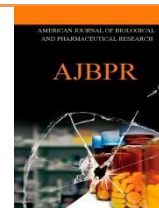




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PYRIDAZINONES: A WONDER NUCLEUS WITH SCAFFOLD OF PHARMACOLOGICAL ACTIVITIES

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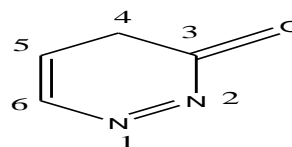
ABSTRACT

During recent years pyridazinones have been a subject of intensive research owing to their wide spectrum of pharmacological activities. The pyridazinone derivatives show a wide spectrum of biological activities, as described in the literature. A number of compounds such as Levosimendan, Amipizone, Indolidan, Imazodan and Pimobedan are few examples of pyridazinones that are active as cardiotoxic agents. The synthesis of novel pyridazinone derivatives and investigation of their chemical and biological activities have gained more importance in recent years. The biological profile of these new generations of pyridazinones presents much progress with regards to the old compounds.

INTRODUCTION

The discovery of novel series of 3(2H)-pyridazinones possess characteristic pharmacological and biological activities. Thus, the pyridazine and its 3-oxo derivatives, i.e., the pyridazinones have attracted a great deal of attention because of the wide spectrum of their pharmaceutical and agrochemical activities. They are widely recognized as versatile scaffolds with a diverse set of biological activities, such as analgesic, anti-inflammatory, antidepressant, antihypertensive, antithrombotic, diuretics and anti-HIV. Certain pyridazinone derivatives containing the 2-phenyl-indolyl moiety have shown anti-tumour activity [1-3]. Siddiqui et al synthesized and evaluated the pyridazin-3(2H)-one antinociceptive, activities of the compound having

6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydroderivatives. 3(2H)-Pyridazinone derivatives have been reported as analgesic and anti-inflammatory agents without gastrointestinal side effect. (3) The synthesis of novel pyridazinone derivatives and investigation of their chemical and biological behaviour have gained more importance in recent decades for biological, medicinal, and agricultural reason.



Pyridazinone are six-member heterocyclic compounds, 2 nitrogen atoms are present at adjacent positions. Pyridazin-3-one, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as a magic moiety (wonder nucleus) which possess almost all types of biological activities [4]. Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds. The pyridazine nucleus represents a versatile scaffold to

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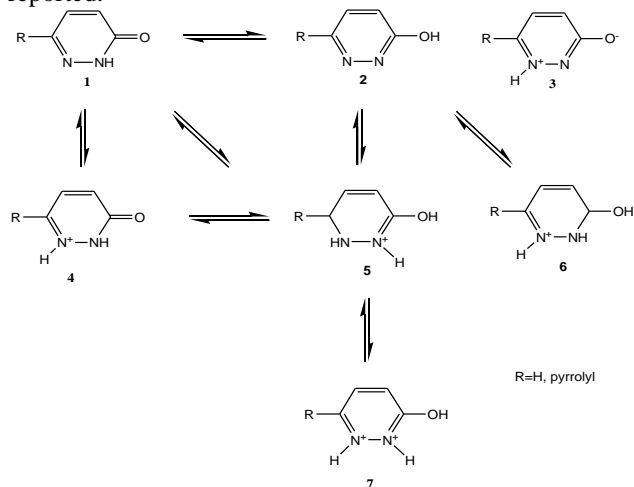
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develop new pharmacologically active compounds. This nitrogen heterocycle is included in chemicals with a wide range of biological activities and can also be used to link other pharmacophoric groups [5].

TAUTOMERIC STUDY OF SOME PYRIDAZINONES

The pyrrolyl substituent enhances the electron densities on the pyridazine ring and has the effect of shifting the positions of the tautomeric equilibrium for **1** \rightleftharpoons **2**, which exist predominantly as the pyridazine-3-one form, towards the hydroxyl structure, compared with those for the parent unsubstituted systems. Protonation of the potentially tautomeric pyridazine systems **1** \rightleftharpoons **2** can lead to three monocationic species: a common N-protonated species **5**, which would be formed from both tautomers and two other monocations **4** and **6**, which would be produced specifically from **1** and **2**, respectively. Thus, the observed pKa values for the conjugated acids of the tautomeric systems **1** \rightleftharpoons **2** would be expected to reflect not only the tautomeric equilibrium constants but also the ratio-averaged values for the ionization of the appropriate monoprotonated conjugate acid pairs **4** \rightleftharpoons **5** and **5** \rightleftharpoons **6**. A third tautomeric (zwitterionic) form **3**, which on protonation would give rise to **4** or **6**, is also possible, but is excluded from this study on the basis of AM1 MO calculations for the three tautomeric forms, which indicate that **3** would contribute less than 0.1% to the tautomeric equilibria. Subsequent protonation of the each of the monocationic species, **4**, **5** and **6**, produces only the single dication **7**. Evidence has been provided indicating that the parent tautomeric systems **1** \rightleftharpoons **2** exist predominantly as the oxo forms and cursory studies indicating similar tautomeric equilibrium positions for substituted derivatives have also been reported.

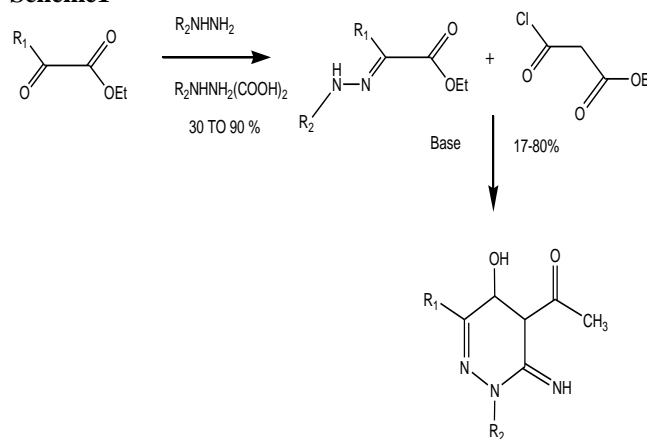


Various Tautomers of Pyridazinones

GENERAL METHODS FOR THE SYNTHESIS OF PYRIDAZINONES: Several conventional methods for synthesis of pyridazinones are available in literature. Some commonly used are given below:

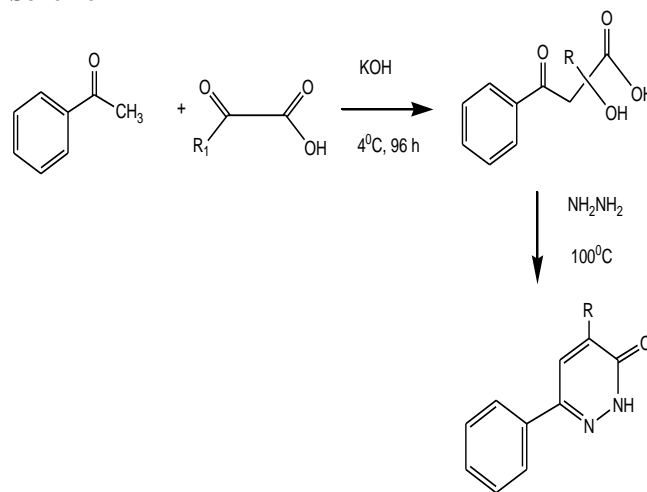
From diketones- To a solution of the corresponding diketone in DMF was added at 80°C, a solution of cyanoacetohydrazide in DMF. The mixture was heated at 100°C until the reaction was completed (TLC). Then the solution was concentrated under vacuum. The residue was purified by re-crystallisation from the appropriate solvent or by column chromatography using the appropriate eluents (Scheme 1) [7].

Scheme 1



From 1,2-diketones- It is a useful synthesis of 3(H) pyridazine (pyridazinone) involve the reaction of ketones with hydrazinederivatives in the presence of an ester containing an active methylene group (Scheme 2).

Scheme 2

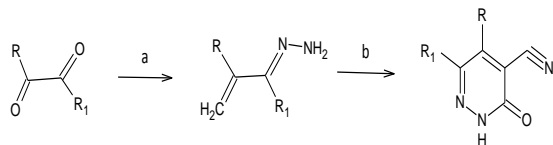


Synthesis from monohydrazone and dimethylmalonate derivatives

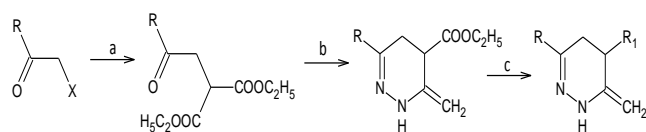
General methods for the preparation of monohydrazone

The method utilised for the synthesis of pyridazines derivative is outlined in scheme. The necessary 1, 2- dicarbonyl compounds were commercially available or easily prepared following previously described methods. A suspension of the corresponding diketone in absolute ethanol containing an excess of $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ was heated at reflux temperature until the reaction was completed. After the solution was cooled, the formed was isolated by filtration and purified by re-crystallisation from the appropriate solvent or by column chromatography using the appropriate eluents (Scheme 3).

Scheme 3



Reagents: (a) NH_2NH_2 , $\text{C}_2\text{H}_5\text{OH}$; (b) Na, $\text{C}_2\text{H}_5\text{OH}$, ethylcyanoacetate; (2) 1N HCl; (c) cyanoacetohydrazide, $\text{C}_2\text{H}_5\text{OH}$, or DMF

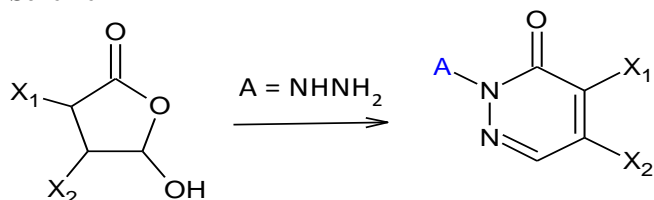


X = Cl, Br

(a) diethylmalonate, K_2CO_3 , KI; (b) NH_2NH_2 , $\text{C}_2\text{H}_5\text{OH}$; (c) Br_2 , AcOH

Direct ring synthesis- Most preparation of the pyridazinone derivatives depend on the nucleophilic substitution of the starting material of these derivatives, prepared from monochloric acids. 4, 5-dihalo-3(2H)-pyridazinone derivatives were prepared by different reaction such as direct ring synthesis, alkylation, and halogen exchange reaction (Scheme 4).

Scheme 4



A = H, Ph, Py, Bu

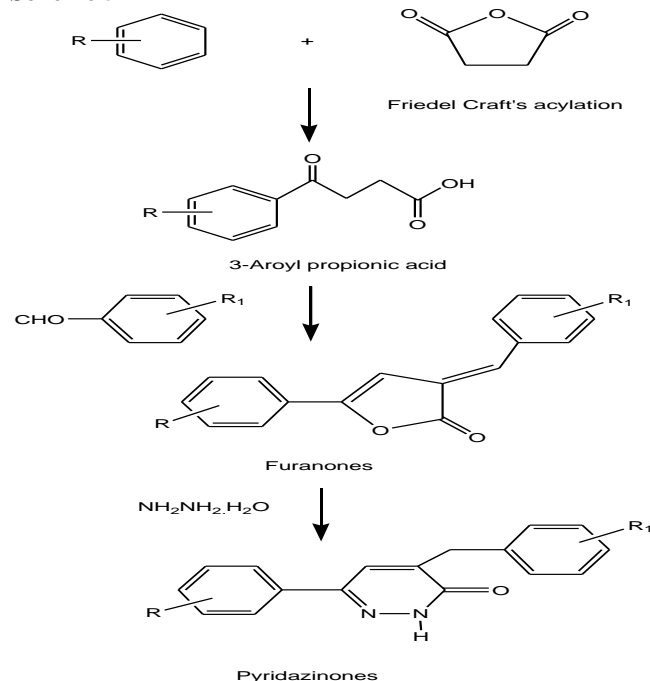
X₁ X₂ Cl, Br

From furanones

Various 2(3H)-Furanones on reaction with hydrazine hydrate in n-propanol yielded various pyridazinone derivatives i.e. 5-(substituted benzyl)-3-aryl-

1,6-dihydro-6-pyridazinone derivatives. 2(3H)-Furanones were prepared using 3-(4-substituted benzoyl) propionic acid following the previously reported methods of modified Perkin's reaction in higher yields. The 3-(4-substituted benzoyl) propionic acid was synthesized according to Friedel Craft's acylation reaction condition using chlorobenzene or toluene (Scheme 5) [9].

Scheme 5



PYRIDAZIN-3(2H)-ONES: THE VERSATILE PHARMACOPHORE OF MEDICINAL SIGNIFICANCE [9]

Pyridazin-3(2H)-one derivatives have attracted the attention of medicinal chemists during the last decade due to their diverse pharmacological activities. Easy functionalization of various ring positions of pyridazinones makes them an attractive synthetic building block for designing and synthesis of new drugs. The incorporation of this versatile biologically accepted pharmacophore in established medicinally active molecules results in wide range of pharmacological effects. Pyridazinones constitute an interesting group of compounds, many of which possess wide spread pharmacological properties such as antihypertensive, platelet aggregation inhibitory, cardiotoxic activities and some are also well known for their pronounced analgesic, anti-inflammatory, antinociceptive, and antiulcer activities. Recently pyridazinones have also been reported as antidiabetic, anticonvulsant, antiasthmatic, and antimicrobial agents. These encouraging reports suggest that this privileged skeleton should be extensively studied for the therapeutic benefits.



Anti-inflammatory Activity

Abouzid et al synthesized a series of pyridazinone containing compounds as congeners for diclofenac, the most potent and widely used NSAID. Seven of the tested compounds demonstrated more than 50% inhibition of carrageenan-induced rat paw edema at a dose 10 mg/kg. The compounds, 6-(2-bromophenylamino)pyridazin-3(2H)-one (Fig 8) and 6-(2,6-dimethylphenylamino)pyridazin-3(2H)-one (Fig 9) displayed 74 and 73.5% inflammation inhibitory activity, respectively which is comparable to diclofenac (78.3%) at the same dose level after 4h. The most active compounds as anti-inflammatory agents in Fig 1 and Fig 2 displayed fewer numbers of ulcers and milder ulcer score than indomethacin in ulcerogenic screening.

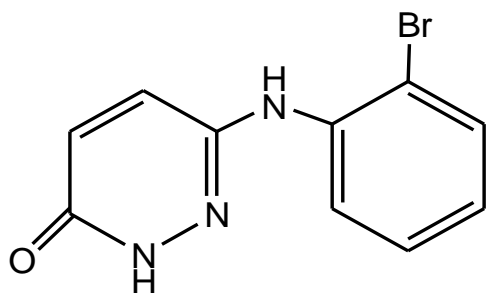


Fig 8

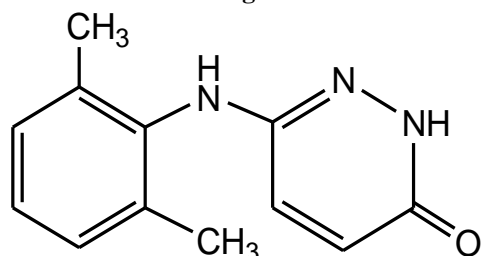


Fig 9

The presence of bromine at position 2 in Fig 8 or 2,6-dimethyl group in Fig 9 in the aromatic ring gave rise to an increased anti-inflammatory activity (74 & 75%), respectively. It was observed that substituting 2-chloropyridyl function at the 6-aminopyridazinone seems preferable for obtaining an effective anti-inflammatory agent [10].

Rafia Bashir et al synthesized seven novel 6-aryl-2-(p-sulfamoylphenyl)-4,5-dihydropyridazin-3(2H)-ones by the condensation of appropriate aroylpropionic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol. Structure of all compounds was elucidated by elemental analysis IR, ¹H NMR, ¹³C NMR, DEPT and MS spectroscopy.

These compounds were tested for their anti-inflammatory activity in carrageenan-induced rat paw edema model. Compound in Fig 10 exhibited anti-inflammatory activity comparable to that of celecoxib (at

5h). Two other compounds in Fig 11 and Fig 12 showed promising anti-inflammatory activity (edema reduction more than 80% at 5h) [11].

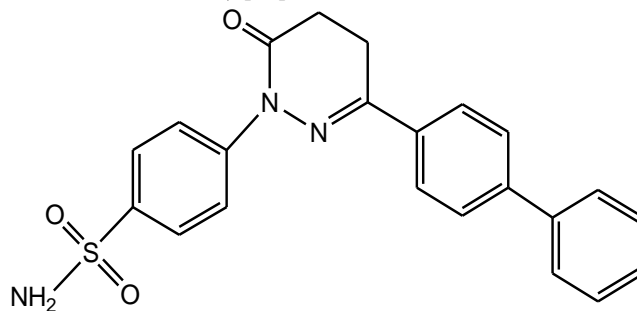


Fig 10

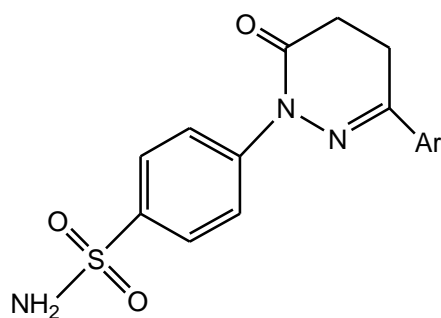
Ar=C₁₀H₇

Fig 11

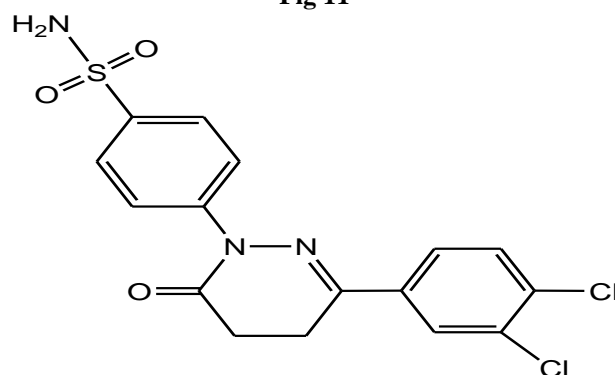


Fig 12

Khaled AM Abouzid et al designed compounds containing central bicyclic quinoxaline scaffold carrying only one phenyl ring and pyridazinone moiety as a replacement of sulfamoylphenyl or sulfonylphenyl group. The benzene portion of the fused quinoxaline ring was used to cover the area occupied by the CF₃ group of celecoxib. Bicyclic quinoxaline nucleus attached to pyridazinone and phenyl substituents formed potent anti-inflammatory novel structures especially chloroanalogue in Fig 13. The *in vivo* high potency of compound in Fig 13 is comparable to that of diclofenac. This combination constitutes an important development of the nonclassic bicyclic COX-2 inhibitors because it is a novel bicyclic nonsulfonated compound with high *in vivo* anti-inflammatory activity. The structure-based



molecular design accurately predicted the inherent activity of the scaffold and the rank of potency of the compounds in Fig 13-15 [12].

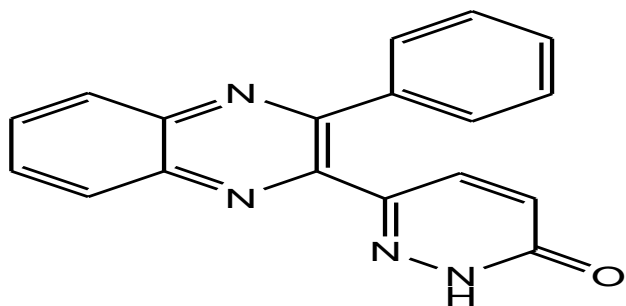


Fig 13

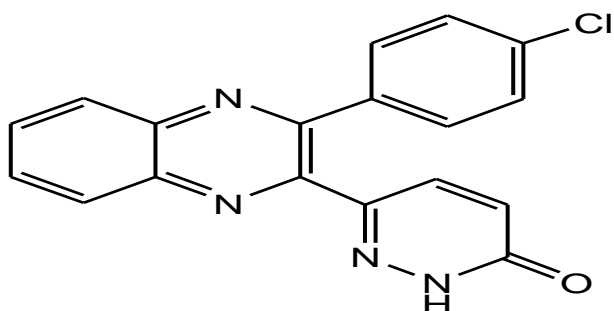


Fig 14

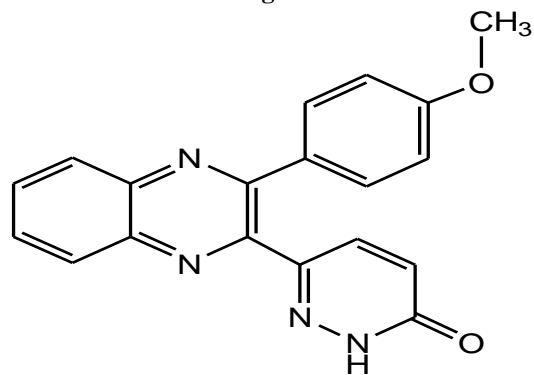


Fig 15

Khaled Abouzid et al reported the design, synthesis, and pharmacological properties of a series of arylolethylpyridazinones and arylolethylpyridazinone derivatives from the corresponding arylohexenoic and arylohexanoic acids respectively. A series of pyridazine derivatives linked at C(6) to aryl or biphenyl moieties through two carbon spacers. The synthesized compounds exhibited anti-inflammatory activity and superior gastrointestinal safety profile. The results of biological screening also revealed that Compound in Fig 16: 6-[2-(Biphenyl-4-yl)ethyl]-4,5-dihydropyridazin-3(2H)-one and Compound in Fig 17: 6-[2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)ethyl]-4,5-

dihydropyridazin-3(2H)-one in which ethyl spacer between the dihydropyridazinone ring and the aryl moiety exhibits the highest activity compared to the ethenyl analogs. Therefore, these compounds could be speculated as selective COX-2 inhibitors [13].

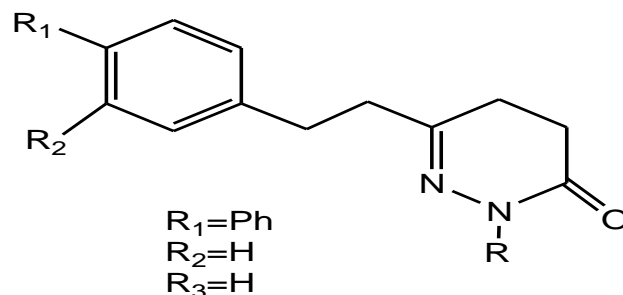


Fig 16

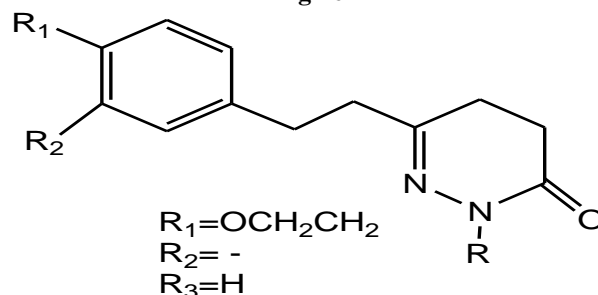
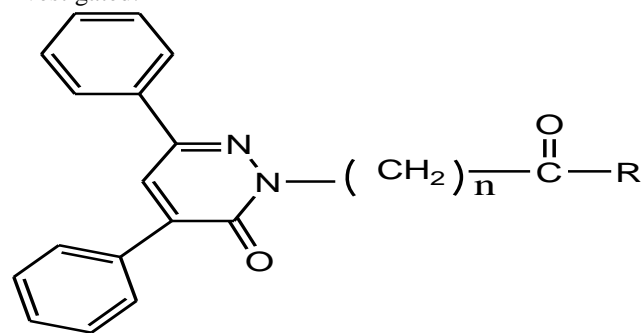


Fig 17

Deniz S. Dogruer et al synthesized new 4,6-diphenyl-3(2H)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonylalkyl moieties Fig 18 on the nitrogen atom in the 2nd position of the pyridazinone ring and their analgesic and anti-inflammatory activity was investigated.



R= piperazines_{n=1,2}

Fig 18

All compounds showed significant analgesic activity at 100 mg/kg dose level in ratios from 55.6 to 82.7%. However, the more active compounds in terms of anti-inflammatory activity were found in acetamide derivatives in general. When the chemical structures of the active compounds are taken into consideration, it appears that substitutions on the phenyl ring of the phenylpiperazine moiety by *o*- or *p*-fluoro groups or a 2-pyridyl group



increased both the analgesic and anti-inflammatory activity of acetamide derivatives markedly [14].

Analgesic Activity

Mohammad Asif et al synthesized three 6-Phenyl-4-Substituted Benzylidene tetrahydropyridazin-3(2H)-one derivatives (Fig 19-21) from 6-phenyl-4,5-dihydropyridazin-3(2H)-one. All three title compounds in Fig 19-21 exhibited significant ($p < 0.001$) analgesic activities when compared with control group by using hot plate model and less active than Aspirin 100 mg/Kg that was used as reference drug. All the tested compounds exhibited significant analgesic activity when compared to control group. The compound in Fig 20 was found to be most potent. All the compounds were less potent than reference drug aspirin. The result favoured and proved that different substituted pyridazinone compounds play an important role in the analgesic activity [15].

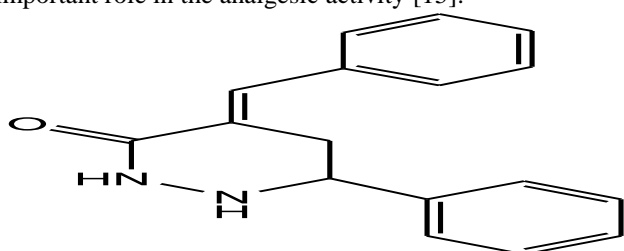


Fig 19

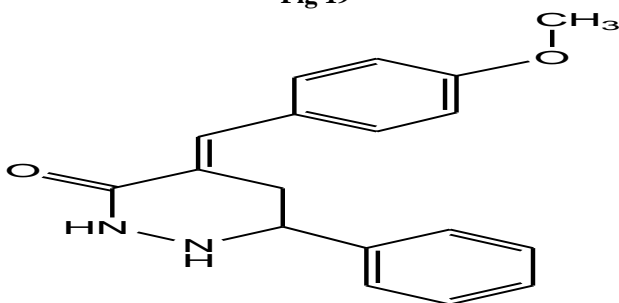


Fig 20

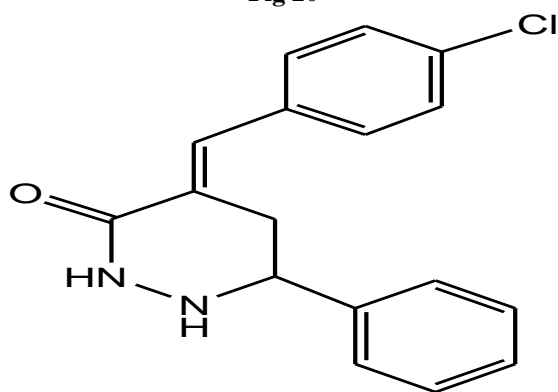


Fig 21

Claudio Biancalani et al designed and synthesized a new series of pyridazinones bearing an

arylpiperazinylalkyl chain. Analgesic activity was assessed in a model of acute nociception induced by thermal stimuli in mice (tail flick). Using a prototypical compound of the series, *in vitro* radioligand binding studies were performed on a panel of adrenergic receptors in order to define the pharmacological profile. These studies led us to identify compound 4-Amino-6-methyl-2-[3-(4-p-tolylpiperazin-1-yl)propyl]-5-vinylpyridazin-3(2H)-one as an exceptionally potent antinociceptive agent and showed an $ED_{50} = 3.5 \mu\text{g}$, a value about 3-fold higher with respect to morphine by the same route of administration [16].

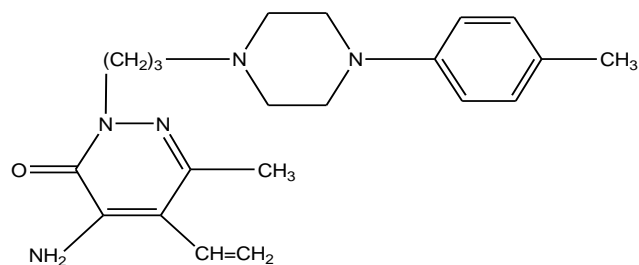
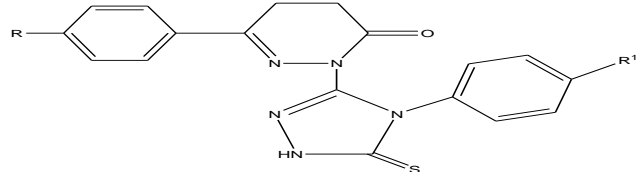


Fig 22

Antihypertensive Activity

Anees A. Siddiqui et al synthesized 6-(substituted phenyl)-2-(4-substituted phenyl-5-thioxo-4, 5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydropyridazin-3(2H)-one derivatives by a sequence of reactions starting from respective aryl hydrocarbons. Amongst the compounds synthesized these compounds showed maximum antihypertensive activity 6-(4-methylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2H)-one, 6-(4-methoxyphenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2H)-one and 6-(4-ethylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]-4,5-dihydropyridazin-3(2H)-one. Therefore, it was concluded that triazole incorporated 4,5-dihydro-3(2H)-pyridazinone derivatives can be further modified to exhibit better potency than the standard drugs. The 4,5-dihydro-3(2H)-pyridazinone derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of hypertension [17].



R = H, CH₃, OCH₃, C₂H₅, CH₂CH(CH₃)₂, C₆H₅, Cl

R¹ = H, Cl, CH₃

Fig 23

Cardiotonic Agents

Dinesh Kumar et al synthesized and pharmacological evaluated 2-substituted-6-(4-



acylaminophenyl)-4,5-dihydropyridazin-3(2H)-ones as potent inodilating agents. The synthesis of target compounds was achieved by Friedel-Crafts acylation of appropriate anilide derivative with succinic anhydride or methylsuccinic anhydride and subsequent cyclization of intermediary keto acids with various hydrazine derivatives. The newly synthesized pyridazinone derivatives were evaluated for cardiotoxic activity using isolated rat atria and for vasorelaxant activity using descending thoracic aortic rings of Wistar rats precontracted with phenylephrine (10^{-6} mol L $^{-1}$). 6-(4-Methanesulfonamidophenyl)-2-phenyl-4,5-dihydropyridazin-3(2H)-one (Fig 24) exhibited significant inodilatory properties and showed vasorelaxant activity in a nanomolar range ($IC_{50} = 0.08 \pm 0.01$ mmol L $^{-1}$) [18].

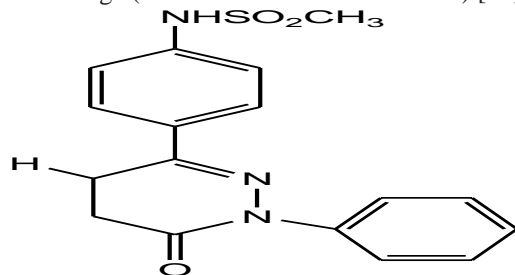
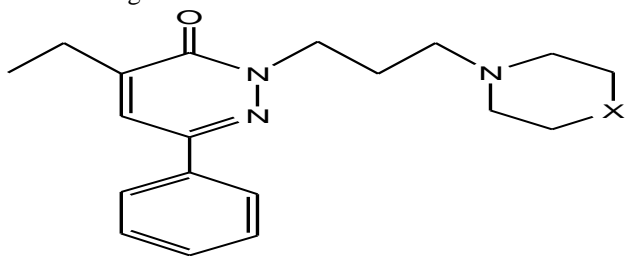


Fig 24

Anticancer Activity

MSR Murty et al synthesized a series of new 4-(aryl/heteroaryl-2-ylmethyl)-6-phenyl-2-[3-(4-substituted piperazine-1-yl)propyl] pyridazin-3(2H)-one derivatives. All the compounds were evaluated for their cytotoxicity toward five human cancer cell lines of different origins viz; HeLa (Cervical), SKBR3 (Breast), HCT116 (Colon), A375 (Skin) & H1299 (Lung) at different concentrations and the IC_{50} values were determined. One of them displayed moderate cytotoxicity against SKBR3. All these compounds possess common 6-phenyl-2H-pyridazin-3(2H)-one nucleus. The substitutions at N-2 and C-4 positions of the pyridazinone moiety play an important role in determining the potency of the compounds. Compounds in Fig 25a, 25b and 25c exhibited good activity against cervical cancer cell line (HeLa). Thus, the activity profile of these pyridazinone-piperzine compounds can be used as new lead molecules in the development of effective anticancer agents.

Fig 25a: R= Phenyl, X= -CH $_2$ CH $_3$ Fig 25b: R= Furyl, X= -CH $_2$ CH $_3$ Fig 25c: R= 2-Thienyl, X= -CH $_2$ CH $_3$

Nahed F Abd El-Ghaffar et al synthesized some new pyridazinones containing the 2-phenyl-1H-indolyl moiety and evaluated these compounds for anti-cancer activity. β -aroylacrylic acid was condensed with hydrazines and hydroxylamine hydrochloride. Simultaneous cyclization of the condensed products yields pyridazinones and Oxazinone. Cytotoxicity and IC_{50} values of the tested compounds were measured. The survival fractions was gradually decreased as the concentration of the tested compounds were increased. Compound in Fig 26 was used as very potent cytotoxic drug for breast carcinoma cell [19].

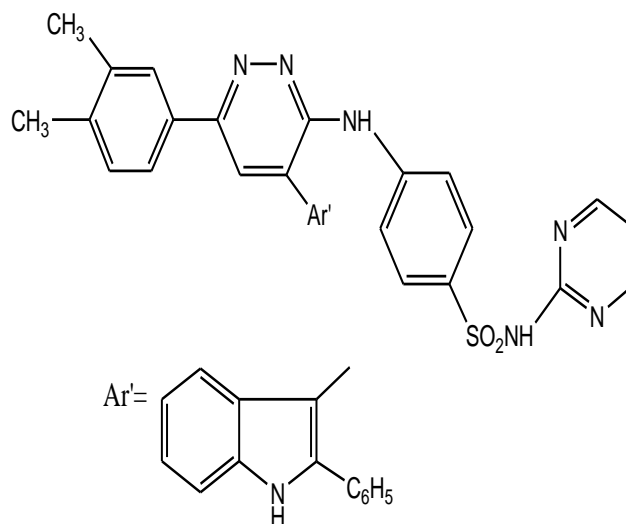


Fig 26

Taleb H. Al-Tel et al synthesized polyfunctional tetrahydro-2H-pyrano[3,2-c]pyridazin-3(6H)-one derivatives and evaluated them biologically as novel anticancer agents. Compounds in Fig 27 and 28 showed antiproliferative activity against the SK-BR-3 breast cancer cell line. Importantly compounds in Fig 27a and 27b showed the highest efficacy, being approximately 30-fold more potent against SK-BR-3 (IC_{50} 0.21 and 0.15 mM, respectively) compared to other cancer cell lines tested. In addition, 21a and 21b displayed about 295 fold less toxicity against normal breast cell line MCF10A compared to SKBR-3 breast cancer cells. These compounds form the foundation for further investigation in our continuing efforts to develop potent anticancer agents [20].

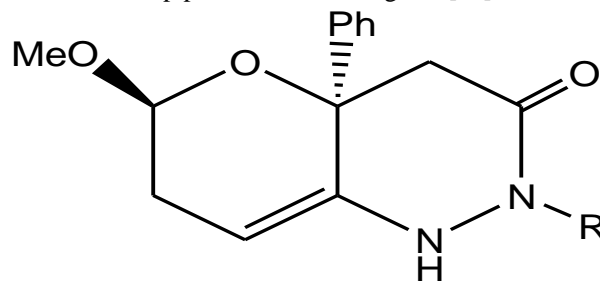
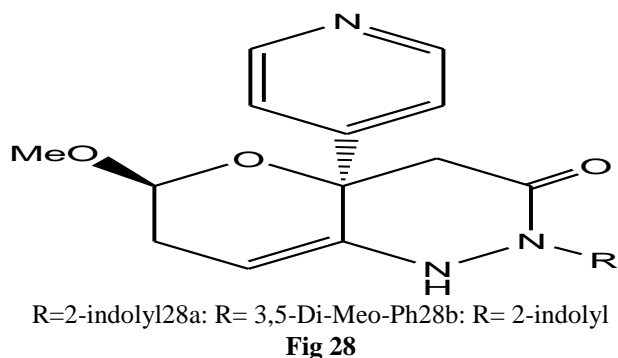


Fig 27





Antibacterial Activity

Alang Gaurav et al synthesized six new derivatives of Pyridazinone and evaluated them for anti-bacterial activity. The experimental work involves the synthesis of benzoyl propionic acid, then 6-phenyl-2,3,4,5-tetrahydro pyridazine-3-one which was then condensed with various aldehydes to form respective derivatives. The antimicrobial activity was performed on the compounds synthesized against *Staphylococcus aureus* (MTCC 737), *Staphylococcus epidermis* (MTCC3615), *Pseudomonas aeruginosa* (MTCC 424) and *Escherichia coli* (MTCC1687). Compounds in Fig 29a and 29b showed excellent activity against E.coli and P.aeruginosa when tested at 50 mg/ml concentration taking ampicillin as the standard. It was concluded that the derivatives of pyridazinone possess moderate to potent antimicrobial activity when compared to standard, ampicillin [21].

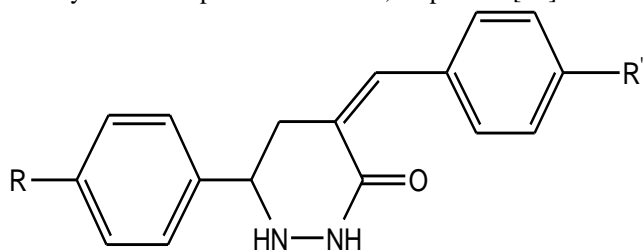


Fig 29a: R= H, R' = Cl
Fig 29b: R=Cl, R' = OCH₃

Anticonvulsant Activity

Mohammad Asif et al synthesized 4-(Benzylidene or substituted benzylidene)-6-(3-nitrophenyl)-4,5-dihydropyridazin- 3(2H)-ones in Fig 30a, 30b, 30c from 6-(3-aminophenyl)-4,5-tetrahydro pyridazin-3(2H)-one by condensation reaction with different benzaldehydes. The title compounds (51a-51c) were evaluated for anticonvulsant activity by maximal electro shock (MES) induced seizure method and these synthesized compounds exhibited significant anticonvulsant activity against MES induced seizure in albino mice after intra-peritoneally administration of 50mg/Kg body weight dose. The potency order of the test compound on the extensor phase:

compounds in Fig 30a>30b>30c>. So, these compounds may be regarded as anticonvulsant [22].

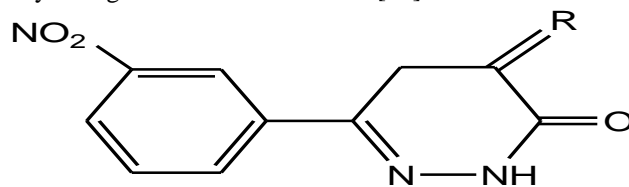


Fig 30a: R= C₆H₅
Fig 30b: R= O-C₆H₄OH
Fig 30c: R= p-C₆H₅OCH₃

Pooja S. Banerjee et al synthesized a series of substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones and 6-aryl-2,3,4,5-tetrahydro-3-thiopyridazinones in Fig 31 and were evaluated for anticonvulsant activity. The anticonvulsant activity of synthesized compounds was evaluated by the maximal electroshock-induced seizure test. Out of the ten compounds subjected to anticonvulsant screening by the M.E.S. method, two compounds showed significant activity. Rest showed moderate anticonvulsant activity [23].

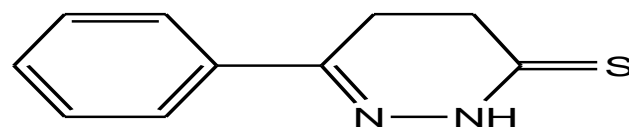


Fig 31

Antifungal Activity

XIA-JUAN ZOU et al synthesized a series of novel 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxadiazoles, which was fungicidally active, based on bioisosterism and tested *in vivo* against wheat leaf rust, *Puccinia recondita*. The 3D-QSAR modes gave good correlation between the variations on percent inhibition and the steric-electrostatic properties. The results are consistent with a common mode of action for the pyridazinone-substituted 1,3,4-thiadiazoles and the pyridazinone-substituted 1,3,4-oxadiazoles, which further confirms that the 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. These offer important structural insights into designing highly active compounds prior to their synthesis [24].

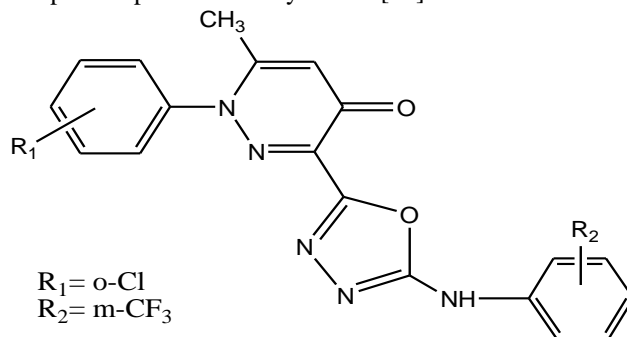
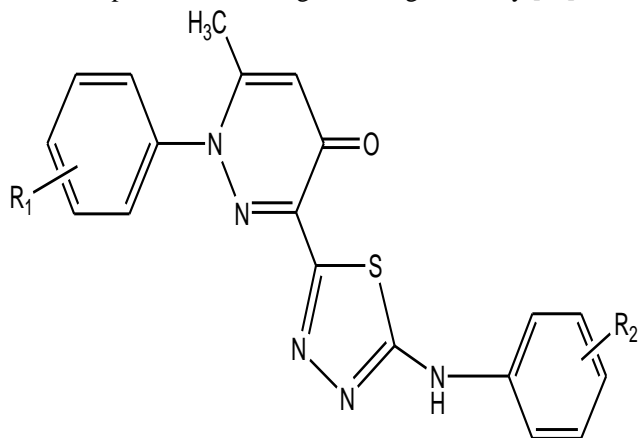


Fig 32



Pyridazinonethiadiazoles used as Anti-fungal agents:

Xia Juan ZOU et al synthesized several 5-[1-aryl-1, 4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles. The preliminary bio-active test shows that these compounds exhibit high antifungal activity [25].

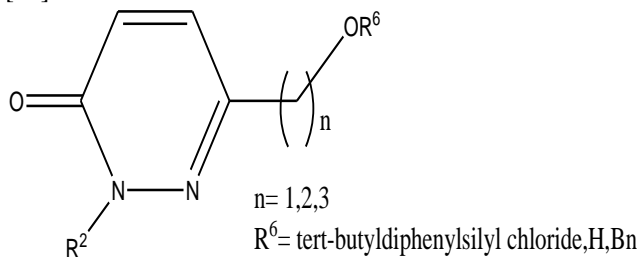


R₁ = p-Cl, R₂ = o-F
 R₁ = p-Cl, R₂ = m-CF₃
 R₁ = o-Cl, R₂ = m-CF₃

Fig 33

Vasorelaxant Activity

Tamara Costas et al synthesized new 6-substituted and 2,6-disubstituted pyridazinone derivatives. These derivatives were obtained starting from easily accessible alkyl furans by using oxidation with singlet oxygen to give 4-methoxy or 4-hydroxybutenolides. The target compounds could show a pharmacological profile as antiplatelet drugs similar to that of aspirin. The new pyridazinone derivatives have been studied as vasorelaxant and antiplatelet agents [26].

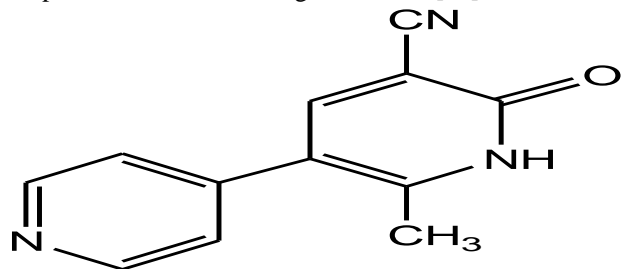


n = 1,2,3
 R⁶ = tert-butyl diphenylsilyl chloride, H, Bn
 R² = H, CH₃, Bn

Fig 34

Khaled Abouzid et al synthesized three series of pyridazinones to identify potential vasodilatory cardiotoxic lead compounds. Compounds with higher fit scores to the developed pharmacophore were synthesized namely; 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2H)-pyridazinones (Fig 35), 6-[4-(2,6-disubstituted-quinolin-4-ylamino)phenyl]-4,5-dihydropyridazin-3(2H)-ones (Fig 36), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino]-

3(2H)pyridazinone (Fig 37). The vasodilator activity of the newly synthesized compounds was examined on the isolated main pulmonary artery of the rabbit. Some of the tested compounds showed moderate vasorelaxant activity compared with standard drug, Milrinone [27].



Milrinone (Std drug)

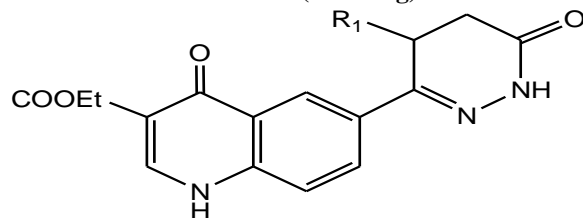
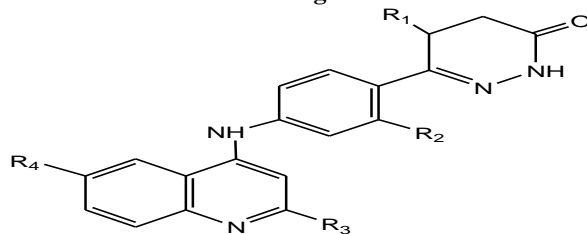


Fig 35



R₁ = H, R₂ = R₃ = CH₃, R₄ = OCH₃

Fig 36

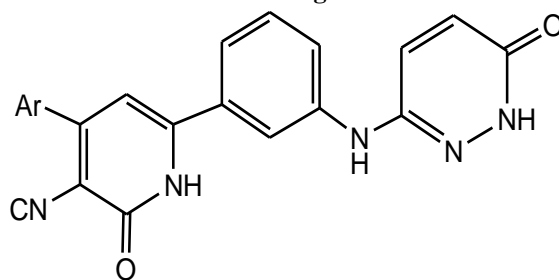


Fig 37

Platelet aggregation inhibitory Activity

Sridhar Thota et al synthesized a series of 6-(4-(substituted - amino)phenyl)-4,5-dihydro-3(2H)-pyridazinones. All of the newly synthesized pyridazinone derivatives exhibited significant platelet aggregation inhibitory activity. The compounds (6-(4-(2-hydroxybenzylamino)phenyl)-4,5-dihydropyridazin-3(2H)-one (Fig 38) and 6-(4-(1H-indol-3-ylmethylamino)phenyl)-4,5-dihydropyridazin-3(2H)-one (Fig 39) were found to be more than twice as potent as standard drug aspirin. A range of 4-substituted-amino phenylpyridazinones on



pharmacological evaluation were found to possess antiplatelet activity. These results showed that the introduction of aryl-amino substituent at para position of 6-phenylpyridazinone results in significant platelet aggregation inhibitory activity [28].

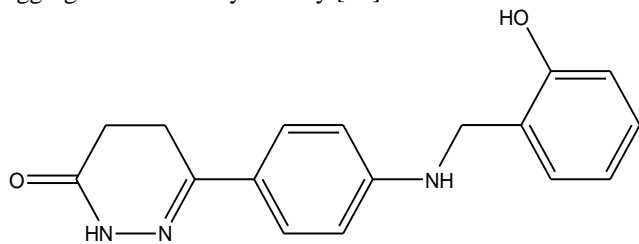


Fig 38

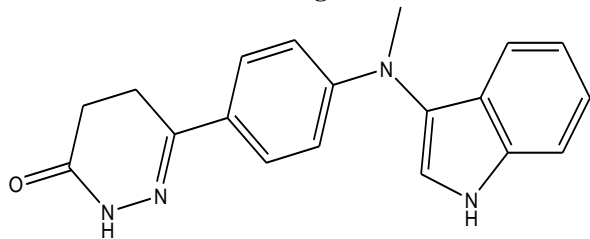


Fig 39

Eddy Sotelo et al synthesized a series of 6-phenyl-3(2H)-pyridazinones with a diverse range of substituents in the 5-position have been prepared and evaluated in the search for new antiplatelet agents. The pharmacological study of these compounds confirms that modification of the chemical group at position 5 of the 6-phenyl-3(2H)-pyridazinone system influences both variations in the antiplatelet activity and the mechanism of action. Many of the compounds studied inhibit platelet aggregation in a dose-dependent manner. The compound in (Fig 40) shows the highest efficacy as a platelet aggregation inhibitor and has an IC₅₀ value in the micromolar range (15 mM) [29].

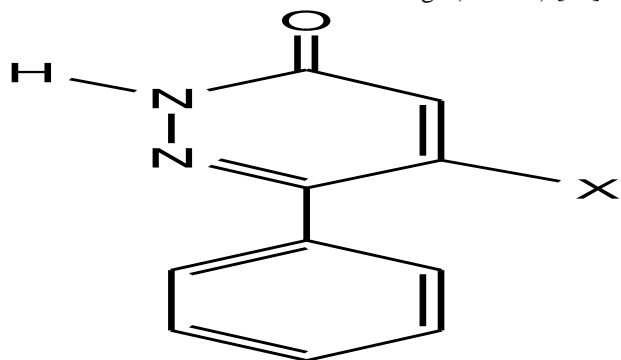


Fig 40

Antimicrobial Activity

Deniz S. Dogruer et al synthesized various 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives. The synthesized compounds were evaluated for their antibacterial activity against various gram-positive and

gram-negative strains of bacteria and their clinical isolates and for their antimycobacterial activity against *M. tuberculosis* H37Rv.

The results showed that the synthesized compounds were generally active against *B. subtilis* and its clinical isolate. Among the target compounds, compound in Fig 41 exhibited the best antibacterial activity, with a MIC value of 15.62 μg/mL against *B. subtilis*. Compound in Fig 42 had the highest antimycobacterial activity [30].

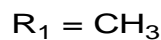
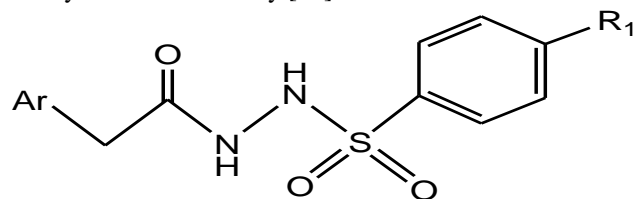


Fig 41

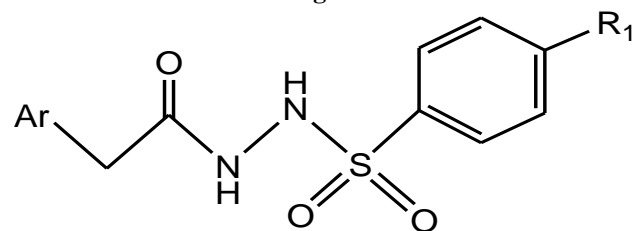


Fig 42

Antitubercular Activity

Husain Asif et al synthesized two series of pyridazinone derivatives and evaluated them for antitubercular activities against *Mycobacterium tuberculosis* H37Rv strain. The results illustrated that among the synthesized compounds, compound in Fig 43, 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone emerged as a lead compound with good antitubercular activity. This compound showed best antitubercular activity among the synthesized compounds with MIC-12.5 μg/mL. Rests of the compounds showed MIC-values of 50 μg/mL. Pyridazinones derived from 4-chloro-furanones were found to have better activity than those derived from 4-methyl-furanones. Among the mono-substituted phenyl rings at 5th position of pyridazinone ring, presence of nitro group in Fig 44 showed significant antitubercular activity [31].

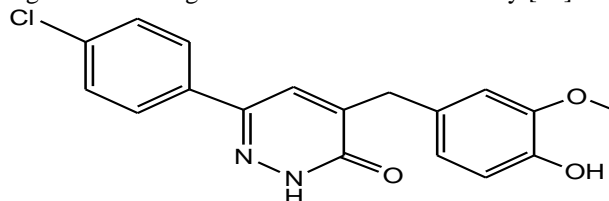


Fig 43



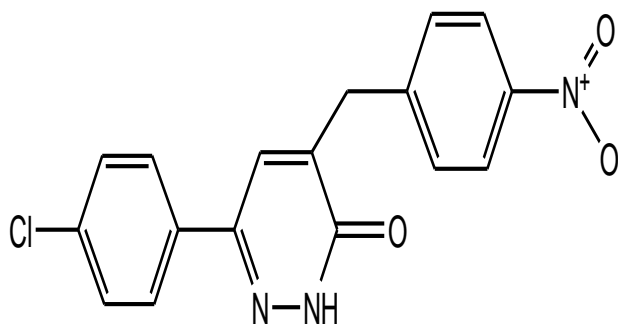


Fig 44

Anees A Siddiqui et al synthesized a series of 5-{3'-oxo-6'-(substituted aryl)-2',3', 4', 5'-tetrahydropyridazin-2'-yl methyl}-2-substituted 1,3,4-oxadiazole. The antitubercular activity of synthesized compounds was performed by adopting Alamar blue susceptibility test (MABA). All the final compounds were tested for antitubercular activity at 6.25 $\mu\text{g/ml}$, showed percentage of inhibition ranging from 45 to 90%. The compound in Fig 44 emerged as highly active analogue of the series with 91% inhibition against *M.tuberculosis* H37 Rv. The order of activity was found to be H>Cl.>O-toluidine>m-xyloyl>Di-phenyl ether. From the above result, it concluded that compound in Fig 45 are highly active against *M.tuberculosis* H37 Rv [32].

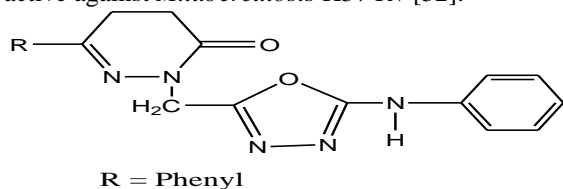


Fig 45

Phosphodiesterase Inhibitory Activity

Pierfrancesco Biagini et al synthesized a series of pyrazoles and pyrazolo[3,4-d]pyridazinones and their PDE4 inhibitory activity was evaluated. All the pyrazoles were found devoid of activity, whereas some of the novel pyrazolo[3,4-d]pyridazinones showed good activity as PDE4 inhibitors. SARs studies demonstrated that the best arranged groups around the heterocyclic core are 2-chloro-,

2-methyl- and 3-nitrophenyl at position 2, an ethyl ester at position 4 and a small alkyl group at position 6. All compounds were evaluated for their ability to inhibit PDE4 from U-937 cells at 1M concentration. Most compounds showed more than 50% inhibition at this concentration and dose response curves were constructed to calculate IC_{50} value.

All the pyrazole derivatives were found to be inactive at the tested concentration being only 35% at 1 μM . A number of pyrazolopyridazinones were synthesized and amongst them the most potent compound Fig 46 [33].

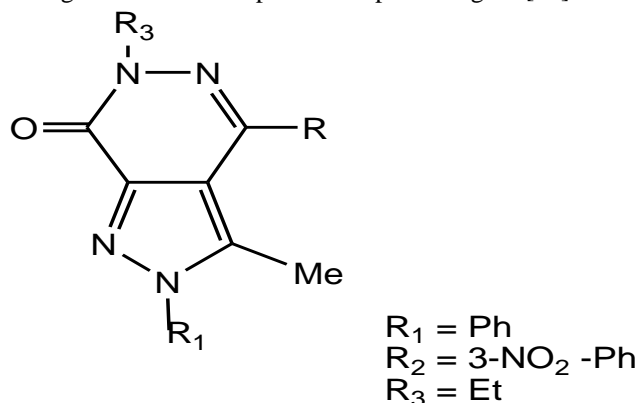


Fig 46

The literature review reveals pyridazinones as a lead structure and as a part of central scaffold have diverse biological potential. By the present scenario it can be concluded that pyridazinone have a great potential to be disclosed till date. Pyridazinones further drew attention because of their easy functionalization at various ring positions, which makes them attractive synthetic building blocks for designing and development of novel pyridazine as analgesic agents. The incorporation of substituents in pyridazinone ring either in the form of functional groups or as a fused component often leads to incredible diverse biological activity. The biological profile of these new generations of pyridazinones presents much progress with regards to the old compounds.

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