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Review Article

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Biological Activity of Pyrimidine Derivatives

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ABSTRACT

Anti-inflammatory efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) has been related to their properties as inhibitors of cyclooxygenase (COX)-mediated prostaglandin (PG) synthesis. However, recent studies have suggested that variations of the in vivo anti-inflammatory actions among different NSAIDs could not be solely explained by COX inhibition. Here, we have analyzed the effects on T cell activation of novel pyrazole derivatives. Pyrazoles represent a most active classes of compounds possessing a wide spectrum of biological activities. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry**.** The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals.

Key-words: Pyrimidine, Anti-inflammatory activity, anticancer activity

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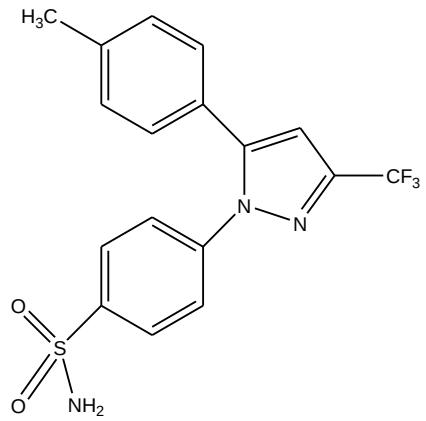
INTRODUCTION

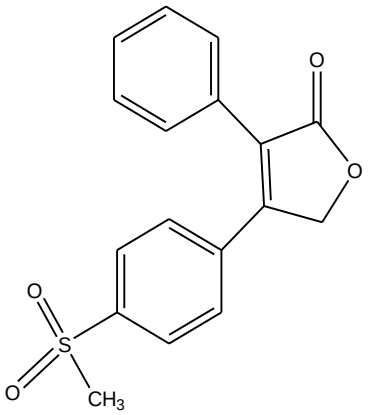
Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. Pyrazole and its derivatives, a class of well known nitrogen containing heterocyclic compounds, occupy an important position in medicinal chemistry [1].

The pyrazole skeleton constitutes an important central template for a wide variety of biologically active compounds, such as anti-microbial, antiviral, anti-inflammatory, antidepressant, hyperglycaemic and pesticidal activity. In particular some of pyrazole derivatives were in depth investigated as non-steroidal anti-inflammatory drugs (NSAIDs). The mechanism of action of this class of compounds is linked to the nonselective or selective inhibition of two cyclooxygenase isoforms, namely COX-1and COX-2 [2]. While COX-1 is a constitutive enzyme and is necessary for the proper function of the kidney and stomach through the synthesis of prostaglandins, COX-2 is an inducible form of the enzyme that mediates the inflammatory processe [3]. It is generally showed that anti-inflammatory activity and analgesic efficacies non-steroidal anti-inflammatory drugs (NSAIDs) arise from inhibition of the enzymatic activity of cyclooxygenases (COXs) which convert arachidonic acid to prostaglandins (PGs). The role of the cyclooxygenase-2 (COX-2) isoform inflammation [4], and the attractiveness of COX-2 as a therapeutic target for the development of anti-inflammatory drugs are very well recognized [5, 6]. COX-2 selective inhibitors have proven to be effective anti-inflammatory and analgesic medicines with lower chronic gastrointestinal (GI) toxicity than traditional non-steroidal anti-inflammatory drugs (NSAIDs), which non-selectively inhibit COX-2 and COX-1. Three COX-2 selective inhibitors, celecoxib [7], rofecoxib [8] and valdecoxib [9], are currently prescribed for the treatment of arthritis and inflammatory diseases. They show anti-inflammatory activity with reduced GI side effects. Although relieving pain and inflammation at least as effectively as standard NSAIDs, COX-2 selective inhibitors fail to inhibit LT biosynthesis, and they do not ameliorate any potentially adverse downstream effects of the LTs, e.g. activation on cartilage-destroying enzymes by tumor necrosis factor-a (TNF-a) and interleukin-1b (IL-1b).



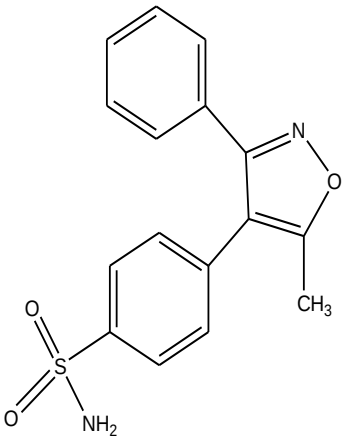
Celecoxib

Figure 1



Rofecoxib

Figure 2



Valdecoxib

Figure 3

Pyrimidines are the most important six member heterocyclic, containing two nitrogen atoms on 1, 3 positions as shown in fig 1.

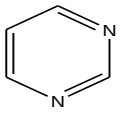
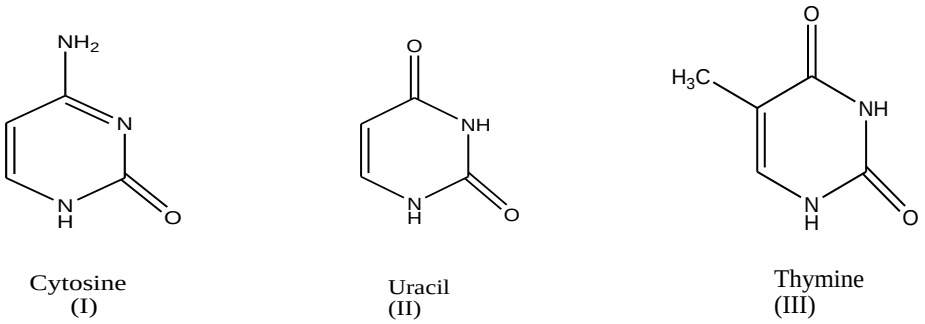


Figure 1

Pyrimidines are present among the three isomeric diazines. Several pyrimidines mainly cytosine (I), uracil (II) and thymine (III) have been isolated from the nucleic acid hydrolysis as shown in Fig 2. The nucleic acid are

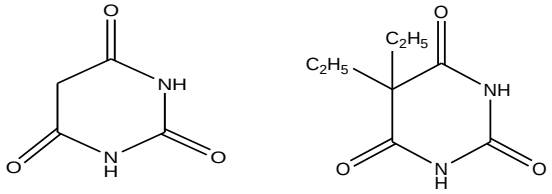
essential constituent of all cell and thus of all living matter cytosine is found to be present in both types of nucleic acid i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) [6].



Cytosine (I) Uracil (II) Thymine (III)

Figure 2

In addition to this, Pyrimidines ring is also found in Vitamin B_1, Barbituric acid (IV) and its several derivatives e.g. Veranal (V) which are used as hypnotics (fig. 3) [7].

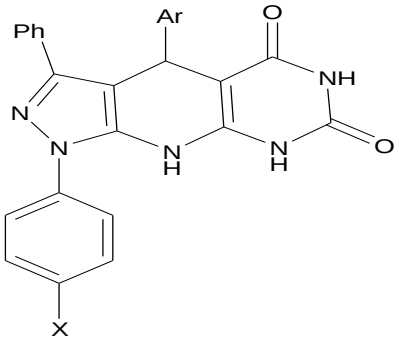


Barbituric acid (IV) Veranal (V)

Figure 3

Antimicrobial activity:

Bazgir *et al.* [13] synthesized a new series of compound in which pyrazolo[4′,3′:5,6] pyrido[2,3-d]pyrmidine-dione **(1)** determined highest antimicrobial activity against *Pseudomonas aeruginosa, Enterococcus faecalis* and *Bacillus pumilus* as compared to standard drug, Tetracycline and Gentamicin. Compounds 1a–j were found to be more active than Tetracycline against *Bacillus pumilus*, *Micrococcus luteus*, *Streptococcus mutans*, *Escherichia coli*, and *Pseudomonas aeruginosa*. 1a–e were more active, reinforcing the pharmacophoric contribution of carbonyl moiety.

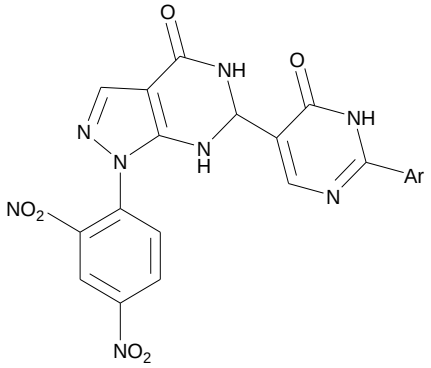


(1)

Compounds	Ar	X
1a	C_6H_5	H
1b	4-Cl-C_6H_4	H
1c	4-Br-C_6H_4	H
1d	4-Me-C_6H_4	H
1e	3-NO_2-C_6H_5	H
1f	C_6H_5	NO_2

1g	4-Cl-C_6H_4	NO_2
1h	4-Br-C_6H_4	NO_2
1i	4-Me-C_6H_4	NO_2
1j	3-NO_2-C_6H_4	NO_2

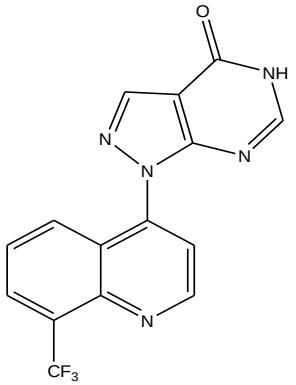
Bakavoli *et al.* [14] prepared a new series of pyrazolo[3,4-d]pyrimidine derivative **(2)** and its antibacterial activity determined against several pathogenic representative Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis;* Gram-negative bacteria *Escherichia coli and Pseudomonas aeruginosa* as compared to standard drug Streptomycin. The compounds bearing 4-BrC_6H_4– (2e) and 2-OHC_6H_4 (2i) substituents has shown the highest sensitivity against *E. coli* and *Pseudomonas aeruginosa*, respectively. Compounds (2h) and (2j) with other substituents of 3-$NO_2C_6H_4$– and 3-OH–C_6H_4– respectively exhibited the best activity against the *Staphylococcus aureus* strains while *Bacillus Subtilis* has been more sensitive against compound (2f) with substituent 4-ClC_6H_4–. Therefore the good activity can be attributed to the presence of group 4-bromo, 2 and 3-hydroxy and 4-chloro which are directly attached to the phenyl ring of the diazine system.



(2)

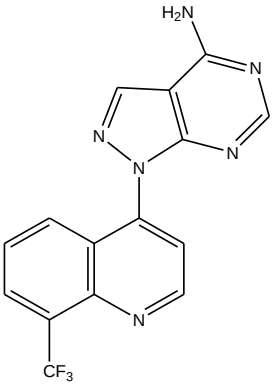
Compounds	Ar
2a	C_6H_5
2b	4-MeC_6H_4
2c	4-MeOC_6H_4
2d	3-MeOC_6H_4
2e	4-BrC_6H_4
2f	4-ClC_6H_4
2g	4-$NO_2C_6H_4$
2h	3-$NO_2C_6H_4$
2i	2- HOC_6H_4
2j	3-HOC_6H_4

Holla *et al.* [15] synthesized new series of 5-substituted 6-methyl-1-[8-(trifluoromethyl) quinolin-4-yl]-1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-ones **(3)**, this compound shows maximum antibacterial activity against *Staphylococcus aureus* as comparison to standard drug Streptomycin. Basically pyrazolo [3, 4-d] pyrimidines are analogs of purine nucleus and various structural changes of the natural purines have resulted in potent antagonists in biological systems. In this study, replacement of the H atom of the pyrazole ring by 8-trifluoromethylquinoline as an active moiety these structural changes made fused pyrimidines more active towards tested organisms. Further, incorporation of CF_3 group in the quinoline ring increased lipophilicity as well as biological activity.

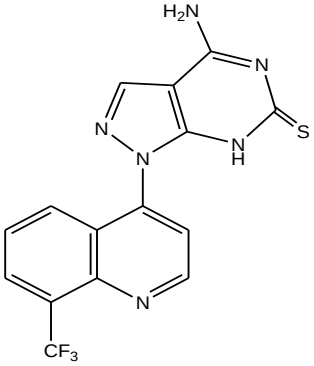


(3)

Karthikeyan *et al* [16] synthesized a new series of compound in which 4-amino-1-[8-(trifluoromethyl) quinolin-4-yl]-1*H*-Pyrazolo [3, 4-d] pyrimidine **(4)** exhibit good activity against *Aspergillus flavus, Aspergillus fumigatus* and *Trichophyton mentagrophytes* as compared to standard drug Flucanazole.

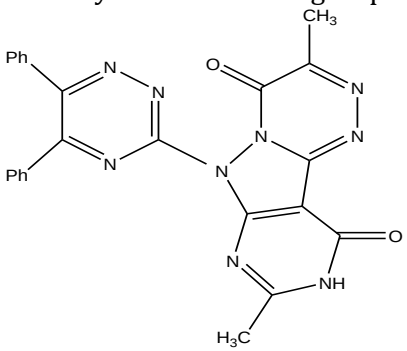


(4)

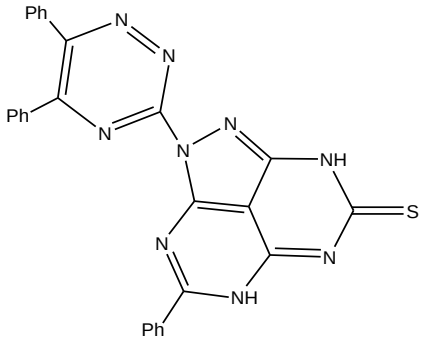


(5)

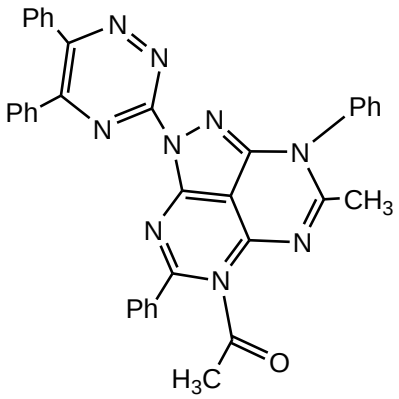
Ali *et al* [17] was synthesized a new series of pyrazolopyrimidine derivatives (5,6-diphenyl-1,2,4-triazin-3-yl)-3,8-dimethylpyrimido [4′,5′:3,4]pyrazolo[5,1-c][1,2,4] triazine-4,10-(6H,9H)-dione **(6)** which possess antibacterial activity against *Escherichia coli* as compared to standard drug Tetracycline. **(7)** 5-((Z)-2-cyano-2-isocyano-1-(methylthio)vinylamino)-3-(methylthio)-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbonitrile showed good inhibitions against *Streptococcus aureus* (MTCCB 737) and *Staphylococcus epidermidis* (MTCCB 1824) due to the presence of methylthio and nitrile groups.



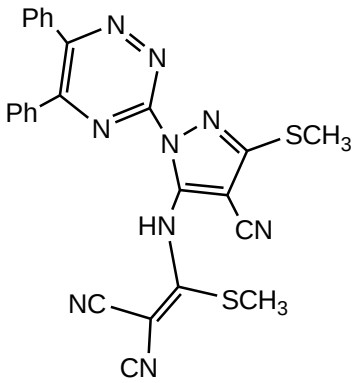
(6)



(7)



(8)



(9)

Rashad *et al* [18] was synthesized a new series of pyrazolopyrimidine derivatives, compound (1S) -1-C-(8,9-*Dihydronaphtho*[1′2′:4,5] thieno-[3,2-e][1,2,4]triazolo[1,5-c] pyrimidine-2-yl) polyols and acyclic and cyclic *C*-nucleosides **(11)** Non-acetylated sugar pyrimidine derivatives showed more significant antimicrobial activity against *Aspergillus Niger, Candida Albicans and Aspergillus niger* as compared to standard drug Ampicillin.

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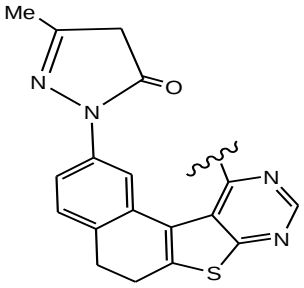
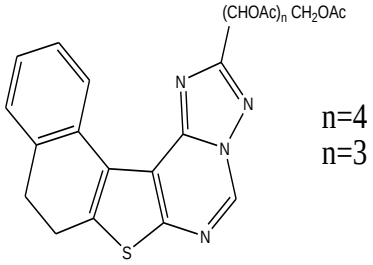


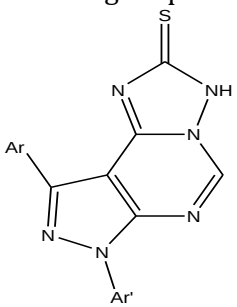
(10)



n=4
n=3

(11)

Abunada *et al* [19] synthesized a new series of pyrazolopyrimidine derivatives 9-aryl-7-(4-nitrophenyl)-7H-pyrazolo[4,3-e][1,2,4] triazolo [1,5-c] pyrimidine-2(3H)-Thiones **(12)** active against *Staphylococcus aureus* and *Candida albican* as compared to standard drug Amphotericine B.

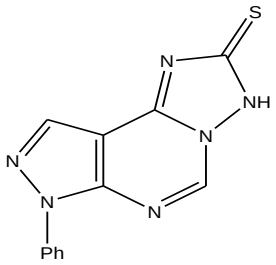


Where Ar= 4-FC_6H_4, 2,4- di-ClC_6H_3
Ar' = 4-$NO_2C_6H_4$

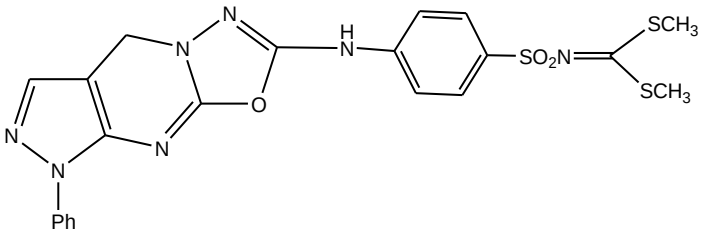
(12)

3.2. Anticancer activity:

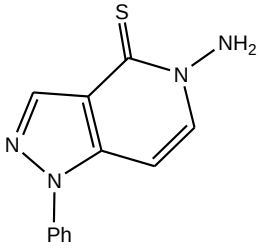
Mostafa Ghorab *et al* [20] synthesized new series of pyrazolopyrimidine derivatives. Among these 5-Amino-1-phenyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidine **(15)** active against Ehrlich Ascites Carcinoma (EAC) cell line as compared to standard drug Doxorubicin.



(13)

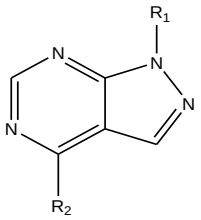


(14)



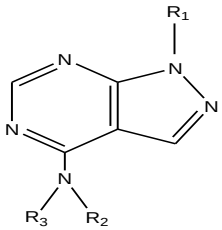
(15)

Cheng *et al* [21] synthesized pyrazolopyrimidine derivatives a compd 1-alkyl(aryl)-4-substituted-pyrazolo[3,4-*d*]*pyrimidines* and 1-alkyl(aryl)-4-substituted-aminopyrazole[3,4-*d*]pyrimidine as potential purines antagonists. In these series 1-methyl-4-amino pyrazolo [3, 4-*d*] pyrimidine **(16)** showed antitumor activity and 1-methyl-4-methylamino pyrazolo [3, 4-*d*] pyrimidine **(17)** has recently been found to exhibit similar activity against adenocarcinoma 755 and leukemia 5178.



Where R_1= CH_3, C_6H_5, p-Cl-C_6H_4
R_2= OH, Cl, NH_2,SH

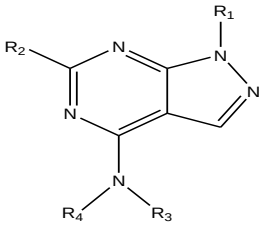
(16)



R_1= CH_3, C_6H_5,p-Cl-C_6H_4
R_2= H,CH_3, C_2H_5
R_3= CH_3, C_2H_5, NH_2

(17)

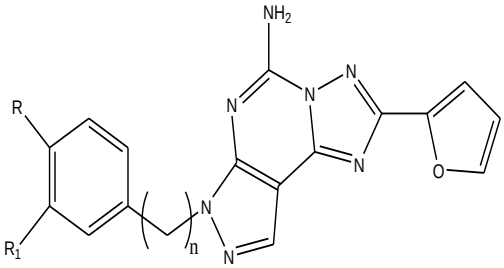
Cheng *et al* [22] have reported the synthesis of pyrazolopyrimidine derivatives in which 6-alkyl-1,4-disubstituted-pyrazolo[3,4-*d*]pyrimidines and 6-alkyl-4-N-substituted-pyrazolo[3,4-*d*] pyrimidines as potential purine antagonists. The screening of these compounds against tumors in mice not revealed any antitumor activity in these series; it inhibits the growth of *Neurospora crassa*. **(18)**, 4-dimethylamino-6-methyl-1-(p-tolyl)pyrazolo[3,4-*d*]pyrimidine at low doses showed relatively pronounced inhibition, however at large doses growth was supported by the same compound.



R_1= H, CH_3, C_6H_5, p-CH_3-C_6H_4
R_2= CH_3, C_2H_5
R_3= CH_3,C_2H_5,NH_2
R_4= H, CH_3, C_2H_5

(18)

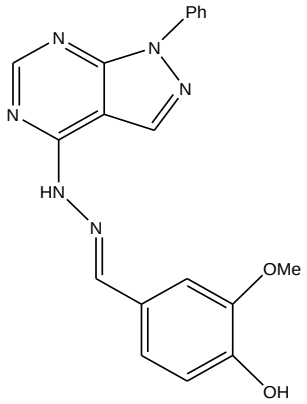
Baraldi *et al* [23] have reported the design, synthesis and biological evaluation of a second generation of pyrazolo[4,3-*e*]1,2,4-triazolo[1,5-*c*]pyrimidines **(19)** as potent and selective A_{2A} adenosine receptor antagonists. The results showed that all the tested compounds display high affinity at A_{2A} receptors: high r A_{2A} vs rA_1 and most importantly, rA_{2A} vs hA_3 selectivity.



Where, R= OBn, OH, OCH_3
R_1= H, OH, OCH_3

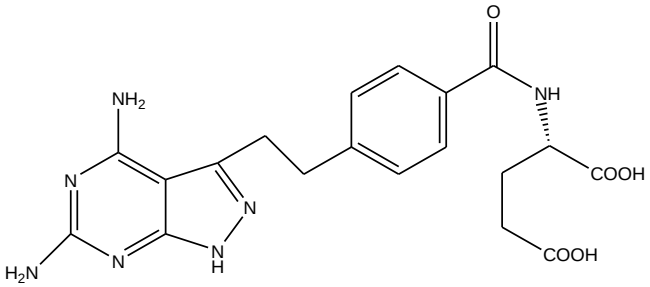
(19)

Peat *et al* [24] have reported synthesis of series of (1-aryl-1*H*- pyrazolo [3, 4-*d*] pyrimidin-4-yl) aryl hydrazones **(20)** as GSK-3 (Glycogen Synthase Kinase) inhibitors and was determined to bind in a competitive manner with ATP.



(20)

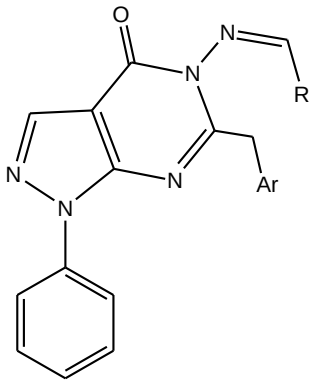
Taylor *et al* [25] synthesized a compound pyrazolo[3,4-*d*]pyrimidine analogues of the potent antitumor agent N-{4-[2-(2-amino-4[3*H*]-oxo-7*H*-pyrrolo[2,3-*d*] pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (LY231514) *in-vitro* cell growth inhibition studies revealed that only **(21)** (S)-2-(4-(2-(4, 6-diamino-1*H*-pyrazolo [3,4-d] pyrimidin-3-yl)ethyl) benzamido) pentanedioic acid exhibit cytotoxic activity.



(21)

3.3. Anti-inflammatory and analgesic activity:

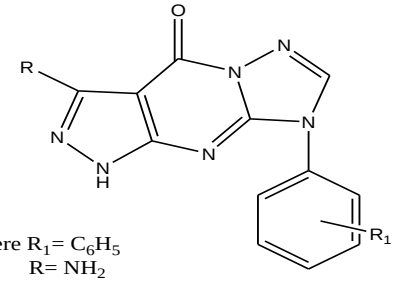
Mohammed *et al* [26] synthesized a series of pyrazolopyrimidine derivatives, (5-arylideneamino-6-substituted-1-phenyl-1H-pyrazolo [3,4-d]-pyrimidin-4(5H)-one, in which **compounds (22 a, 22 d and 22f)** shows good anti-inflammatory activity.



Compound 22

Compounds	Ar	R
22a	naphthyloxy	2-C_6H_4OH
22b	naphthyloxy	C_6H_5
22c	naphthyloxy	4-$C_6H_4OCH_3$
22d	naphthyloxy	4-$C_6H_4N(CH_3)_2$
22e	naphthyloxy	2,4-$C_6H_4N(CH_3)$
22f	naphthyloxy	2- C_6H_4Br

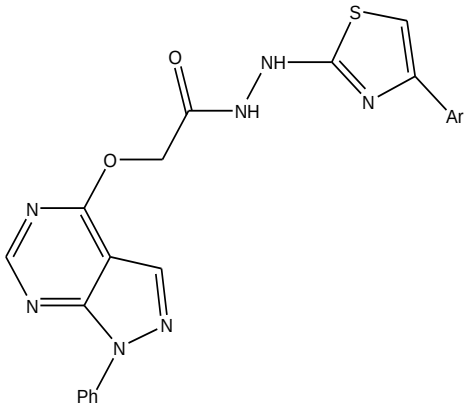
Russo *et al* [27] have synthesized Pyrazolotriazolopyrimidine derivatives **(23)** screened for anti-inflammatory analgesic activity. The results shows good anti-inflammatory activity associated with non-narcotic analgesic property with remarkable systemic and gastric tolerance.



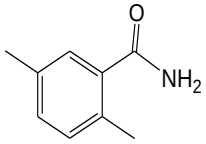
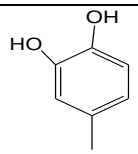
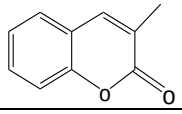
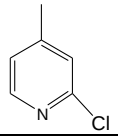
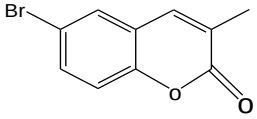
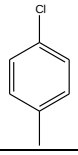
Where $R_1 = C_6H_5$
$R = NH_2$

(23)

Raj *et al* [28] have reported few new series of 2-1[(1-phenyl -1H-pyrazolo [3, 4-*d]* pyrimidin-4-yl) oxyl]-N'-(4-aryl-1, 3 thiazol-2-yl) acetohydrazide derivatives and screened for analgesic activity. Among the tested **(24)** (24 g) 2-1[(1-phenyl -1H-pyrazolo [3, 4-*d]* pyrimidin-4-yl) oxyl]-N'-(4-chlorophenyl)-1, 3 thiazol-2-yl) acetohydrazide exhibited promising analgesic activity compound 24a, and 24b also exhibited a moderate analgesic activity. Therefore compound 24f shows higher activity compared to other compounds due to the presence of 4-chlorophenyl moiety.

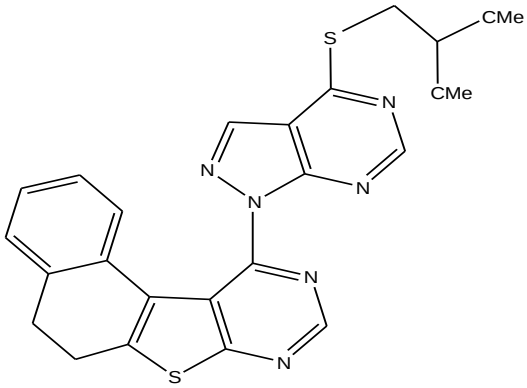


(24)

Compounds	Ar
24a	
24b	
24c	
24d	
24e	
24f	

3.4. Antiviral activity:

Aymn Rashad *et al* [29] synthesized a new series of compounds in which 4-(Dimethoxyethylsulfanyl)-1-(5, 6-dihydronaphtho [1', 2':4, 5] thieno[2, 3-d] pyrimidine-11yl)- 1*H* – pyrazolo [3, 4-d] (**25)** have antiviral activity against hepatitis-A virus (HAV) and herpes simplex virus stype-1 (HSV-1).



(25)

Conclusion:

NSAIDs are very important anti-inflammatory drugs that are widely accepted to exert this function mainly through inhibition of COX enzymatic activity. Pyrazole possess analgesic and anti-inflammatory activity. It has been reported that novel series of pyrazole derivatives displaying properties as COX- 2 selctive enzymatic inhibitors have an important immunosuppression and anti-inflammatory effect inhibiting T cell activation. These immunomodulatory properties are likely to be independent of their ability to inhibit COX enzymatic activity and could explain some of the COX-independent anti-inflammatory actions of related NSAIDs

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