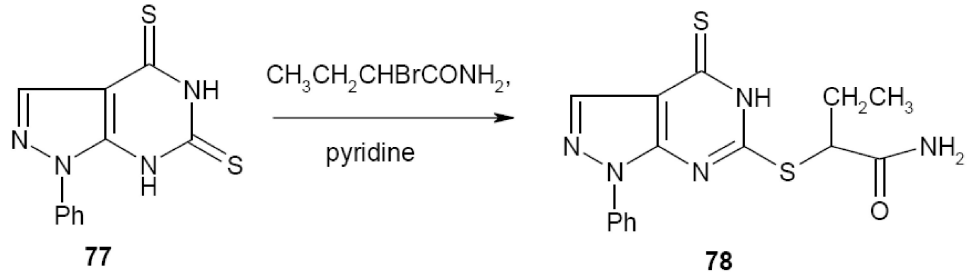
75 : R = $CH_2CH$=CH-Ph

76 : R = $CH_2CH$=$CH_2$

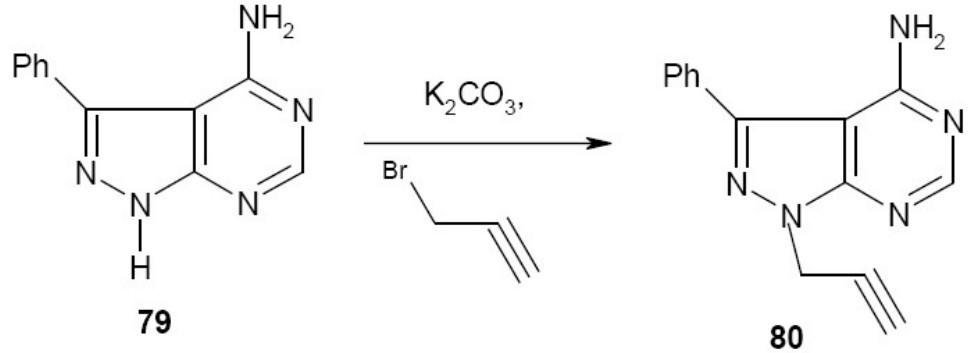
philic substitution of the latter compound with benzhydryl piprazine gave compound **(72)**[57].

### iii- Thionation reactions

Thionation of the 5-amino derivative **(27)** with phosphorous pentasulfide in pyridine gave the unexpected pyrazolopyrimidotetrazine **(73)**. While, on repeating the




77 78

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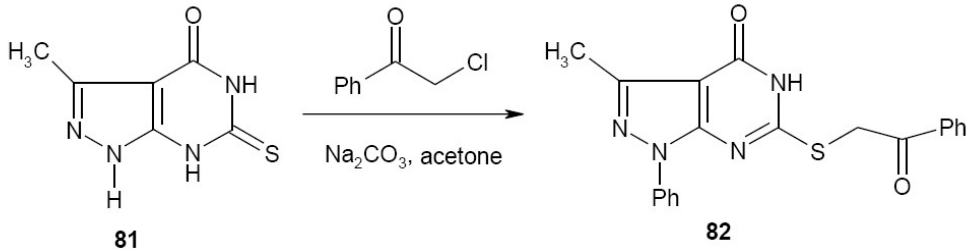



81 82

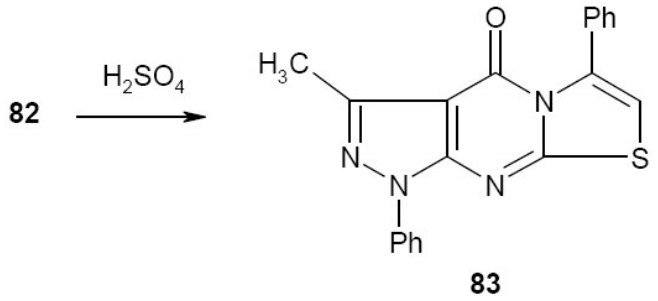
same reaction in xylene the mono thione derivative **(74)** was obtained[40].

### iv- Alkylation reactions

Liquid-liquid phase transfer alkylation of pyrazolo[3,4-*d*]pyrimidine **(70)** with a mixture of dichloromethane/dibromomethane afforded the N(1)-N(1)-, methylene-bridged dimeric heterocycles **(62a)**[54].

Alkylation of pyrazolo[3,4-*d*]pyrimidine-6-thione **(74)** with alkyl bromide using KOH or sodium ethoxide in ethanol were used to give the thioethers **(75)** and **(76)**[58].

When pyrazolopyrimidine derivative **(77)**, in dry pyridine, was treated with 2-bromoamide derivative, it afforded $\alpha$-substituted pyrazolo[3,4-*d*]pyrimidine de-

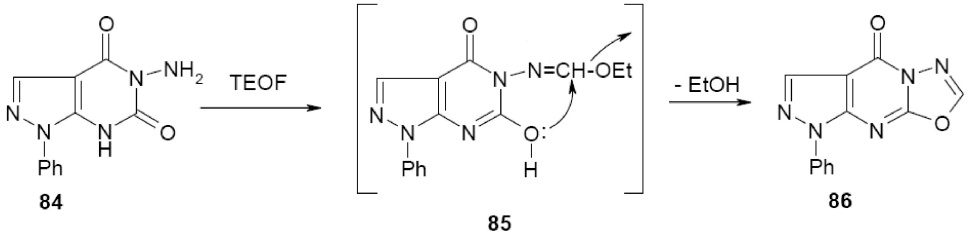



83

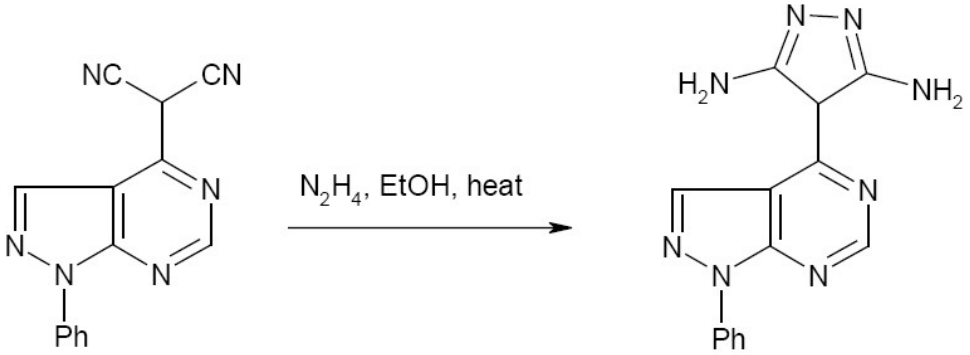
rivative **(78)**[59].

Reaction of pyrazolo[3,4-*d*]pyrimidine **(79)** with 3-bromopropyne, in $K_2CO_3$, afforded the corresponding $N^1$-propynyl derivative **(80)**[60].

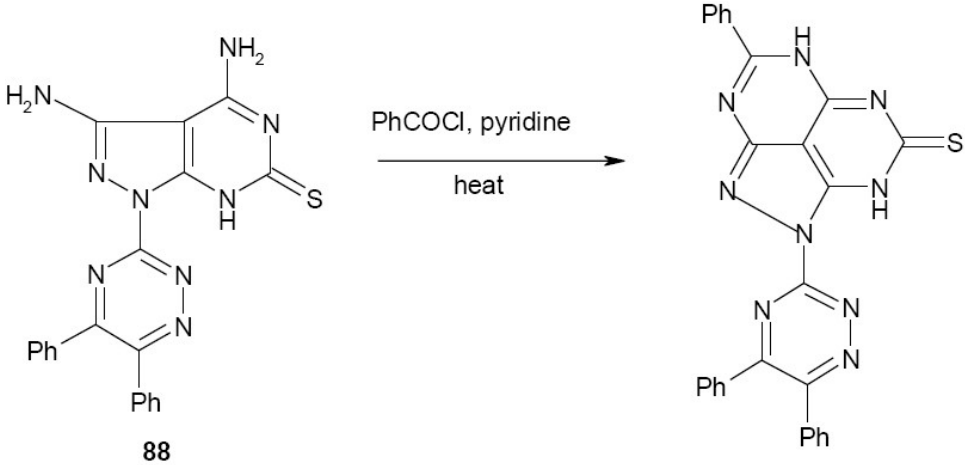
Treatment of **(81)** with 2-chloroacetophenone, in acetone in the presence of sodium carbonate at room temperature, gave substituted pyrazolo[3,4-*d*]pyrimidine derivative **(82)**[61].




84 85 86




64 87



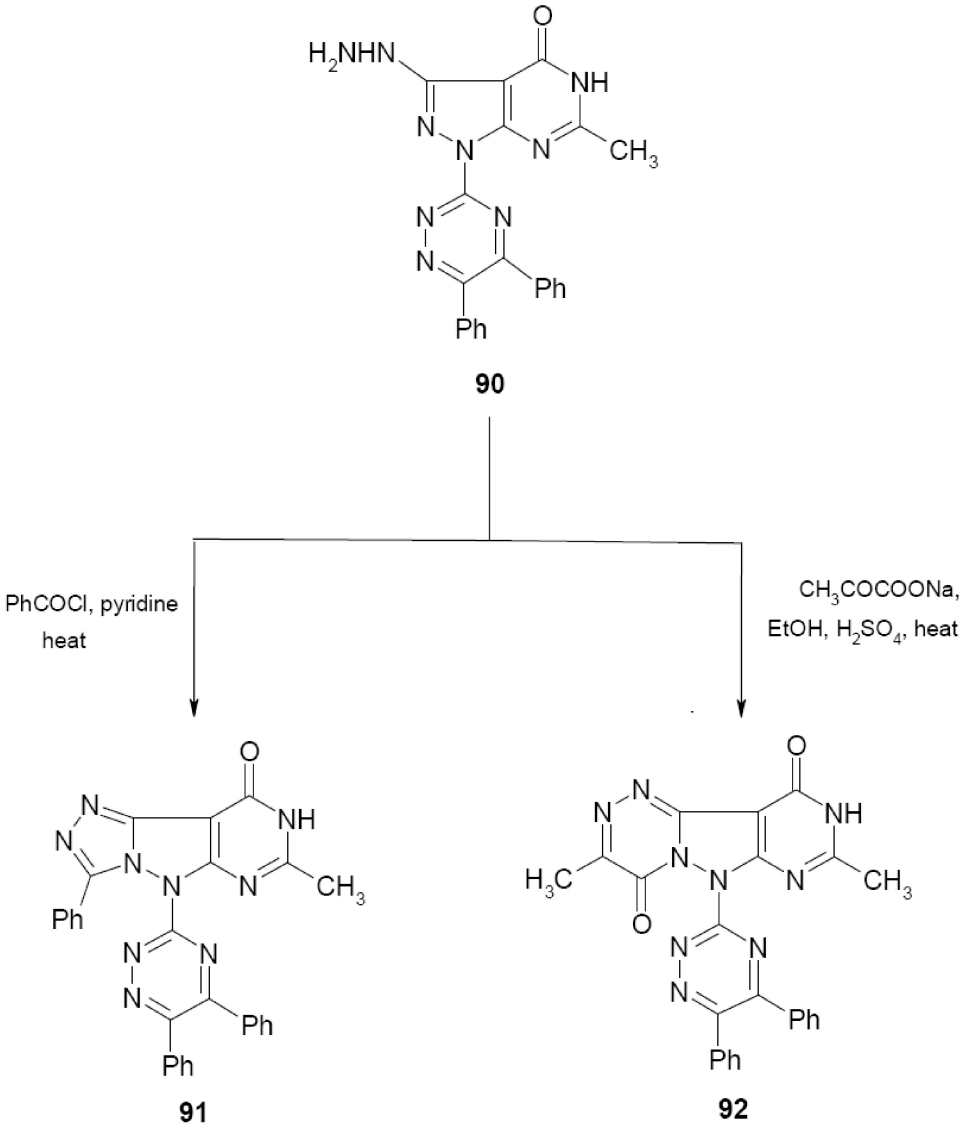

88 89

## v- Side chain reactions

Treatment of pyrazolo[3,4-*d*]pyrimidine derivative **(82)** with 98% sulphuric acid yielded the pyrazolothiazolopyrimidin-4-one derivative **(83)**[61].

On the other hand, 1,3,4-oxadiazolopyrazolopyrimidinone **(86)** was obtained *via* reaction of compound **(84)** with triethyl orthoformate as one carbon cyclizing reagent. Compound **(86)** was produced *via* initial formation of intermediate **(85)** followed by intramolecular cyclization with elimination of ethanol[40].

Treatment of 2-(1-phenylpyrazolo[3,4-*d*]pyrimidin-4-ylidene)-malononitrile **(64)** with hydrazine hydrate in ethanol furnished the 4-(1-phenylpyrazolo[3,4-




*d*]pyrimidin-4-yl) -4*H*-pyrazole-3,5-diamine **(87)**[55].

Treatment of 3,4-diaminopyrazolo[3,4-*d*]pyrimidine-6-(7*H*)-thione derivative **(88)** with benzoyl chloride, in pyridine, afforded the pyrazolopyrimidopyrimidine derivative **(89)**[62].

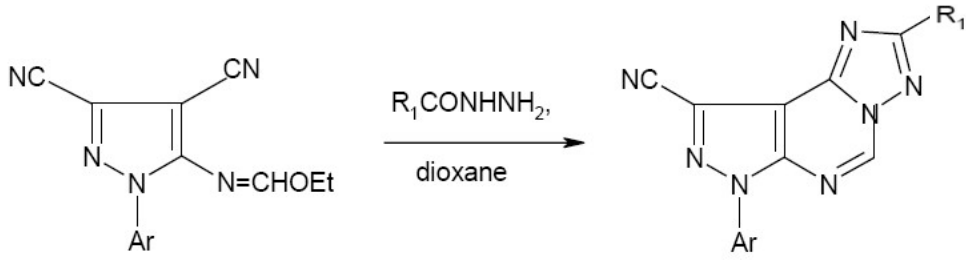
In addition, heterocyclization of 4-hydrazinopyrazolo[3,4-*d*]pyrimidine derivative **(90)** with benzoyl chloride or sodium pyruvate, afforded the corresponding polynuclear heterocycles pyrazolotriazolopyrimidine and pyrazolopyrimidotriazine derivatives **(91)** and **(92)**, respectively[62].

### vi- Synthesis of some pyrazolotriazolopyrimidine ring systems

The imidate **(93)** gave 2-arylpyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*c*]pyrimidine systems **(94-96)** when reacted with 2-furancarboxylic acid hydrazide, 2-thiophenecarboxylic acid hydrazide and 4-pyridinecarboxylic acid hydrazide, respectively[63].

Reaction of 5-amino-4-iminopyrazolo[3,4-*d*]pyrimidine **(97)** with triethyl orthoformate or carbon disulfide, afforded the corresponding pyrazolotriazolopyrimidines **(98a,b)** ($R_2$ = H or SH), respectively[64].

Recently, Nassar *et al*[65], allowed compound **(99)** to react with carbon disulfide, in dry ethanol, to afford 7-tosyl-3,7-dihydro-2*H*-pyrazolo[4,3-*e*][1,2,4] triazolo[1,5-*c*] pyrimidine-2-thione **(100)**. The reaction proceeds *via* addition of one mole of carbon disulfide on the imine group followed by elimination of one mole of $H_2S$ to produce the triazolo-pyrimidine moiety[65]. Moreover, compound **(100)** was reacted with methyl iodide or ethyl bromide in ethanol and

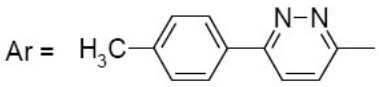


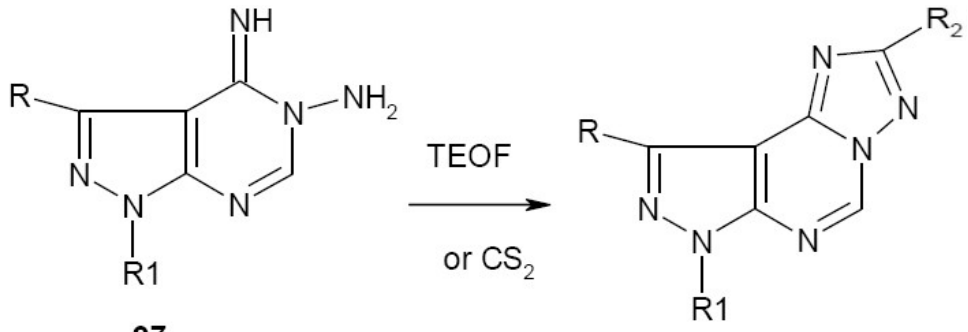

**93**

**94 :** $R_1$ = furyl-**2**

**95 :** $R_1$ = thienyl-**2**

**96:** $R_1$ = pyridinyl-**4**

Ar = 



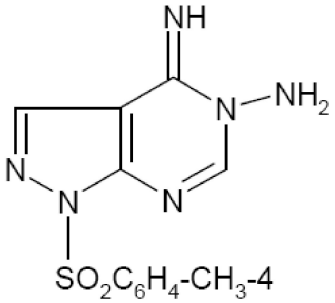

**97**

R = -$C_6H_4$-F-4

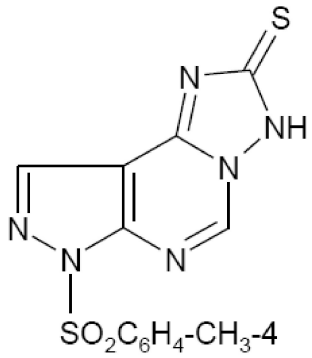
R1 = -$C_6H_4$- $NO_2$-4

**98a :** $R_2$ = H

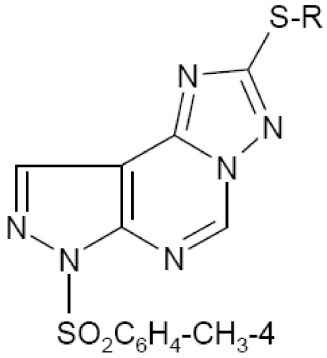
**98b :** $R_2$ = SH




**99**

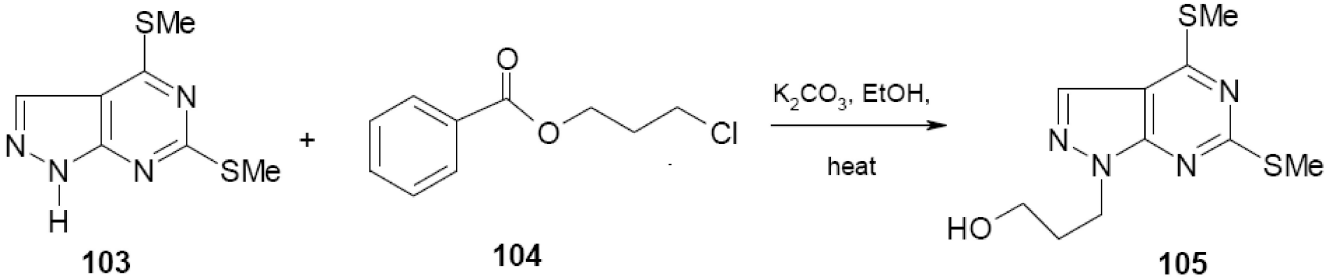



**100**

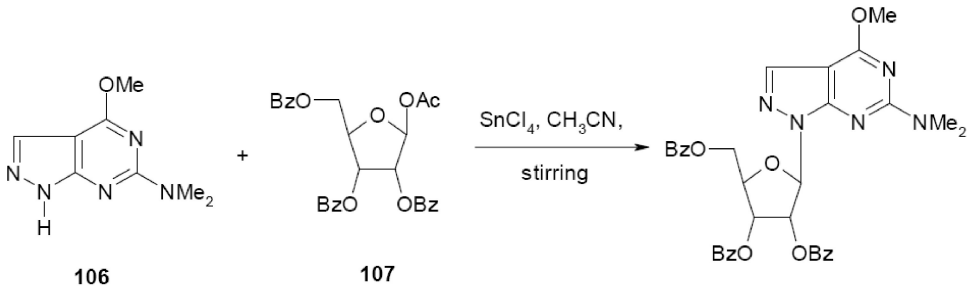



**101:** R = $CH_3$

**102:** R = $C_2H_5$




**103** **104** **105**




106 107 108

sodium acetate to afford 2-(alkylthio)-7-tosyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **(101)** and **(102)**, respectively[65].

### vii- Formation of some pyrazolopyrimidine acyclic and cyclic nucleosides

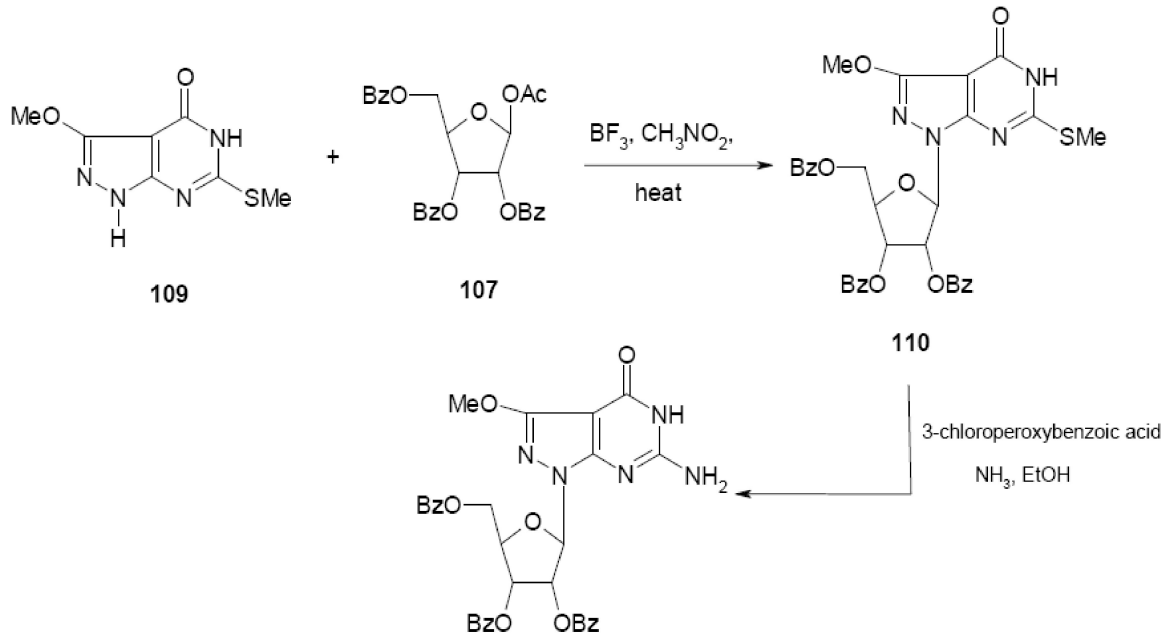
Formation of azoloazine nucleosides is widely reported in the literature[66]. When 4,6-dimethylthiopyrazolo[3,4-*d*]pyrimidine **(103)** was treated with 1-chloromethyl-2-bezoyloxyethane **(104)**, it afforded the *N*-acyclic nucleoside **(105)**[67].

Quintela *et al*[38], reported that 4-methoxypyrazolo[3,4-*d*]pyrimidine **(106)** was ribosylated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **(107)** in the presence of $SnCl_4$ to afford the β-$N^1$-coupled nucleoside **(108)**.

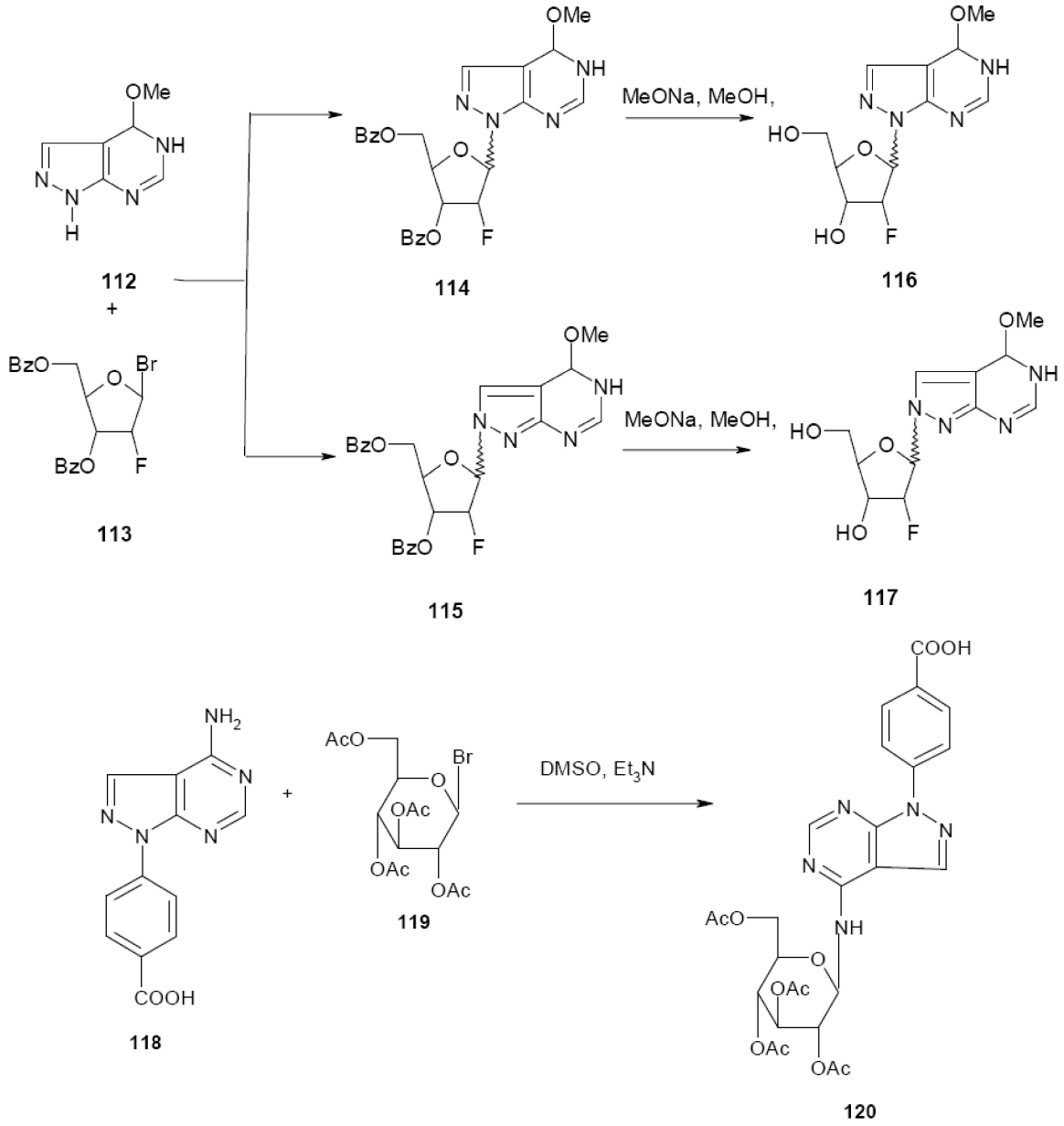
Similarly, reaction of pyrazolo[3,4-*d*]pyrimidine derivative **(109)** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **(107)** and $BF_3$ gave 3-methoxy-6-methylthio-1-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-one **(110)**[68]. The latter nucleoside was converted to 3-methoxy-6-amino-1-*β*-D-ribofuranosyl)-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **(111)** by treatment with 3-chloroperoxybenzoic acid followed by methanolic ammonia[68].

Coupling of 4-methoxypyrazolo[3,4-*d*]pyrimidine **(112)** with 2-fluoro-3,5-di-*O*-benzoyl-*α*-D-arabinofuranosyl bromide **(113)** gave *α*-D/*β*-D-mixture of $N^1$- and $N^2$-coupled products **(114)** and **(115)**, respectively. Debenzoylation of **(114)** and **(115)** with MeONa/MeOH, produced the free nucleosides **(116)** and **(117)**[69].

The amino group on pyrazolopyrimidine allowed modifications of the molecules through binding to sugars or amino acids. Thus, alkylation of the pyrazolopyrimidine **(118)** with α-bromoacetoglucose **(119)** in DMSO in the presence of triethylamine was




109 107 110 111







carried out to afford the N-$\beta$-D-glycoside **(120)**[70].

In addition, treatment of the persilylated 4-chloro-6-methyl-pyrazolo[3,4-*d*] pyrimidine **(121)** with tetra-*O*-acetylribofuranose **(122)** provided 4-chloro-6-methyl-1-(2,3,5-tri-*O*-acetyl-$\beta$-D-ribofuranosyl) pyrazolo[3,4-*d*]pyrimidine **(123)**.

Ammonolysis of the latter compound gave 4-amino-6-methyl-1-$\beta$-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidine **(124)**. While, treatment of nucleoside **(123)** with thiourea followed by deacetylation, provided 6-methylpyrazolo[3,4-*d*]pyrimidine-4(5*H*)-thione ribonucleoside **(125)**[71].

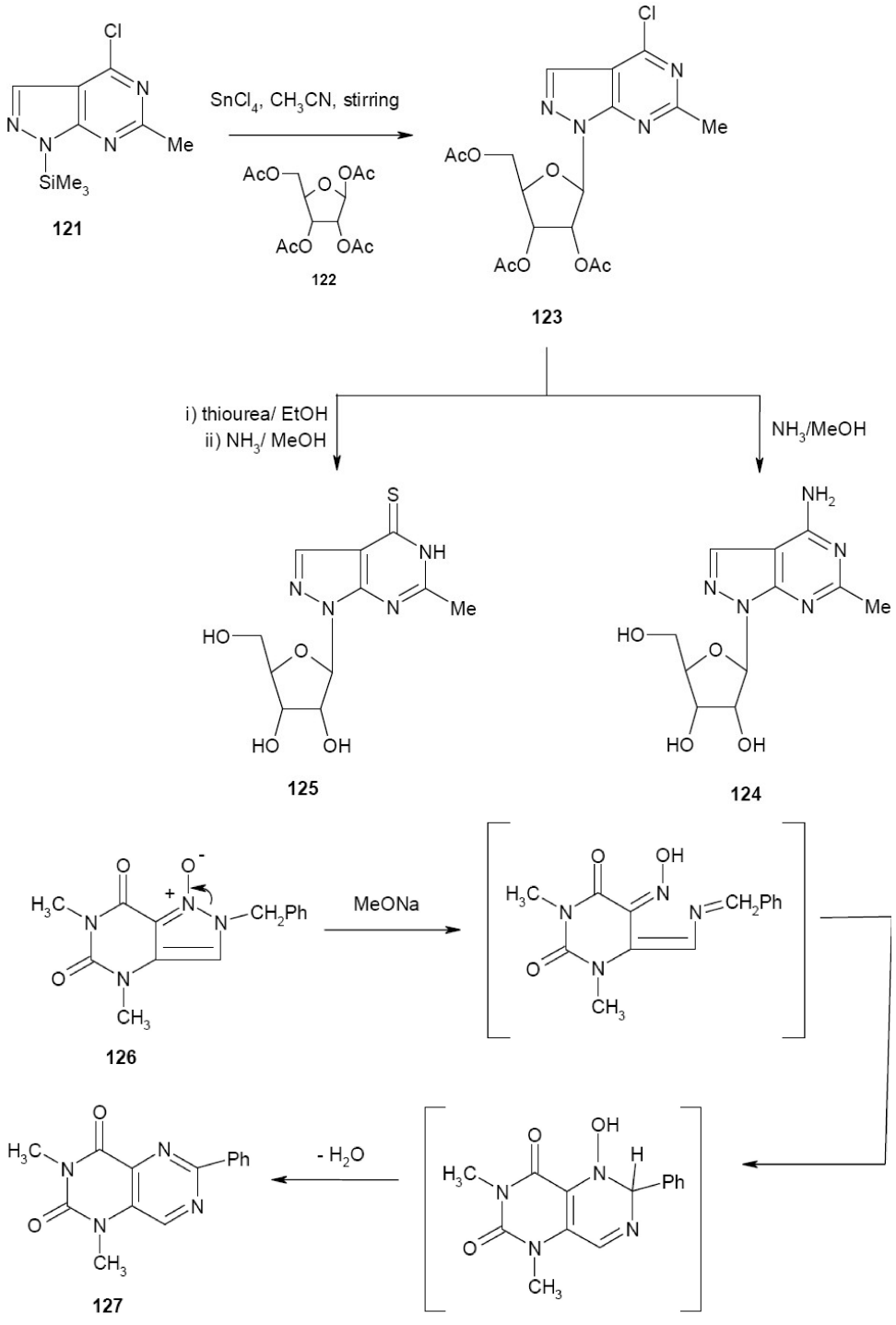
**viii- Rearrangement and ring cleavage**

2-Benzyl-4,6-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidinedione-1-oxide **(126)** afforded pyrimido[5,4-*d*]pyrimidine derivative **(127)** upon treatment with EtONa[72,73].

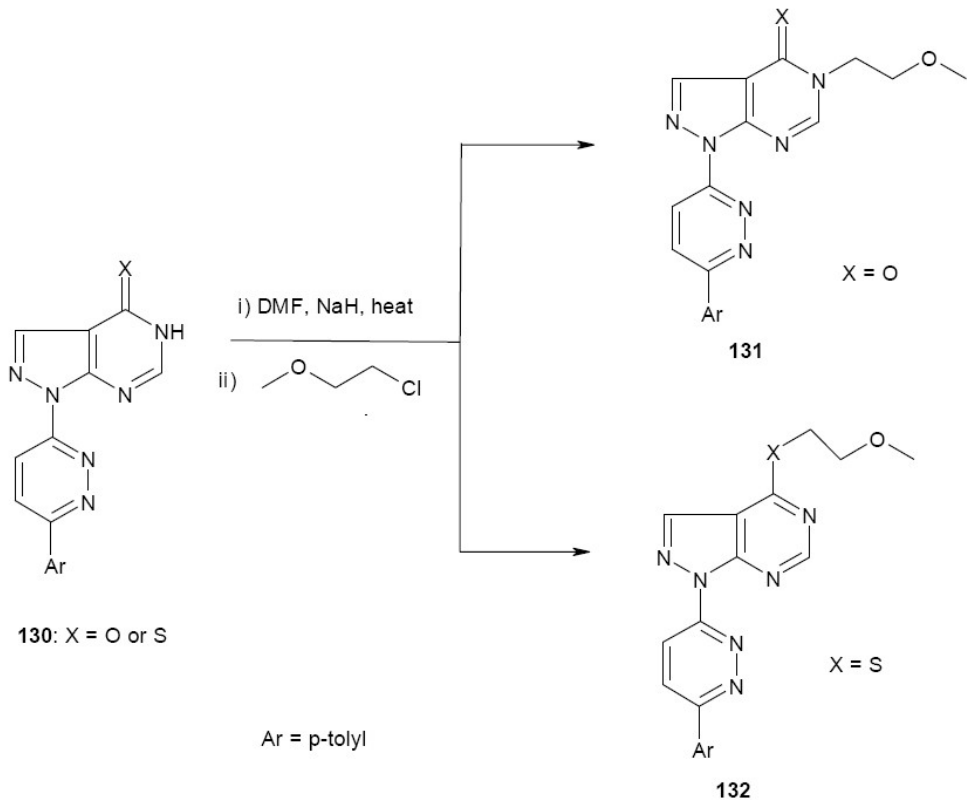
While, treatment of pyrazolo[3,4-*d*]pyrimidine **(128)** with sodium ethoxide in dimethyl sulfoxide resulted in pyrazole ring cleavage and yielded the pyrimidine derivative **(129)**[74].

## CONTRIBUTIONS OF OUR LABORATORY

The chemistry of pyrazolopyrimidine derivatives has prompted many authors in the National Research Cen-



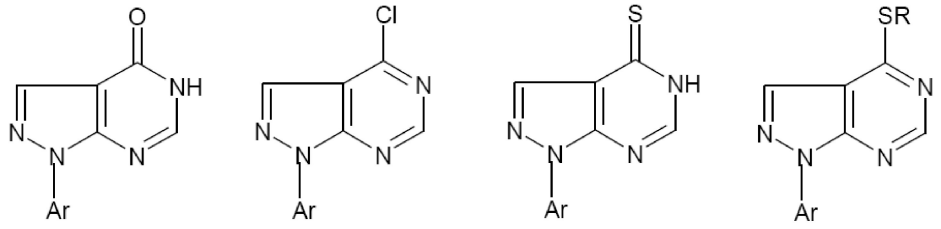

tre to study the synthesis and reactions of such compounds. Particularly, our research group gave a considerable attention for construction of new derivatives of pyrazolo[3,4-*d*]pyrimidines on the account of their reported biological activities. Thus, Shamroukh *et al*[75], prepared compounds **(130)** and treated their sodium salts with 2-chloroethyl methyl ether to give the corresponding acyclic nucleosides **(131)** and **(132)**, respectively.



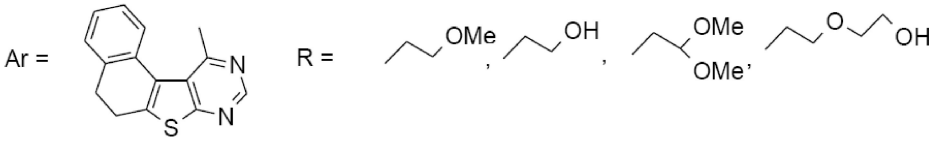

130: X = O or S

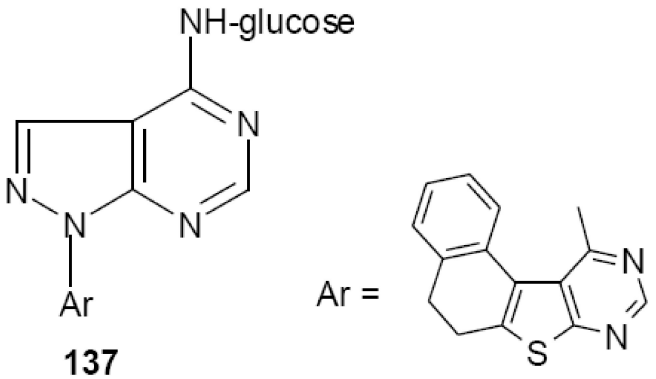
131

132



133 134 135 136



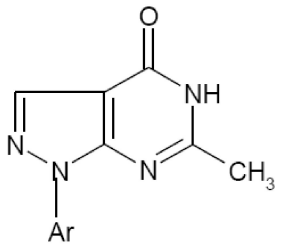




137

Also, Rashad *et al*[76], synthesized some new substituted pyrazolo[3,4-*d*]pyrimidine derivatives **(133-135)** and their acyclic *S*-nucleosides **(136)** *via* the reaction of pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-thione derivative **(135)** with some acyclic sugars.

Moreover, when compound **(134)** was refluxed with glucosamine hydrochloride in the presence of triethylamine, the reaction afforded *N*-pyrazolo[3,4-*d*]pyrimidine-4-glucosamine **(137)**[76].

Also, our research group prepared another new substituted pyrazolo[3,4-*d*]pyrimidine derivatives **(138–140)**. Compound **(140)** was isomerized by Dimroth rearrangement, upon refluxing in ethanol, in the presence of few drops of hydrazine hydrate to the corresponding more thermodynamically stable pyrazolo[3,4-*d*]pyrimidin-4-ylhydrazine **(141)**[77].

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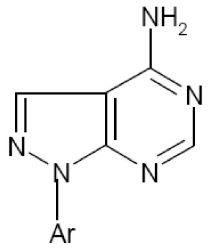


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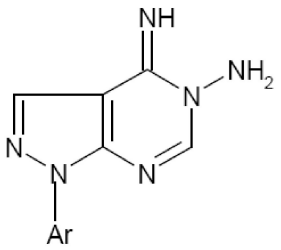


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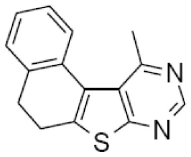


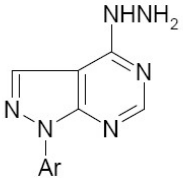


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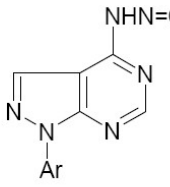
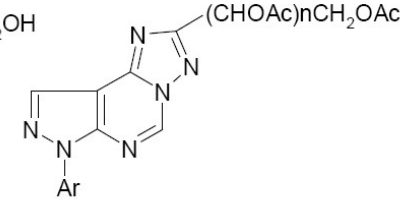
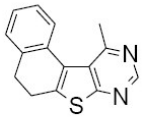



142 a,b

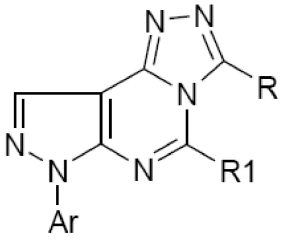



143 a,b

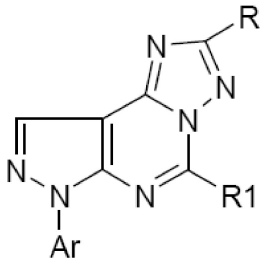
Ar =




a: n = 3
b : n = 4

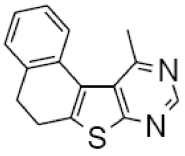



144




145

Ar =




R, R1 = H or $CH_3$

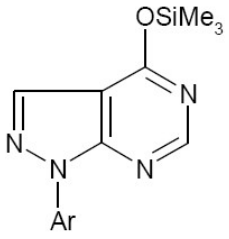
In addition, the preparation of sugar hydrazone derivatives **(142a,b)** and their annulated C-nucleosides **(143a,b)** were described by condensation of pyrazolo[3,4-*d*]pyrimidin-4-ylhydrazine **(141)** with some monosaccharides: namely, D-glucose or D-ribose in the presence of a catalytic amount of glacial acetic acid[77].

On the other hand, our research group reported the formation of pyrazolotriazolo[4,3-*c*]pyrimidines **(144)** and their transformation to pyrazolotriazolo[1,5-*c*]pyrimidine regioisomers **(145)** in different reaction conditions[78]. Actually, our observations revealed that [1,2,4]triazolo[4,3-*c*]pyrimidine can isomerize by a Dimroth rearrangement under the effect of acid, base, or by heat to the more thermodynamically stable [1,2,4]triazolo[1,5-*c*]pyrimidine[78].

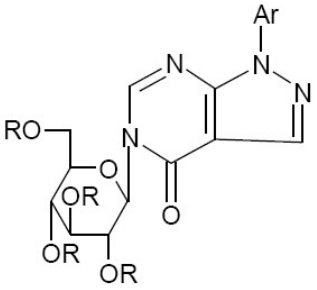
When the siloxy derivative **(146)** was ribosylated (with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-$\beta$-D-ribofuranose) and glycosylated (with $\beta$-D-glycopyranose pentaacetate) in the presence of $SnCl_4$, it afforded the corresponding *N*-riboside **(47)** and *N*-glycoside **(148)**, respectively. Deprotection of the latter nucleosides, in ethanolic ammonia, produced the free nucleosides **(149)** and **(150)**, respectively[79].

Similarly, another series of new *S*-cyclic and acyclic nucleosides of pyrazolo[3,4-*d*]pyrimidine derivatives **(151-155)** were synthesized by treatment of compound **(135)** with various cyclic sugars and alkyl halides[80].

On the other hand, Swelam *et al*[81], prepared pyrazolo[3,4-*d*]pyrimidines **(156)** and pyrazolo[4,3-*e*]triazolo[1,5-*c*]pyrimidine derivative **(157)** and the structures of these products were identified in light of

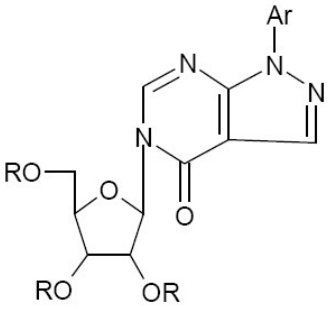


**146**



**147**, R = Ac

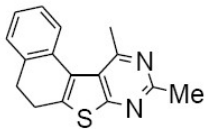
**149**, R = H

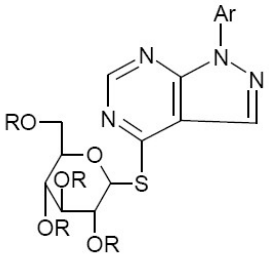


**148**, R = Bz

**150**, R = H

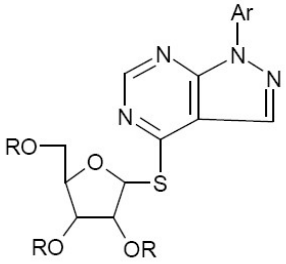
Ar =





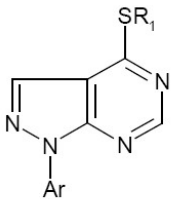
**151**, R = Ac

**152**, R = H



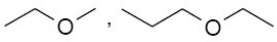
**153**, R = Bz

**154**, R = H

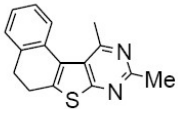


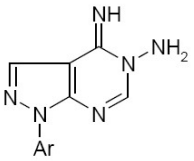
**155**

$R_1$ = Et,

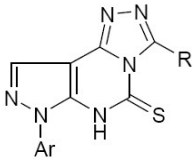


Ar =

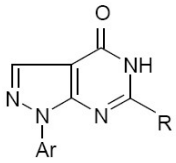




**156**



**157**



**158**

Ar= Ph, R = H, $CH_3$ or Ph

Ar = pyridazinyl-4

R = H, Me, Ph

their elemental analyses and spectral data. Also, Shamroukh *et al*[82], have been prepared some novel pyrazolo[3,4-*d*]pyrimidines of structure **(158)**.

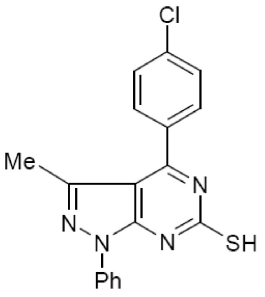
Recently, Swelam *et al*[83], have described the synthesis of some pyrazolo[3,4-*d*]pyrimidine derivatives using readily available starting materials. A one-pot multi component cyclocondensation reaction was used to prepare 3-methyl-4-chlorophenyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiol **(159)**[83].

Finally, Sayed *et al*[84], prepared pyrazolopyrimidine derivative **(160)** and treated it with chloroacetic acid to afford pyrazolothiazolopyrimidinone derivative **(161)** in good yield.

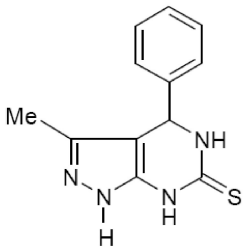
## APPLICATIONS

### Biological and medicinal applications

Pyrazolo[3,4-*d*]pyrimidine derivatives received considerable attention due to their pharmaceutical importance[2,80,81]. In the last few decades, the synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives had reported as a way to develop new simple route for synthesis of functionally substituted heterocyclic of anticipated biological activity as potential therapeutic agents. Some examples of the biological activity of pyrazolo[3,4-



159



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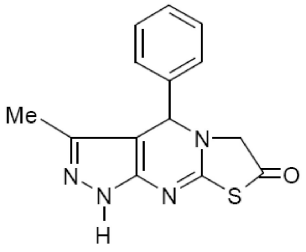

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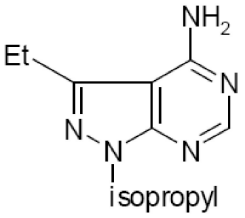
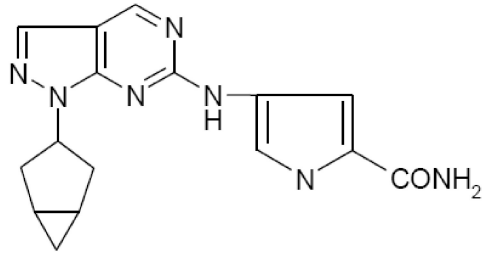


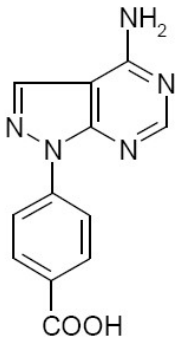
RET protein kinase inhibitors

162



AKA/CDK1 dual inhibitors

163



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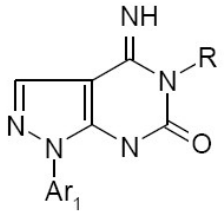

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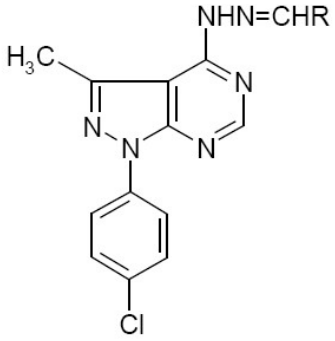
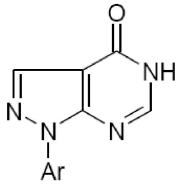
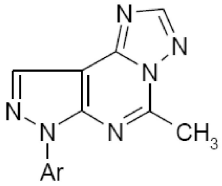


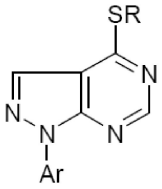
166 (R = -Ph-OH-2)



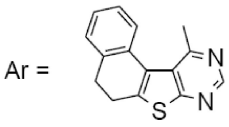
167



168



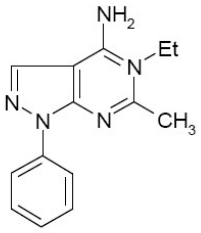
155



d]pyrimidine are displayed.

## i-As antitumor agents

Pyrazolo[3,4-*d*]pyrimidine derivatives have considerable potential in the field of cancer chemotherapy, as they were found to exhibit their antitumor activity by inhibiting different types of enzymes such as cyclin-dependent kinase[33,35,85], (GSK-3) glycogen synthase kinase-3[86,87], adenosine deaminase[88], adenosine kinase inhibitors[89], p70S6K inhibitors[90], and epidermal growth factor receptor protein tyrosine kinase[91]. Recently, a series of 3-substituted-1-isopropyl-pyrazolo[3,4-*d*]pyrimidin-4-amines has been designed, synthesized, evaluated as RET protein kinase inhibitors and compound **(162)** inhibited MCF-7 breast cancer cells at low concentrations (as low as 100 nM)[92]. Furthermore, the synthesis, SAR evaluation of 1,6-disubstituted-1*H*-pyrazolo[3,4-*d*]pyrimidine **(163)** as dual inhibitors of Aurora Kinases and CDK1 were reported[93].



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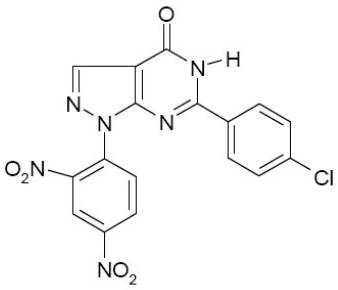

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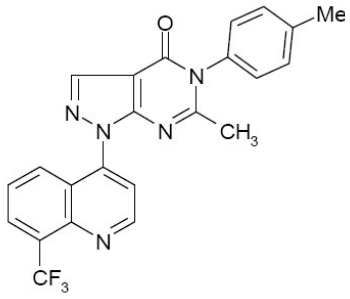
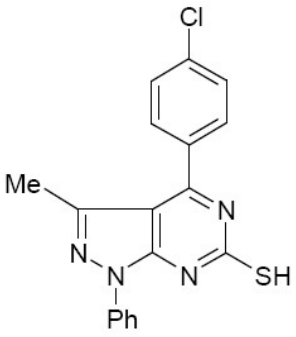
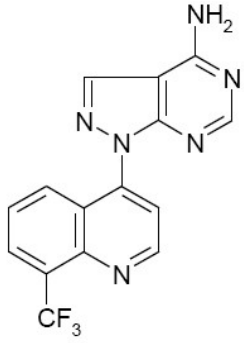


171



159



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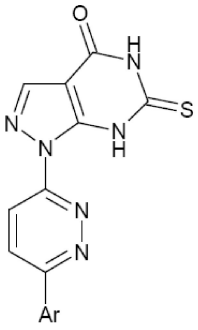

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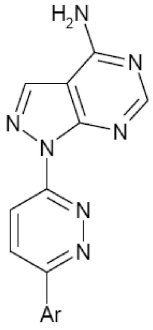

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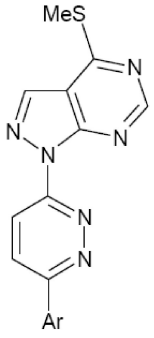


175

Ar = p-tolyl

The pyrazolo[3,4-*d*]pyrimidine derivatives have been discovered as antitumor agents by the NCI (National Cancer Institute, USA) on human colon tumor cell line HCT116,[42,70] *in vitro* anticancer potential against hepatocellular carcinoma HepG2 and cervical carcinoma HelaS3 cell lines[94]. In addition, several substituted pyrazolo[3,4-*d*]pyrimidines **(164)** and **(165)** (substituted Ph) were reported as potent antitumor gents[40,95].

In addition, a new series of pyrazolo[3,4-*d*]pyrimidines has been tested for their antitumor activity on 60 different cell lines and some of the tested compounds were found to have potent antitumor activity. In particular, 2-hydroxybenzaldehyde[1-(4-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazone **(166)** was found to be the most effective among the other derivatives, showing IC50 values of 0.326 to 4.31 μM on 57 different cell lines[37].

Also, our research group has identified the *in vivo* antitumor evaluation of some prepared pyrazolo[3,4-*d*]pyrimidine, pyrazolotriazolopyrimidine and derivatives **(167)**, **(168)** revealed promising activity in comparison to that of Cisplatin[78].

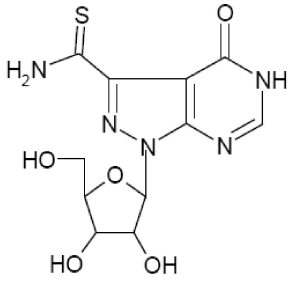
Recently, our research group prepared a series of novel substituted pyrazolo[3,4-*d*] pyrimidines were synthesized and their *in vitro* cytotoxicity against human breast adenocarcinoma (MCF-7) cell lines has been investigated. Most of the tested compounds exploited potent cytotoxic activity against MCF-7 cell lines comparable to the activity of the commonly used anticancer drug Cisplatin. In general, acyclic nucleoside derivative **(155)** revealed the highest anticancer activity among the other tested compounds[80].

### ii- As antimicrobial agents

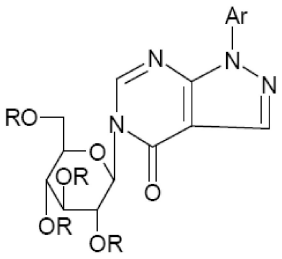
New derivatives of 6-methyl-1-phenyl-5-substituted-1*H*-pyrazolo[3,4-*d*]pyrimidine **(169)** were prepared and their preliminary screening revealed that several of the synthesized compounds exhibited *in vitro* growth inhibitory activity against gram positive and gram negative bacteria and yeast[96,97]. Also, a new series of pyrazolo[3,4-*d*]pyrimidine derivatives **(170)** was prepared in a single step and their antibacterial activity comparable to Streptomycin as a reference drug was evaluated[98].

Moreover, Holla *et al*[99], synthesized pyrazolo[3,4-*d*]pyrimidines containing 8-(trifluoromethyl)quinoline **(171)** and the antimicrobial activity of the newly synthesized pyrazolo[3,4-*d*]pyrimidine ring system was promising.

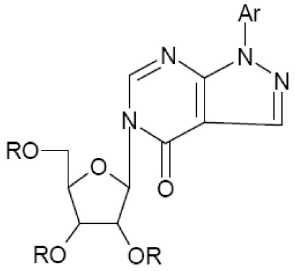
Recently, the antimicrobial activities of selective synthesized pyrazolo[3,4-*d*]pyrimidines have been evaluated and compound **(159)** was found to have moder-



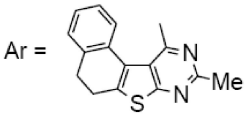
176

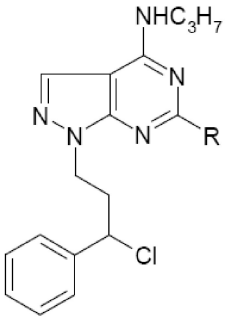


149, R = H



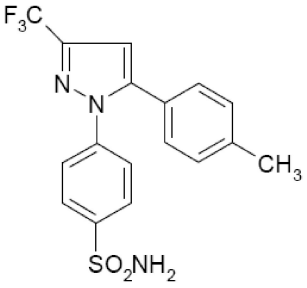
150, R = H



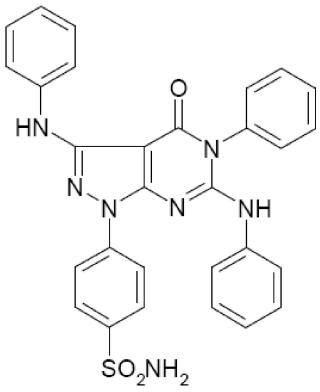


177

R = $NMe_2$, SEt, S-$iC_3H_7$



Celecoxib



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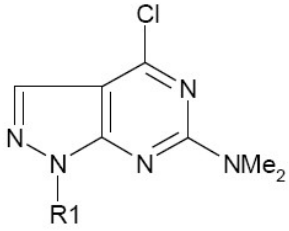
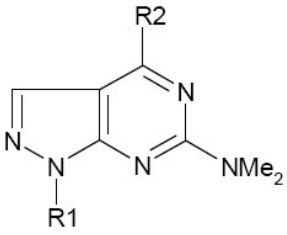


**179a**; R1 = Ph-

**179b**; R1 = t-but

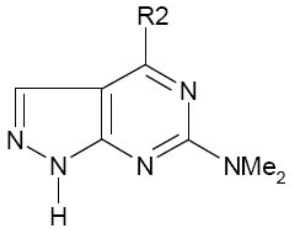


**180a**; R1 = Ph-, R2=OMe

**180b**; R1 = Ph-, R2=$NHCH_2Ph$

**180c**; R1 = t-but, R2=piperidino

**180d**; R1 = t-but, R2=OMe



**181a**; R2 = OMe

**181b**; R2 = $NHCH_2Ph$

**181c**; R2=piperidino

ate to strong antimicrobial activity in comparison to the reference drugs. Molecular modeling of the most biologically active new compound **(159)** compared to the reference drugs Tobramycin and Fluconazole was carried out using Field-align 2.0 software[83].

Also, Karthikeyan *et al*[100], synthesized 4-amino-1-[8-(trifluoromethyl)quinolin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine **(172)**; which exhibited good activity against *A. flavus, A. fumigatus* and *T.mentagrophytes* as compared to srtandard drug Flucanazole.

Our research group identified the antimicrobial activity for a series of substituted pyrazolo[3,4-*d*]pyrimidines **(132)**, **(173-175)** which showed more significant activity than some known drugs (standards)[75].

### iii-As antiviral agents

Several pyrazolo[3,4-*d*]pyrimidine-4(5*H*)-selone ribonucleosides were prepared and tested *in vitro* against certain viruses and exhibited significant activity against HSV-2 with a very low toxicity[101]. Another pyrazolo[3,4-*d*]pyrimidine derivatives were prepared and evaluated for their inhibitory effects against the replication of Human Immunodeficiency Viruses (HIV-1, HIV-2) and various DNA viruses[102]. Moreover, some derivatives proved to be highly effective in inhibiting enterovirus replication at nanomolar concentrations and SAR studies revealed that the phenyl group at the N-1 position was identified as potential entienteroviral agent[103]. Also, 4-oxo-1-$\beta$-D-ribofurano-sylpyrazolo [3,4-*d*]pyrimidine-3-thiocarboxamide **(176)** was evaluated in cell culture and in animals for antiviral activity against DNA and RNA viruses. The latter compound was highly active against strains of adeno-, vaccinia, influenza B, paramyxo-, picorna-, and reoviruses, with 50% inhibition of virus-induced cytopathology at 1 to 10 $\mu$M[104].

In the last few years, our research group identified the antiviral activity for a series of substituted pyrazolo[3,4-*d*]pyrimidine derivatives and some of their acyclic and cyclic N, S, C-nucleosides. Plaque reduction infectivity assay was used to determine virus count reduction as a result of treatment with tested compounds, and titled compounds **(138)**, **(139)** and **(167)** observed to be active as antiviral agents on virus replication for HAV, HSV-1. Moreover, addition of sugar moieties to the pyrazolopyrimidine derivative increases the antiviral activity (compounds **142** and **143**) in comparison with Amantadine and Acyclovir as controls[76,77].

In addition, our research group carried out the anti-H5N1 bioassays for some substituted pyrazolo[3,4-*d*]pyrimidines. The concentrations of the tested compounds, which exhibited 50% cytotoxicity (LD50) and the 50% effective antiviral concentration (EC50), were determined in addition to the cytotoxicity (CT) and the therapeutic index (TI). Structural activity correlations of the obtained results indicated that substituted acyclic nucleoside analogs of pyrazolo[3,4-*d*]pyrimidine revealed more anti-H5N1 activity than the parent pyrazolo[3,4-*d*]pyrimidin-4-one derivative **(133)**. In general, the free cyclic *N*-nucleosides of pyrazolo[3,4-*d*]pyrimidine (derivatives **(149)** and **(150)**) showed the highest anti-H5N1 activity among the other tested compounds[79].

### iv-As analgesic and anti-inflammatory agents

Pyrazolo[3,4-*d*]pyrimidines were early documented as anti-inflammatory agents and some of these compounds inhibited COX-1 and COX-2 in human monocytes with selectivity for COX-2 inhibition[105]. Alcaro *et al*[106], reported a small library of pyrazolo[3,4-*d*]pyrimidines endowed with virtual screening against two COX isoforms and compounds of type **(177)** were identified as potentially selective COX-2 inhibitors with potency and selectivity comparable to known drugs. Also, the molecular modeling studies confirmed that 5-benzamido-pyrazolo[3,4-*d*]pyrimidin-4-one derivative **(36)** has potential anti-inflammatory activity with superior inhibitory profile against COX-2, when compared to that of reference standards NS398 and indomethacin[43].

Recently, a novel series of pyrazolo[3,4-*d*]pyrimidines was prepared, screened for the anti-inflammatory activity and evaluated for ulcerogenic potential and 3-substituted-1-aryl-5-phenyl-6-anilinopyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one **(178)** exhibited superior anti-inflammatory activity in comparison with Diclofenac sodium and comparable activity with Celecoxib at a dose of 25 mg/kg[107].

### v- As antihistaminic agents

A series of 1*H*-pyrazolo[3,4-*d*]pyrimidines **(179-181)** substituted at positions 1 ($R_1$= Ph, H, *tert*-butyl), 4 ($R_2$ = chlorine, nitrogen and oxygen nucleophiles), and 6 (dimethylamino) has been synthesized and their effect on the release of histamine from rat peritoneal mast cells was measured[38]. After chemical stimulation, several compounds (i.e. **(179b)**, **(180a)**, **(180b)**, **(180c)**, **(180d)**, **(181a)**), produce inhibition two to three times higher (40–60%) than DSCG. **(180b)** ($R_1$=Ph, $R_2$=NHCH$_2$Ph) and **(181a)** ($R_2$ = OMe) are the most active ones in both experiments. Moreover, compounds **(180d)** ($R_1$ = *t*-butyl, $R_2$ = OMe) and **(180c)** ($R_1$ = *t*-butyl, $R_2$ = piperidino) are inducers of the release of histamine (60 and 150% increase)[38].

### vi- Other applications

It was proved that, some pyrazolo[3,4-

*d*]pyrimidines are potent and selective inhibitors of PDE1 and PDE5 $_c$GMP phosphodiesterase in *vitro*[108]. Several 3-substituted pyrazolo[3,4-*d*]pyrimidine derivatives have xanthine oxidase inhibitor activity like allopurinol which was first synthesized by Robins[109], and still the drug for the treatment of hyperuracemia and gouty arthritic disease[110]. Its effeciency was attributed to xanthine oxidase inhibition, which is responsible of purines conversion into uric acid. Also, pyrazolo[3,4-*d*]pyrimidines are known to exhibit pharmacogical activities such as CNS depressant[111], neuroleptic[112], potent oral antihypertensive[113], tuberculostatic and antidiabetic activity[114]. Moreover, some acyclic nucleoside of pyrazolo[3,4-*d*]pyrimidine derivatives exhibited inhibition of amastigotes of leishmania donovani to the extent of 89% at 30 μg/mL *in vitro*. The maximum inhibitory response against amastigotes multiplication was observed to be 94% at 50 mg/kg single dose for 5 consecutive days[115].

## CONCLUSIONS

The heterocyclic fusion of pyrimidine and pyrazole ring resulted in formation of pyrazolopyrimidines. The structure and several applications of the known four types of pyrazolopyrimidines were stated. Moreover, the synthesis, reactions, and applications of pyrazolo[3,4-*d*]pyrimidines were discussed including anticancer, antimicrobial, antiviral, analgesic and anti-inflammatory, antihistaminic and other biological applications. The results revealed that pyrazolo[3,4-*d*]pyrimidines have a high significance in the field of pharmaceutical and biotechnologcal sciences with wide spectrum of biological activities. Furthermore, the SAR evaluation of substituted pyrazolo[3,4-*d*]pyrimidine revealed that the acyclic nucleosides and the variation of substituents either on the pyrazole (especially at the N-1 position) or pyrimidine rings enhance the biological potency.

## REFERENCES

[1] V.S.Dinakaran, B.Bomma, K.K.Srinivasan; Der Pharm.Chem., **4(1)**, 255 **(2012)**.
[2] M.Chauhan, R.Kumar; Bioorg.Med.Chem., **21**, 5657 **(2013)**.
[3] V.J.Rao, R.Shankar, K.Mukkanti, N.A.Vekariya; Der Pharm.Chem., **5(4)**, 184 **(2013)**.
[4] M.C.Bagley, M.Baashen, V.L.Paddock, D.Kipling, T.Davis; Tetrahedron, **39**, 8429 **(2013)**.
[5] V.Masevicius, R.Juskenas, S.Tumkevicius; J.Heterocycl.Chem., **49**, 315 **(2012)**.
[6] M.H.Elnagdi, M.R.H.Elmoghayar, G.H.Elgemeie; Adv.Heterocycl.Chem., **41**, 319 **(1987)**.
[7] J.Yoo, K.Thai, D.Kim, J.Y.Lee, H.Park; Bioorg. Med.Chem.Lett., **17**, 4271 **(2007)**.
[8] J.Yuan, M.Gulianello, S.De Lombaert, R.Brodbeck, A.Kieltyka, K.J.Hodgetts; Bioorg. Med.Chem.Lett., **12**, 2133 **(2002)**.
[9] D.Wang, Y.F.Zhao, D.Sh.YU, P.Gong; Chin. Chem.Lett., **14**, 1223 **(2003)**.
[10] V.N.Devegowda, J.H.Kim, K.Han, E.G.Yang, H.Choo, A.N.Pae, G.Nam, K.I.Choi; Bioorg.Med. Chem.Lett., **20**, 1630 **(2010)**.
[11] R.Jorda, L.Havliìcek, I.W.McNae, M.D.Walkinshaw, J.Voller, A.Sturc, J.Navraìtilovaì, M.Kuzma, M.Mistriìk, J.Baìrtek, M.Strnad, V.Krystof; J.Med.Chem., **54**, 2980 **(2011)**.
[12] A.A.El-Kateb, N.M.Abd El-Rahman, T.S.Saleh, I.F.Zeid, M.F.Mady; Life Science Journal, **9**, 711 **(2012)**.
[13] N.Gommermann, P.Buehlmayer, A.Matt, W.Breitenstein, K.Masuya, B.Pirard, P.Furet, S.W.Cowan-Jacob, G.Weckbecker; Bioorg.Med. Chem.Lett., **20**, 3628 **(2010)**.
[14] I.Kim, J.H.Song, C.M.Park, J.W.Jeong, H.R.Kim, J.R.Ha, Z.No, Y.Hyun, Y.S.Cho, N.S.Kang, D.J.Jeon; Bioorg.Med.Chem.Lett., **20**, 922 **(2010)**.
[15] S.Selleri, P.Gratteri, C.Costagli, C.Bonaccini, A.Costanzo, F.Melani, G.Guerrini, G.Ciciani, B.Costa, F.Spinetti, C.Martini, F.Bruni; Bioorg.Med.Chem., **13**, 4821 **(2005)**.
[16] C.Almansa, M.Merlos, A.F.de Arriba, F.L.Cavalcanti, L.A.Gomez, A.Miralles, M.Merlos, J.G.Rafanell, J.Forn; J.Med.Chem., **44**, 350 **(2001)**.
[17] M.E.Fraley, W.F.Hoffman, R.S.Rubino, R.W.Hungate, A.J.Tebben, R.Z.Rutledge, R.C.McFall, W.R.Huckle, R.L.Kendall, K.E.Coll, K.A.Thomas; Bioorg.Med.Chem.Lett., **12**, 2767 **(2002)**.
[18] W.E.Kirkipatrick, T.Okabe, I.W.Hillyard, R.K.Robins, A.T.Dren, T.Novinson; J.Med. Chem., **20**, 386 **(1977)**.

**[19]** O.A.Fathala, M.E.A.Zaki, S.A.Swelam, S.M.Nofal, W.I.El-Eraky; Acta Pol.Pharm., **60**, 51 **(2003)**.

**[20]** B.M.Shaikh, Sh.G.Konda, S.S.Chobe, G.G.Mandawad, O.S.Yemul, B.S.Dawane; J.Chem.Pharm.Res., **3**, 435 **(2011)**.

**[21]** M.J.Di Grandi, D.M.Berger, D.W.Hopper, Ch.Zhang, M.Dutia, A.L.Dunnick, N.Torres, J.I.Levin, G.Diamantidis, Ch.W.Zapf, J.D.Bloom, Y.B.Hu, D.Powell, D.Wojciechowicz, K.Collins, E.Frommer; Bioorg.Med.Chem.Lett., **19**, 6957 **(2009)**.

**[22]** M.R.Shaaban, T.S.Saleh, A.S.Mayhoub, A.Mansour, A.M.Farag; Bioorg.Med.Chem., **16**, 6344 **(2008)**.

**[23]** M.H.Elnagdi, D.H.Fleita, M.R.H.Elmoghayar; Tetrahedron, **31**, 63 **(1975)**.

**[24]** M.G.Marei, M.M.Mishrikey, D.M.Aly; Bull.Chem.Soc.Jpn., **65**, 3419 **(1992)**.

**[25]** E.A.Zvezdina, M.P.A.Zhdanova, I.I.Nechayuk, A.Barchan, Y.N.Simkina, T.A.Buchnaya; Khim.Farm.Zh., **20**, 1328 **(1986)**.

**[26]** M.G.Marei, A.M.A.Hassaan; Transition Met.Chem., **17**, 489 **(1992)**.

**[27]** P.Scovill, D.L.Klayman, C.F.Franchino; J.Med.Chem., **25**, 1261 **(1982)**.

**[28]** S.Gudmundsson, B.A.Johns, J.Weatherhead; Bioorg.Med.Chem.Lett., **19**, 5689 **(2009)**.

**[29]** S.A.Paulsen, D.Young, R.J.Quinn; Bioorg.Med. Chem.Lett., **11**, 191 **(2001)**.

**[30]** K.kino, H.S.Kim, Y.Kurasawa; J.Heterocycl. Chem., **35**, 489 **(1998)**.

**[31]** V.R.Arava, L.Laxminarasimhulu, S.R.Bandatmakuru, U.B.Rao Siripalli; Der Pharm.Chem., **2(3)**, 178 **(2010)**.

**[32]** E.G.Paronikyan, A.S.Noravyan; Kim.Geterotisikl.Soed., **32**, 1413 **(1996)**.

**[33]** D.C.Kim, Y.R.Lee, B.S.Yang, K.J.Shin, D.J.Kim, B.Y.Chung, K.H.Yoo; Eur.J.Med.Chem., **38**, 525 **(2003)**.

**[34]** Y.Tominaga, Y.Honkawa, M.Hara, A.Hosomi; J.Heterocycl.Chem., **27**, 775 **(1990)**.

**[35]** D.A.Ibrahim, A.M.El-Metwally, E.E.Al-Arab; Arkivoc, **7**, 12 **(2009)**.

**[36]** H.Elnagdi; Adv.Heterocyl.Chem., **41**, 319 **(1986)**.

**[37]** M.Kandeel, L.W.Mohamed, M.K.Abd-Elhamid, A.T.Negmeldin; Sci.Pharm., **80**, 531 **(2012)**.

**[38]** J.M.Quintela, C.Peinador, M.J.Moreira, A.Alfonso, L.M.Botana, R.Riguera; Eur.J.Med.Chem., **36**, 321 **(2001)**.

**[39]** S.M.Hassan, H.A.Emam, M.M.Abdelall; J.Chem.Res., (S), 544; (M), 1301 **(2000)**.

**[40]** M.M.Ghorab, F.A.Ragab, S.I.Alqasoumi, A.M.Alafeefy, Sh.A.Aboulmagd; Eur.J.Med. Chem., **45**, 171 **(2010)**.

**[41]** S.Schenone, O.Bruno, F.Bondavalli, A.Ranise, L.Mosti, G.Menozzi, P.Fossa, S.Donnini, A.Santoro, M.Ziche, F.Manetti, M.Botta; Eur.J.Med.Chem., **39**, 939 **(2004)**.

**[42]** M.M.El-Enany, M.M.Kamel, O.M.Khalil, H.B.El-Nassan; Eur.J.Med.Chem., **45**, 5286 **(2010)**.

**[43]** D.Rffa, B.Maggio, F.Plescia, S Cascioferro, M.V.Raimondi, S.Plescia, M.G.Cusimano; Arch.Pharm., **342**, 321 **(2009)**.

**[44]** L.E.Evans, M.D.Cheeseman, K.Jones; Org.Lett., **14**, 3546 **(2012)**.

**[45]** W.Riad, S.Aboul Fetouh; Tetrahedron, **44**, 155 **(1988)**.

**[46]** H.Kanzawa, S.Nishigaki, K.Shenga; J.Heterocycl.Chem., **21**, 969 **(1984)**.

**[47]** L.Farkas, J.Keuler, H.Wamhoff; Chem.Ber., **113**, 2566 **(1980)**.

**[48]** A.Gomtsyan, S.Didomenico, C.H.Lee, A.O.Stewart, S.S.Bhagwat, E.A.Kowaluk, M.F.Jarvis; Bioorg.Med.Chem.Lett., **14**, 4165 **(2004)**.

**[49]** J.Bhuyan, H.N.Borah, J.S.Sandhu; Tetrahedron Lett., **43**, 895 **(2002)**.

**[50]** T.M.Abu Elmaati; Z.Naturforsch.B, **57b**, 1333 **(2002)**.

**[51]** R.G.Hildick, G.Show; J.Chem.Soc., 1610 **(1970)**.

**[52]** S.Leonova, V.G.Yashamokii; Khim.Geterotsikl. Soedin., 982 **(1982)**.

**[53]** Y.Tominaga, K.Nomoto, N.Yoshiola; J.Heterocycl.Chem., **38**, 1135 **(2001)**.

**[54]** H.Rosemeyer, M.Anders, F.Sela; Molecules, **12**, 563 **(2007)**.

**[55]** M.M.Ghorab, Z.H.Ismail, S.M.Abdel-Gawad, A.Abdel Aziem; Heteroatom Chem., **15**, 57 **(2004)**.

**[56]** P.G.Baraldi, G.Saponaro, M.A.Tabrizi, S.Baraldi, R.Romagnoli, A.R.Moorman, K.Varani, P.A.Borea, D.Preti; Bioorg.Med.Chem., **20**, 1046 **(2012)**.

**[57]** J.H.Chen, K.S.Shia, T.A.Hsu, C.L.Tai, C.C.Lee, Y.C.Lee, C.S.Chiang, S.N.Tseng, S.R.Shih; Bioorg.Med.Chem.Lett., **14**, 2519 **(2004)**.

**[58]** V.Svalyavin, M.Yu.Onysko, V.G.Lendel; Chem. Heterocycl.Comp., **45**, 827 **(2009)**.

[59] M.Chebib, D.Mckeveney, R.J.Quinn; Bioorg. Med.Chem., **8**, 2581 **(2000)**.
[60] A.Kumar, I.Ahmad, B.S.Chhikara, R.Tiwari, D.Mandal, K.Parang; Bioorg.Med.Chem.Lett., **21**, 1342 **(2011)**.
[61] S.Guccione, L.M.Scolaro, F.Russo; J.Heterocycl. Chem., **33**, 459 **(1996)**.
[62] T.E.Ali; Eur.J.Med.Chem., **44**, 4385 **(2009)**.
[63] E.I.Al-Afaleq, S.A.Abubshait; Molecules, **6**, 621 **(2001)**.
[64] N.M.Abunada, H.M.Hassaneen, N.G.Kandile, O.A.Miqdad; Molecules, **13**, 1501 **(2008)**.
[65] I.F.Nassar, S.A.El Assaly; Der Pharm.Chem., **3(1)**, 229 **(2011)**.
[66] **(a)** A.J.S.Larsen, M.A.Zahran, E.B.Pedersen, C.Nielsen; Monatsh.Chem., **130**, 1167 **(1999)**; **(b)** A.E.Rashad, M.S.Mohamed, M.E.A.Zaki, S.S.Fatahala; Arch.Pharm., **339**, 664 **(2006)**; **(c)** J.Ravn, K.Qvortrup, C.Rosenbohm, T.Koch; Bioorg.Med.Chem., **15**, 55440 **(2007)**.
[67] K.Deo, K.Avasthi, R.Pratap, K.Kar, D.S.Bhakuni; lndian J.Chem., **26B**, 963 **(1987)**.
[68] D.Nord, G.R.Revankar, R.K.Robins; J.Heterocycl. Chem., **27**, 439 **(1990)**.
[69] T.Fowler, K.N.Tiwari, J.A.Montgomery, R.W.Buckheit, J.A.Secrist, F.Seela; Helv.Chim. Acta, **82**, 2240 **(1999)**.
[70] S.Gupta, L.M.Rodrigues, A.P.Esteves, A.M.F.Oliveira-Campos, M.S.J.Nascimento, N.Nazareth, H.Cidade, M.P.Neves, E.Fernandes, M.Pinto, N.M.F.S.A.Cerqueira, N.Bras; Eur.J. Med.Chem., **43**, 771 **(2008)**
[71] B.G.Ugakar, H.B.Cottam, P.A.McKernan, R.K.Robins, G.R.Revankar; J.Med.Chem., **27**, 1026 **(1984)**.
[72] T.Higashino, Y.Iwai, E.Hayashi; Chem.Pharm. Bull., **25**, 535 **(1977)**.
[73] S.Senda, K.Hirota, T.Asoa, Y.Yamada; Tetrahedon Lett., 2295 **(1978)**.
[74] T.Higashino, Y.Matsushita, M.Takemoto, E.Hayashi; Chem.Pharm.Bull., **31**, 3951 **(1983)**.
[75] A.H.Shamroukh, A.E.Rashad, H.H.Sayed; Phosphorus, Sulfur, Silicon, **180**, 2347 **(2005)**.
[76] A.E.Rashad, M.I.Hegab, R.E.Abdel-Megeid, J.A.Micky, F.M.E.Abdel-Megeid; Bioorg.Med. Chem., **16**, 7102 **(2008)**.
[77] A.E.Rashad, M.I.Hegab, R.E.Abdel-Megeid, N.A.Fatahala, F.M.E.Abdel-Megeid; Eur.J.Med. Chem., **44**, 3285 **(2009)**.
[78] A.E.Rashad, M.I.Hegab, R.E.Abdel-Megeid, M.M.Ali, F.M.E.Abdel-Megeid; Phosphorus, Sulfur, Silicon, **185**, 74 **(2010)**.
[79] A.E.Rashad, A.H.Shamroukh, R.E.Abdel-Megeid, A.Moustafa, M.A.Ali, K.Banert; Nucleosides, Nucleotides, **29**, 809 **(2010)**.
[80] A.E.Rashad, A.E.Mohamed, M.Ali; Eur.J.Med. Chem., **46**, 1019 **(2011)**.
[81] S.A.Swelam, O.I.Abd-El-Salam, M.E.A.Zaki; J.Serb.Chem.Soc., **64**, 655 **(1999)**.
[82] A.H.Shamroukh, A.E.Rashad, H.S.Ali, F.M.E.Abdel-Megeid; J.Heterocyclic Chem., **50**, 758 **(2013)**.
[83] A.F.Eweas, S.A.Swelam, O.A.Fathalla, N.M.Fawzy, Sh.I.Abdel-Moez; Med.Chem.Res., **21**, 3848 **(2012)**.
[84] H.H.Sayed, H.S.Abbas, E.M.H.Morsy, E.M.Flefel; Der Pharm.Chem., **3(1)**, 31 **(2011)**.
[85] J.A.Markwalder, M.R.Arnone, P.A.Benfield, M.Boisclair, C.R.Burton, C.Chang, S.S.Cox, P.M.Czerniak, C.L.Dean, D.Doleniak, R.Grafstrom, B.A.Harrison, R.F.Kaltenbach, D.A.Nugiel, K.A.Rossi, S.R.Sherk, L.M.Sisk, P.Stouten, G.L.Trainor, P.Worland, S.P.Seitz; J.Med.Chem., **47**, 5894 **(2004)**.
[86] A.J.Peat, D.Garrido, J.A.Boucheron, S.L.Schweiker, S.H.Dickerson, J.R.Wilson, T.Y.Wang, S.A Thomson; Bioorg.Med. Chem.Lett., **14**, 2127 **(2004)**.
[87] T.L.Smalley, A.J.Peat, J.A.Boucheron, S.Dickerson, D.Garrido, F.Preugschat, S.L.Schweiker, S.A.Thomson, T.Y.Wang; Bioorg. Med.Chem.Lett., **16**, 2091 **(2006)**.
[88] F.D.Settimo, G.Primofiore, C.L.Motta, S.Taliani, F.Simorini, A.Marini, L.Mugnaini, A.Lavecchia, E.Novellino, D.Tuscano, C.Martini; J.Med.Chem., **48**, 5162 **(2005)**.
[89] A.Gomtsyan, S.Didomenico, Ch.Lee, A.O.Stewart, Sh.S.Bhagwat, E.A.Kowaluk, M.F.Jarvis; Bioorg.Med.Chem.Lett., **14**, 4165 **(2004)**.
[90] J.Bussenius, N.K.Anand, Ch.M.Blazey, O.J.Bowles, L.C.Bannen, D.S.M.Chan, B.Chen, E.W.Co, S.Costanzo, S.C.DeFina, L.Dubenko, S.Engst, M.Franzini, P.Huang, V.Jammalamadaka, R.G.Khoury, M.H.Kim, R.R.Klein, D.Laird, D.T.Le, M.B.Mac, D.J.Matthews, D.Markby, N.Miller, J.M.Nuss, J.J.Parks, T.H.Tsang, A.L.Tsuhako, Y.Wang, W.Xu, K.D.Rice; Bioorg. Med.Chem.Lett., **22**, 2283 **(2012)**.
[91] D.Hubbard, N.Y.Bamaung, F.Palazz, Q.Zhang,

P.Kovar, D.J.Osterling, X.Hu, J.L.Wilsbacher, E.F.Johnso, J.Bouska, J.Wang, R.L.Bell, S.K.Davidsen, G.S.Sheppard; Bioorg.Med.Chem. Lett., **17**, 5406 **(2007)**.

**[92]** P.Dinér, J.P.Alao, J.Söderlund, P.Sunnerhagen, M.Grøtli; J.Med.Chem., **55**, 4872 **(2012)**.

**[93]** J.Le Brazidec, A.Pasis, B.Tam, C.Boykin, C.Black, D.Wang, G.Claassen, J.H.Chong, J.Chao, J.Fan, Kh.Nguyen, L.Silvian, L.Ling, L.Zhang, M.Choi, M.Teng, N.Pathan, S.Zhao, T.Li, A.Taveras; Bioorg.Med.Chem.Lett., **22**, 2070 **(2012)**.

**[94]** H.A.Abd El Razik, A.E.Abdel Wahab; Arch.Pharm., **344**, 184 **(2011)**.

**[95]** W.S.El-Hamouly, K.M.Amin, S.A.El-Assaly, E.A.Abd El-Meguid; Der Pharm.Chem., **3(6)**, 282 **(2011)**.

**[96]** M.Gomha, H.M.E.Hassaneen; Molecules, **16**, 6549 **(2011)**.

**[97]** M.Ghorab; Acta Pharm., **50**, 93 **(2000)**.

**[98]** M.Bakavoli, Gh.Bagherzadeh, M.Vaseghifar, A.Shiri, M.Pordel, M.Mashreghi, P.Pordeli, M.Araghi; Eur.J.Ed.Chem., **45**, 647 **(2010)**.

**[99]** B.S.Holla, M.Mahalinga, M.S.Karthikeyan, P.M.Akberali, N.S.Shetty; Bioorg.Med.Chem., **14**, 2040 **(2006)**.

**[100]** M.S.Karthikeyan, P.M.Akberali, N.S.Shetty; Bioorg.Med.Chem., **14**, 2040 **(2006)**.

**[101]** B.G.Ugarkar, H.B.Cottam, P.A.Mekernam, R.K.Robins, G.R.Revankar; J.Med.Chem., **27**, 1026 **(1984)**.

**[102]** O.Moukha-chafiq, M.L.Taha, H.B.Lazrek, J.J.Vasseur, E.De Clercq; Nucleosides, Nucleotides, Nucleic Acids, **21**, 165 **(2002)**.

**[103]** J.H.Chern, K.S.Shia, T.A.Hsu, C.L.Tai, C.C.Lee, Y.C.Lee, C.S.Chiang, S.N.Tseng, S.R.Shih; Bioorg.Med.Chem.Lett., **14**, 2519 **(2004)**.

**[104]** D.F.Smee, P.A McKernan, L.D.Nord, R.C.Willis, C.R.Petrie, T.M.Riley, G.R.Revankar, R.K.Robins, R.A.Smith; Antimicrob.Agents Chemother., **31**, 1535 **(1987)**.

**[105]** J.M.Quintela, C.Peinador, L.Gonzalez, I.Deversal, M.L.Ferrandiz, M.J.Alcaraz, R.Riguera; Bioorg.Med.Chem., **11**, 863 **(2003)**.

**[106]** S.Alcaro, A.Artese, M.Botta, A.T.Zizzari, F.Orallo, F.Ortuso, S.Schenone, C.Brullo, M.Yanez; Chem.Med.Chem., **5**, 1242 **(2010)**.

**[107]** S.B.Yewale, S.B.Ganorkar, K.G.Baheti, R.U.Shelke; Bioorg.Med.Chem.Lett., **21**, 6616 **(2012)**.

**[108]** H.S.Ahn, A.Bercovici, G.Boykow, A.Bronnenkant; J.Med.Chem., **40**, 2196 **(1997)**.

**[109]** R.K.Robins; J.Am.Chem.Soc., **78**, 784 **(1956)**.

**[110]** R.K.Robins, G.R.Revankar, D.E.O'Brien, R.H.Springer, T.Novinson, A.Albert, K.Senga, J.P.Miller, D.G.Streeter; J.Heterocycl.Chem., **22**, 601 **(1985)**.

**[111]** A.M.Ibrahim, A.M.Saleh, H.F.Zohdi; Molecules, 109 **(2004)**.

**[112]** R.Filler; Chem.Technol., **4**, 752 **(1974)**.

**[113]** Y.Xia, S.Chackalamannil, M.Czarniecki, H.Tsai, H.Vaccaro, R.Cleven, J.Cook, A.Fawzi, R.Watkins, H.Zhawg; J.Med.Chem., **40**, 4372 **(1997)**.

**[114]** A.Pittaluga, M.Feligioni, F.Longordo, M.Arvigo, M.Raiteri; J.Pharm.Exp.Ther., **313**, 242 **(2005)**.

**[115]** A.Hasan, M.Satyanarayana, A.Mishra, D.S.Bhakuni, R.Pratap, A.Dube, P.Y.Guru; Nucleosides, Nucleotides, Nucleic Acids, **25**, 55 **(2006)**.