Vol. 2, No.1, June 2017, 15-25 ISSN: 2456-9720

RNT Journal of Current Discovery in Chemistry
An International Peer Review Journal of Science
www.rntjcdc.com

Research Article

A Review: Biological activity and synthesis of Pyrazole derivatives

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Received:- 03/March /2017 Revised :-27/June /2017 Accepted :- 16/July/2017

Abstract

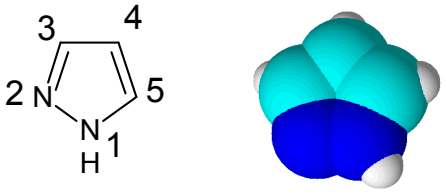
In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. In medicine, derivatives of pyrazoles are used for their analgesic, antinociceptive, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, analeptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic, antifungal, and antibacterial activities. The pyrazole ring is found within a variety of pesticides as fungicides, insecticides and herbicides, including chlorfenapyr, fenpyroximate, fipronil, tebufenpyrad, tolfenpyrad, and tralopyril.

Keywords Pyrazole, Marketed drugs.

Introduction and Review of Pyrazole

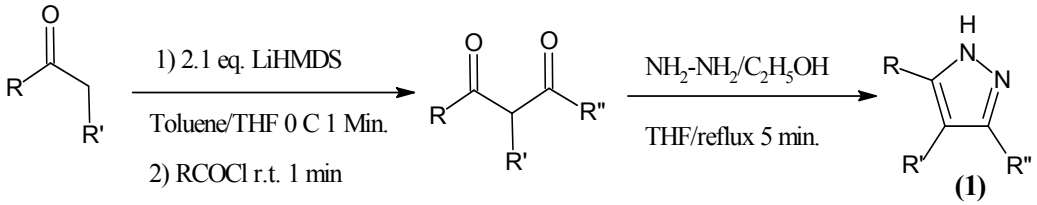
Pyrazoles

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclicdiazole series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, these are classified as alkaloids, although they are rare in nature [1]. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. The term pyrazole was given to this class of compounds by Ludwig Knorr in 1883.



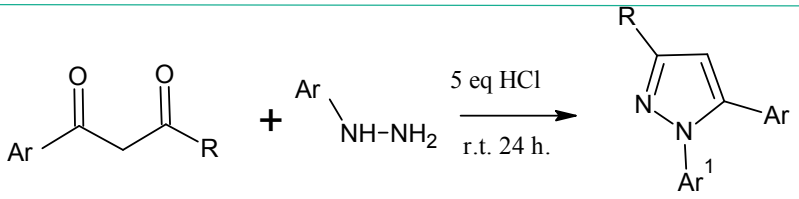
Synthetic aspects Pyrazole:

1,3-Diketones, which were synthesized in situ from ketones and acid chlorides, were converted into pyrazoles **(1)** by the addition of hydrazine. This method allows a fast and general synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole-containing fused rings [2].



(1)

Gosselin [3] and co-workers synthesized a highly regioselective 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones with arylhydrazines proceeds at room temperature in *N,N*-dimethylacetamide and furnishes pyrazoles **(2)** in good yields.



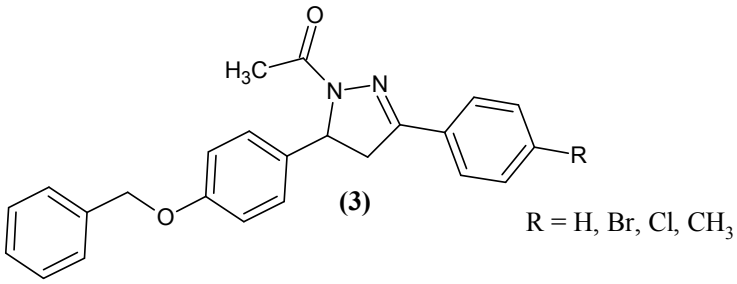
(2)

Pharmacological aspects:

Heterocyclic compounds represent an important class of biologically active molecules. Specifically, those containing the pyrazole nucleus have been shown to possess various biological activities [4] as herbicides, fungicides, analgesics, etc. The pyrazole unit is one of the core structures in a number of natural products. A wide range of biological properties such as analgesic, antiviral, [5,6] antitumor[7] antipyretic, anti-inflammatory[8,9], antidiabetics[10], Insecticidal, matricidal and hypoglycemic activities of pyrazole have been reported [11-13]. Pinto [14] has reported medicinal importance of pyrazole derivatives. Incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages. Much work has been directed toward the design and synthesis of fused-pyrazole derivatives [15-20]. The following paragraphs describe in brief, the biological activities elucidated by the presence of pyrazole moiety in various compounds.

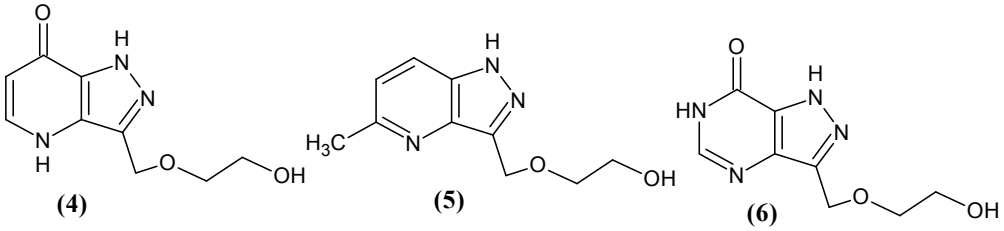
Antiviral activity

Osama *et. al*.,[21] were synthesized new *N*-acetylpyrazole **(3)**derivatives and evaluated for antiviral activity[22,23], against a broad panel of viruses using different cell cultures where as *N*-acetylpyrazole showed the best antiviralactivity against vaccinia virus (Lederle strain) in HEL cell cultures with an EC_{50} value of 7 µg/ml.



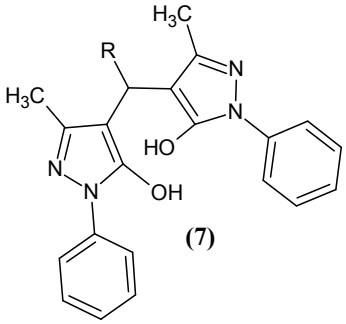
(3) R = H, Br, Cl, CH_3

5-amino or 7-hydroxy substituted pyrazolo[4,3-*b*]pyridine **(4)**, **(5)**and pyrazolo[3,4-*c*]pyridine **(6)** acyclic *C*-nucleosides were synthesized by Nikolaos *et, al*.,[24] and evaluated for their antiviral activity against a wide panel of viruses.



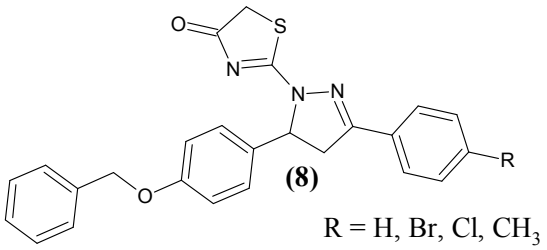
(4) **(5)** **(6)**

Kuppusamy Sujatha *et al*.,[25] synthesized 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) **(7)** by Knoevenagel–Michael reaction of two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one with various aromatic aldehydes catalyzed by ceric ammonium nitrate (CAN) in water. All the synthesized compounds were evaluated for in vitro antiviral activity against *peste des petits ruminant virus* (PPRV).



(7)

Some pyrazolothiazolone **(8)** and pyrazolothiazole **(9)** derivatives have been synthesized by Osama *et al*.,[26] and evaluated against a broad panel of viruses using different cell cultures whereas *N*-acetyl pyrazole showed the best antiviral activity against vaccinia virus (Lederle strain) in HEL cell cultures with an EC_{50} value of 7 μg/ml.



(8)

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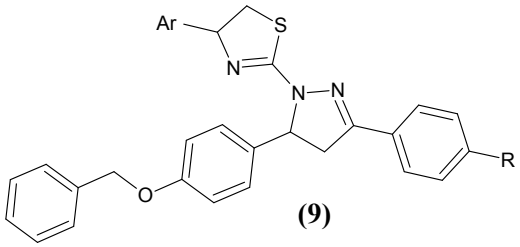
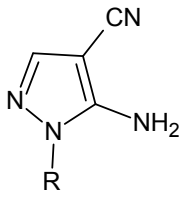


(9)

Aymn E. Rashad [27] and co-workerssynthesized substituted pyrazole **(10)**, **(11)** and **(12)** derivatives. These derivatives showed promising antiviral activity against hepatitis A virus and Herpes Simplex virus type-1 using plaque infective assay.



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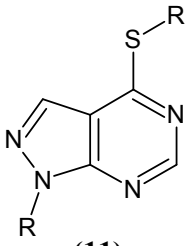

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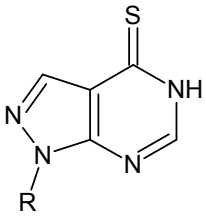
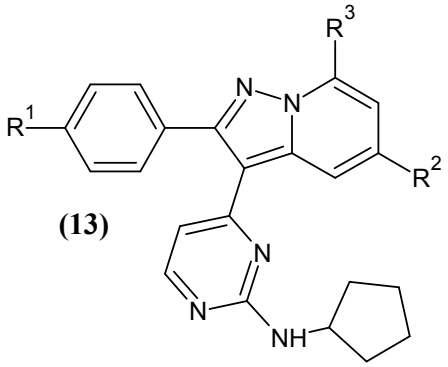


(12)

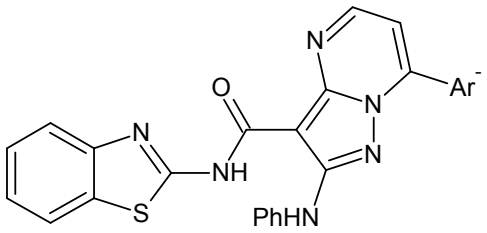
A series of 5-substituted as well as 5,7-disubstituted 3-[2-(cyclopentylamino)-4-pyrimidinyl]-2-phenylpyrazolo[1,5-*a*]pyridin-7-amines [28] **(13)** were synthesized by Kristjan *et al*., and tested with potent activity against herpes simplex viruses is described.



(13)

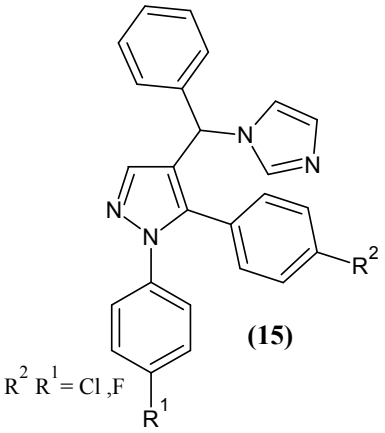
Antimicrobial activity

Sridhar [29] *et al.*, have synthesized a series of substituted pyrazole **(14)** derivatives. The compound was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 μ/ml) against *A. fumigatus* &*F. Oxysporumcomparabe* with *Chloroamphenicol*.



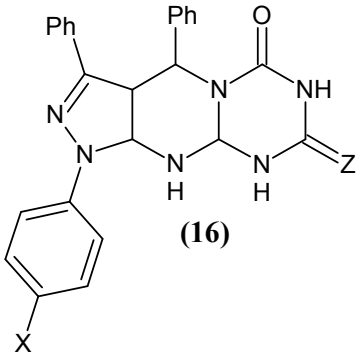
(14)

Pyrazole derivatives of halogenated 4-[1*H*-imidazol-1-yl(phenyl)methyl]-1,5-diphenyl-1*H*-pyrazoles **(15)** were synthesized by Menozzi and co-workers [30].These compounds were screened for antimicrobialactivity.



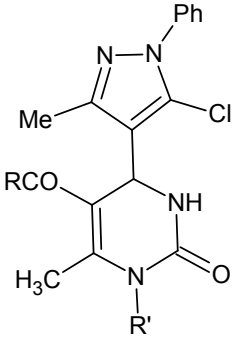
(15)

Ayoob Bazgir [31] and colleagues used one-pot and efficient method for the synthesis of pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-dione **(16)** derivatives by condensation reaction of barbituric acids, 1*H*-pyrazol-5-amines and aldehydes under solvent-free conditions. These products were evaluated *in vitro* for their antibacterial activities.



(16)

Rakesh [32] *et al.*, have synthesized new derivatives of pyrazole **(17)** by hantzsch cyclisation and modified bignelli's reaction and all the compounds showed good to moderate activity.



a= OEt, R=H

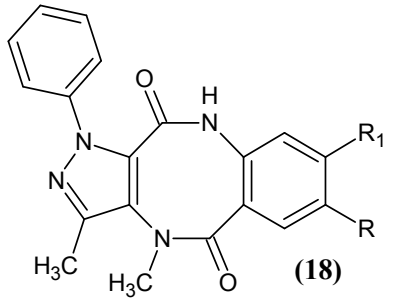
b=OMe, R= H

(17)

Antibacterial activity.

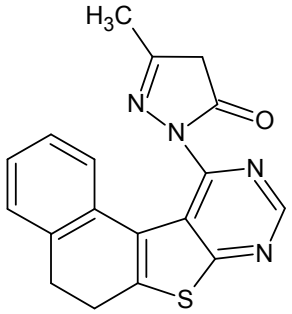
The pyrazole nucleus represents a very attractive scaffold to obtain new molecules endowed with antibacterial activity. As an example, the central ring of Celecoxib, one of the most COX-2- selective inhibitors, has

a pyrazole nucleus[33] Moreover, several Celecoxib analogs showing interesting selective COX-2 inhibition have been synthesized.[34-37] Selective COX-2- inhibiting activity for 1*H*-pyrazolylbenzo[*d*]thiazoles,1*H*-pyrazolylbenzo[*d*]oxazoles, and 1*H*-pyrazolylbenzo [*d*]imida zoles as well as bicyclic pyrazoles have been described.[38,39].Onofrio [40] *et al.* have synthesized 7-R1-8-R2-1-ethyl-3,4-dimethyl-4,10-dihydro-1*H*-pyrazolo[3,4-*c*][1,5]benzodiazocine-5,11-diones **(18)** and evaluated for antibacterial activity.



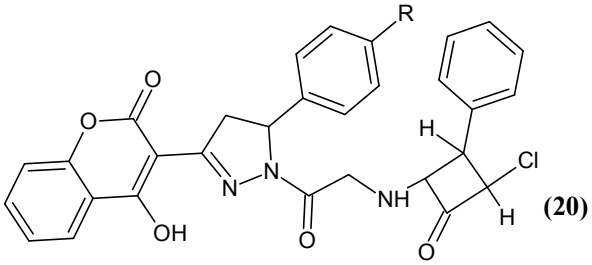
(18)

Aymn El-Sayed Rashad [41] *and* co-workers have synthesized 1-(5,6-dihydro naphtha [1′,2′:4,5]thieno[2,3-*d*]pyrimidin-11-yl)-pyrazole **(19)** derivatives and all the compounds show anti bacterial activity.



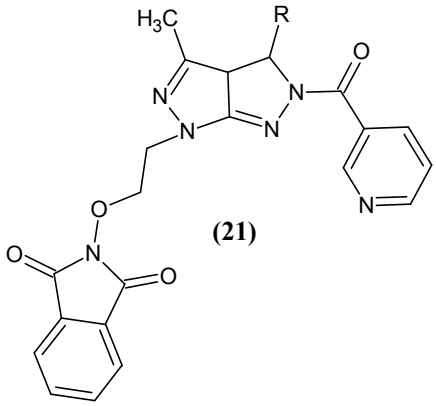
(19)

Pawar [42] *et al.,* reported derivatives of 5-Aryl-N-[(3-chloro-2-oxo-4-phenylazetidin-1-ylamino) acetyl]-3-[2H-4-hydroxy-2-oxo-benzopyran-3-yl]-4,5-dihydropyrazoles (**20)** compounds. All the compounds were screened *in vitro* for their Antimicrobial activity against a variety of bacterial strains such as *Staphylococcus aureus, Salmonella paratyphi,* and *Escherichia coli.*



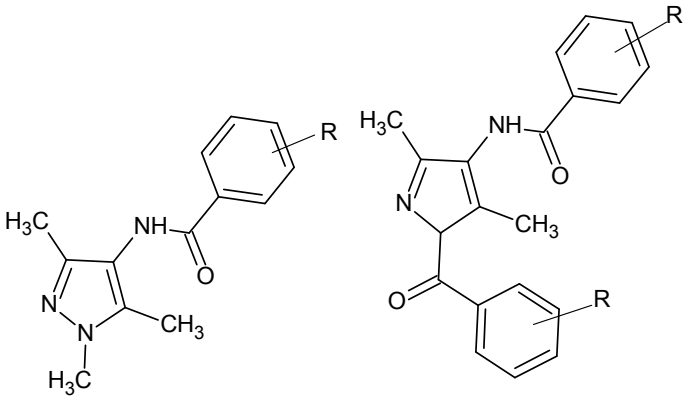
(20)

Derivatives of N-ethoxyphthalimido-3-phenyl-4-methyl-3a,6-dihydropyrazolo[3,4-c]pyrazol-2(3H)-yl(pyridin-3-yl)methanone **(21)** were synthesized by Talesara and co workers [43].The title compounds were screened for their antibacterial and antifungal activities using cup and well method[44]. Antibacterial activity of compounds (500µg/ml) was evaluated against four bacterial strain viz. *E. coli,P. aeruginosa, S. typi* and *B.subtilis*.



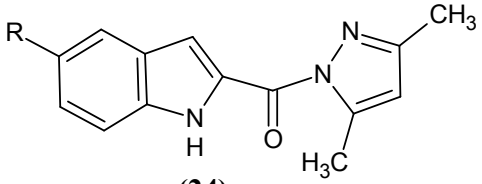
(21)

Some N-(3,5-di-/1,3,5-trimethylpyrazole-4-yl)-4-substitutedbenzamide [45] **(22)** and **(23)** derivatives were prepared by Bedia Kocyigit and all the compounds were screened for anti bacterial activity.



(22) **(23)**

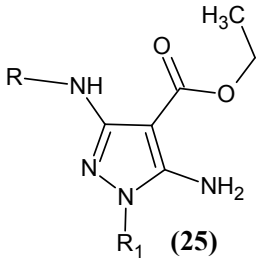
Narayana *et al* [46] have synthesized derivatives of (3,5-dimethyl-1*H*-pyrazol-1-yl)(1*H*-indol-2-yl) methanone **(24)**, screened for anti bacterial activity and anti-inflammatory activity.



(24)

Anti-inflammatory activity

Some new pyrazole **(25)** derivatives have synthesized by Suresh B. and co-workers from propenoates and hydrazines. These compounds were screened for their analgesic and anti-inflammatory activities [47]. A significant correlation between *in vitro* and *in vivo* anti-inflammatory activity was reported.

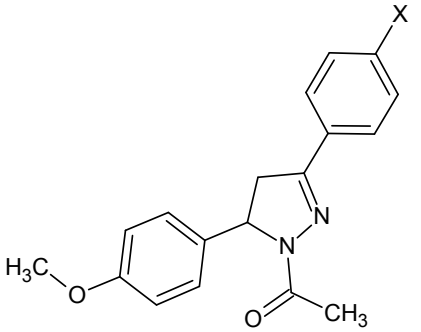


R = p-BrAr, p-ClAr, p-No_2Ar, p-OHAr.

R_1= H, Ph

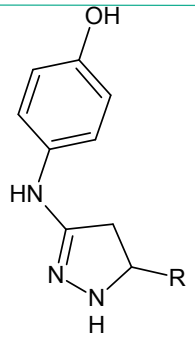
(25)

Kapupara Pankaj [48] *et al.* reported a series of 1-acetyl-3-aryl-5-(4-methoxy phenyl) pyrazoles **(26)** derivatives and were tested for antiinflammatory activity against carrageenan-induced rat paw edema.



(26)

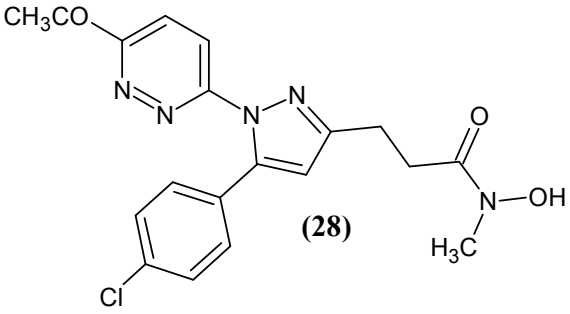
A series of 4-(5-substituted aryl-4,5-dihydropyrazole-3-yl-amino)phenols **(27)** have been synthesized by treating substituted aryl-N-chalconyl amino phenols with hydrazine hydrate.The synthesized compounds were investigated for analgesic, anti-inflammatory [49] and antimicrobial activities.



(27)

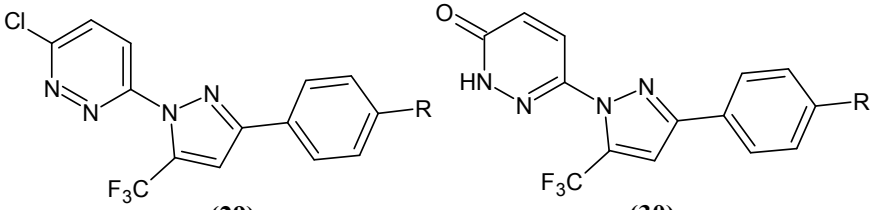
Analgesic activity

The first examples of dual acting analgesic and anti-inflammatory molecules was tepoxalin, which is a diarylpyrazole derivative [50]. Dogruer *et al*. synthesized [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetamide **(28)** and propanamide derivatives and reported that these compounds showed potential analgesic activity [51].



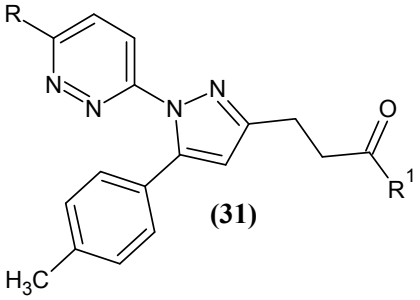
(28)

A series of regioisomeric 1-(3-pyridazinyl)-3-arylpyrazole **(29)** and 1-(3-pyridazinyl)-5-arylpyrazole **(30)** derivatives were synthesized by Serdar U and co-workers [52]. The compounds were preliminarily screened at 8 mM concentration for their analgesic activity against cyclooxygenase enzymes, COX-1 and COX-2, using a human whole blood test.



(29) **(30)**

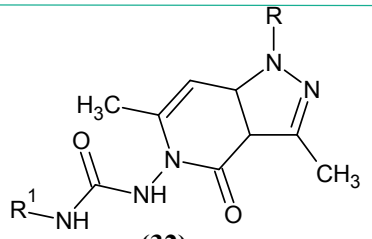
A series of structurally diverse amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl] propanoic acids [53] **(31)** were prepared and tested for their *in vivo* analgesic activity using an acetic acid induced writhing test [54].



(31)

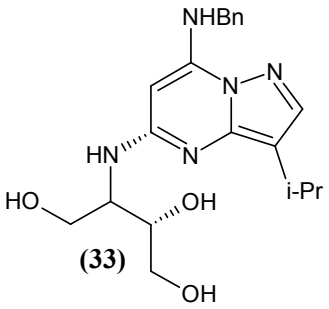
Anticancer activity

Faidallah [55] and co-workers synthesized some polysubstituted fused heterocyclic ring systems namely pyrano[4,3-c]pyrazoles and pyrazolo[4,3-c] pyridines **(32)** respectively and tested for anticancer and antimicrobial activities.



(32)

Dean [56] synthesized pyrazolo[1,5-a]pyrimidine **(33)**, **(34)** derived compound, as a selective and potent CDK inhibitor, which inhibits CDK2, CDK1, CDK5, CDK7, and CDK9 (IC_{50}= 3, 30, 30, 250, and 90 nmol/L, respectively).



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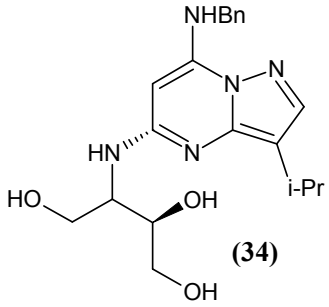
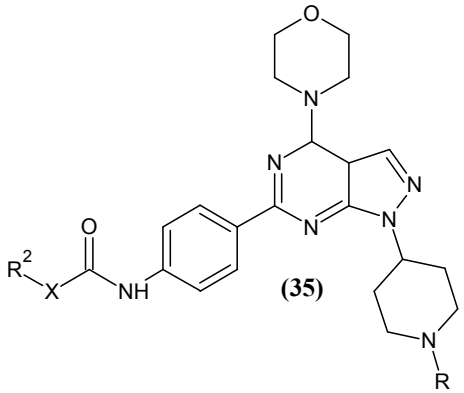


(34)

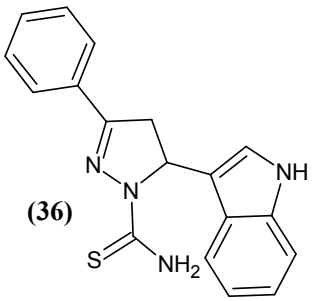
Zask [57] reported the mammalian target of rapamycin pyrazolopyrimidine **(35)** compounds which were high potent of anticancer activity [58-61].



(35)

Antitumor activity

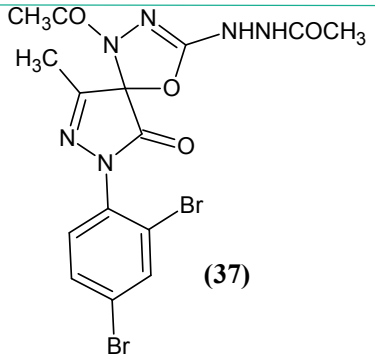
A series of 4,5-Dihydro-5-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)pyrazole-1-carbothioamide **(36)** derivatives were synthesized by Nassar and colleagues and screened against antitumor [62] and antimicrobial activity.



(36)

Cytotoxicity effects

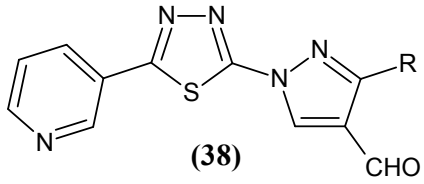
Ahasan [63] *et al*., synthesized pyrazolone heterocyclic compound 5-spiro[-3-methyl-(2′,4′-dibromophenyl)-2-N-acetyl-1,3,4-diazoline **(37)**, Their cytotoxicity effects were measured by brine shrimp lethality bioassay**.**



(37)

Antitubercular activity

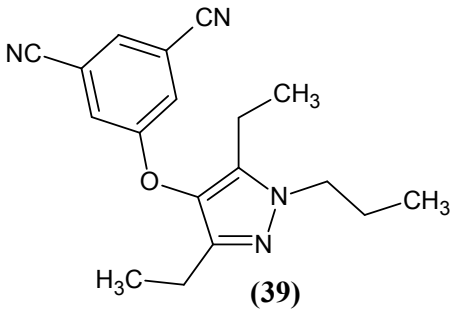
A series of novel 3-Aryl-1-[(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl]-1*H*-pyrazole-4-carbaldehydes [64] **(38)** were synthesized from (Aryl)ethanone-1-(5-(pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-hydrazones by applying Vilsmeier-Haack reaction. Their antioxidant and antitubercular activities have been studied. All the synthesized compounds have shown good antitubercular activity.



(38)

Anti HIV

Charles [65] and coworkers have synthesized 3-cyanophenoxypyrazole **(39)** and evaluated against anti-HIV activity*in vitro*.



(39)

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