International Journal of Pharmaceutical Chemistry
ISSN: 2249-734X (Online)
Journal DOI: 10.7439/ijpc
CODEN: IJPCH3 (American Chemical Society)
Review Article

Mini review on Importance of pyridazinone and phthalazine moiety in medicinal chemistry with scaffold of pharmacological activities

Mohammad Asif

Department of Pharmacy, GRD (PG) Institute of Management & Technology, 248009, Dehradun,(Uttarakhand), India

Abstract

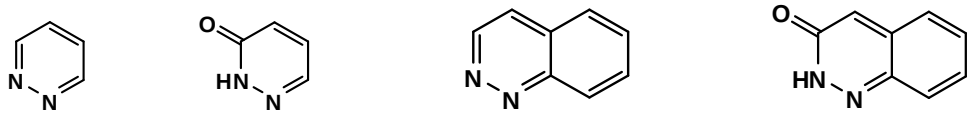
Pyridazinones and phthalazine compounds have drawn a considerable attention in the field of research and development. Pyridazinones and phthalazines have been a subject of intensive research owing to their wide spectrum of pharmacological activities and therapeutic applications. Introduce a new path for researcher by introducing these moieties and develop novel class of molecules who have better therapeutic profile. The synthesis of pyridazinone and phthalazines and investigation of their chemical and biological activities have gained more importance in recent years. The biological profile of these new generations of pyridazinones and phthalazines presents much progress with regards to the old compounds. In this review, different activities of pyridazinones and phthalazines have been discussed by the researcher. This study may produce new way for the researcher to generate new scaffolds of high therapeutic value considering the relevant importance of pyridazinone and phthalazine nucleus.

Keywords: Biological activities, phthalazine, pyridazine, pyridazinones.

1. Introduction

Nitrogen-containing heterocyclic compounds have received much attention by their numerous applicabilities in different area especially as therapeutically active drugs. Pyridazine and phthalazine derivatives are the example of nitrogen heterocycles that possess exciting biological properties. They form the structural profile for several biologically active compounds and hence they are considered important key elements. Several reports have focused on the pharmacological utilities of pyridazine and phthalazine derivatives derivatives and great number of contributions in diverse areas of interest. These systems are widely used in organic chemistry as intermediates for the synthesis of numerous compounds. On the other hand; pyridazine and phthalazine derivatives were extensively studied as bioactive compounds. They possess remarkable biological activity as prescribed.[1] The discoveries of pyridazine and phthalazine derivatives have been possess characteristic pharmacological activities. The pyridazine and phatalzine and its 3-oxo derivatives (pyridazinones and phthalazinone) have attracted a great deal of attention because of the wide spectrum of their pharmacological as well and agrochemical activities. They are widely recognized as versatile scaffolds with a diverse set of pharmacological activities such as analgesic, anti-inflammatory, antimicrobial, antithrombic, antidepressant, diuretics, antihypertensive, antitubercular, and anti-HIV and some other useful activities. Certain pyridazinone derivatives containing the 2-phenyl-indolyl moiety have shown anti-tumour activity.[2-4] Some pyridazin-3(2H)-one have been reported as analgesic and anti-inflammatory agents without gastrointestinal side effect. The pyridazinone derivatives have chemical and biological behaviour have gained more importance in recent decades for biological, medicinal and agricultural reason. Pyridazinone, a saturated or unsaturated form of pyridazine with carbonyl group on third carbon, has been considered as magic moiety which possesses almost all types of pharmacological activities.[5-8]

* Correspondence Info
Mohammad Asif
Department of Pharmacy,
GRD (PG) Institute of Management & Technology,
248009, Dehradun, (Uttarakhand), India
E mail: aasif321@gmail.com



Pyridazine **Pyridazinone** **Phthalazine** **Phthalazinone**

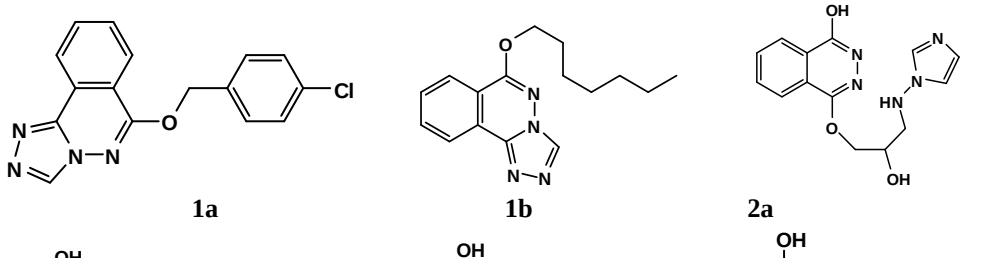
Additionally, phthalazines have recently been reported to potentially inhibit serotonin reuptake and are considered antidepression agents. Phthalazines are also one of the important biological active pharmacophore components in medicinal chemistry, which are of considerable interest due to their antidiabetic, antiallergic, vasorelaxant, PDE4 inhibitors, tyrosine kinase inhibitor as anti-cancer, antiasthmatic agents, herbicidal like activities.A number of compounds such as Levosimendan, Amipizone, Indolidan, Imazodan and Pimobedan are few examples of pyridazinones that are active as cardiotonic agents. A number of established drug molecules like Hydralazine, Budralazine, Azelastine, Ponalrestat and Zopolrestat are prepared from the corresponding phthalazinones. The diverse biological activities of phthalazin-1(2*H*)-one, triazolothiadiazole and triazolo-thiadiazine pharmacophores encouraged us for the construction of new molecular systems has biological active molecules.[5-8]

2. Pharmacological activity of pyridazinones and phtalazines

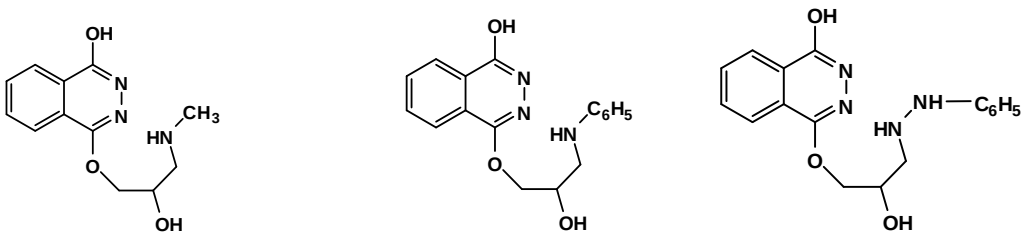
Pyridazinones and phtalazines are the Versatile Pharmacophore of medicinal significance and have attracted the attention of medicinal chemists during the last decade due to their diverse pharmacological activities. Easy functionalization of various ring positions makes them an attractive synthetic building 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 and phtalazines constitute an interesting group of compounds, many of which possess wide spread pharmacological properties such as antihypertensive, platelet aggregation inhibitory, cardiotonic activities and some are also well known for their pronounced analgesic, anti-inflammatory, antinociceptive, and antiulcer activities. Recently pyridazinones and phtalazines have also been reported as antidiabetic, anticonvulsant, antiasthmatic, antimicrobial etc agents. These encouraging reports suggest that this privileged skeleton should be extensively studied for the therapeutic benefits.[3-5]

2.1 Anticonvulsant activity

A series of 6- alkoxy-(1,2,4)triazolo(3,4-a)phthalazine. Evaluated their anticonvulsant activity and neurotoxicity by using maximal electroshock (MES) test and Rota rod test, significant anticonvulsant activity was shown by number of derivatives, but derivative 6-(4-chlorobenzyloxy)-[1,2,4]triazolo[3,4-a]phthalazine (**1a**) and 6-heptyloxy-[1,2,4]triazolo (3,4-a) phthalazine (**1b**) was shown most active derivatives among all the derivatives.[9] A series of 1-substituted-4-hydroxyphthalazines and then these compounds were assayed against seizures induced by MES and pentylenetetrazole (scPTZ) model and neurologic deficit was evaluated by the rotarod test. The decrease in the elevated motor activity by introceptive chemical stimuli (amphetamine antagonistic activity) was studied at the dose level of 25 and 50 mg/kg and cardiac activity was also studied. All the compounds exhibited significant anticonvulsant activity, but compounds (**2a, 2b, 2c** and **2d)** were most active from the synthesized series against MES-induced seizures.[10]

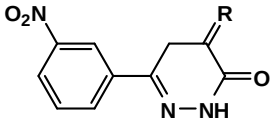


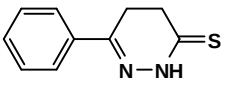
1a **1b** **2a**



2b **2c** **2d**

The 4-(Benzylidene or substituted benzylidene)-6-(3-nitrophenyl)-4,5- dihydropyridazin- 3(2*H*)-ones (**3a, 3b, 3c**) from 6-(3-aminophenyl)-4,5-tetrahydro pyridazin-3(*2H*)-one by condensation reaction with different benzaldehydes. The compounds (**3a-c**) were evaluated for anticonvulsant activity by maximal electro shock (MES) induced seizure method and these compounds exhibited significant anticonvulsant activity against after intra-peritonially administration of 50mg/Kg body weight dose. So, these compounds may be regarded as anticonvulsant.[11] A series of substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones and 6-aryl-2,3,4,5-tetrahydro-3-thio-pyridazinones (**4**) were evaluated for anticonvulsant activity. The anticonvulsant activity of synthesized compounds was evaluated by the MES-induced seizure test. Out of the ten compounds, two compounds showed significant activity. Rest showed moderate anticonvulsant activity.[12]

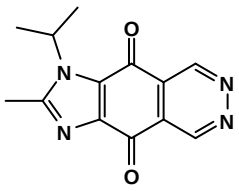




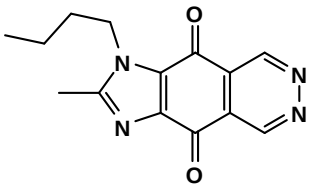
32-c 3aR=C_6H_5, **3b** R=-(2OH)-C_6H_4, **3c**R=(4-OCH_3)C_6H_4 **4**

2.1 Anticancer activity

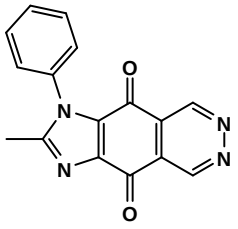
A series of 1- substituted 2-methyl-1H-imidazo [4,5-g] phthalazine-4,9 dione derivatives were evaluated for their in vitro cytotoxicity against several human tumor cell. Most of the tested derivatives showed potential cytotoxicity activity higher than reference compounds. Derivatives 1,2-Dimethyl-1H-imidazo[4,5-g]phthalazine-4, 9-di-one (**5a**), 2-Methyl-1-isopropyl-1H-imidazo [4,5-g]phthalazine-4, 9-dione (**5b**), 1-n-Butyl-2methyl-1H-imidazo [4,5-g]phthalazine-4, 9-di-one (**5c**) and 2-Methyl 1phenyl-1H-imidazo [4,5-g]phthalazine-4,9-di-one (**5d**) was found higher active than other derivatives.[13] A series of novel 1-anilino-4-(aryl sulfanyl methyl) phthalazine and evaluated their anticancer activity by using the micro culture tetrazolium method. They found some derivatives showed higher activity than cisplatin against two different cancer cell lines. Those analogues are 1-(4-fluoro-3-trifluoromethylanilino)-4-(3,4-difluorophenyl-thiomethyl)phthalazine (**6a**) and 1-(3-chloro-4-fluoroanilino)-4-(3,4-difluoro-phenyl-thiomethyl) phthalazine (**6b**).[14]



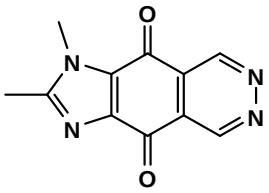
5a



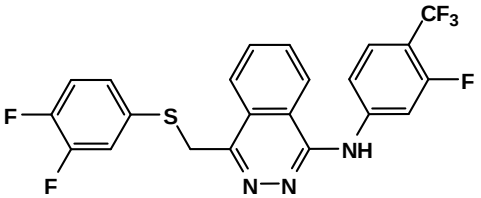
5b



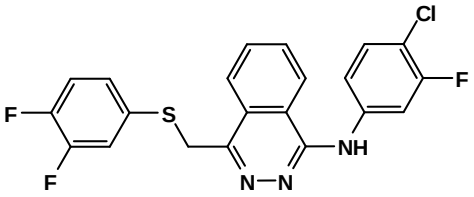
5c



5d



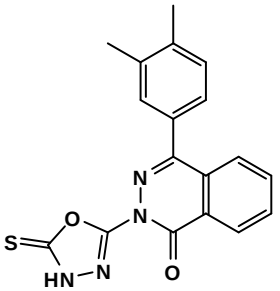
6a



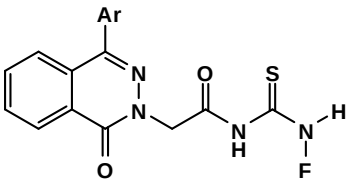
6b

Eight 1,4-disubstituted phthalazine were tested for vitro cytotoxicity evaluated with human liver cancer cell lines. Derivatives containing 3, 4-difluorophenylthimethyl group at position 4 of phthalazine ring exhibited more potent inhibitory activity against two cancer cell lines than cisplatin. It concluded that introduction of substituents to the phenyl thiomethyl moiety would increased the cytotoxicity.[15] In different 4-(3,4-dimethyl-phenyl) phthalazine-1(2H)-ones, most of the derivatives were tested for their anti-inflammatory activity. The results revealed that derivative 4-(3,4-dimethylphenyl)-2-[(4,5-dihydro-5-thiooxo-1,3,4-oxadiazol-2-yl)] phthalazine-1(2H)-one (**7a**),

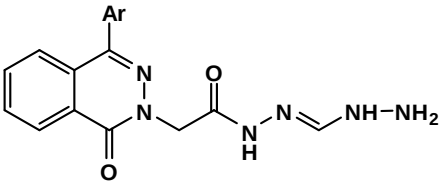
1-{2-[4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl]acetyl}4-benzyl thio-semicarbazide (7**b**), N'-(ethoxymethylene)-2(4-(3,4-dimethylphenyl)-1-oxo-phthalazine-2(1H)-yl)aceto-hydraide (**7c**) and 5-methyl-3-oxo-2[1'(2H)-oxo-4'-(3,4-dimethyl phenyl) phthalazine-2'-ylmethylcarbonyl]-3,4-dihydropyrazol (**7d**) are most active compared to the activity ofindomethacin.[16]



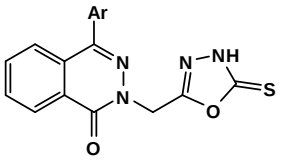
7a



7b

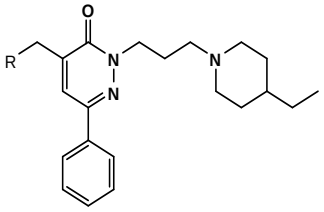


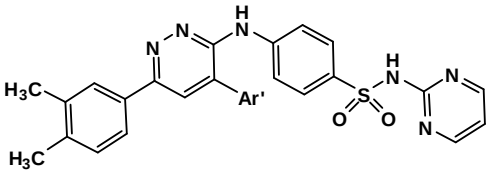
7c



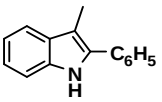
7d

A series of 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 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 (**8a, 8b** and **8c**) were 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.[7] Some pyridazinones containing the 2-phenyl-1H-indolyl moiety were evaluated for anti-cancer activity. Cytotoxicity and IC values of the tested compounds were measured and compound (**9**) was used as very potent cytotoxic drug for breast carcinoma cell.[17]



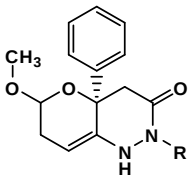


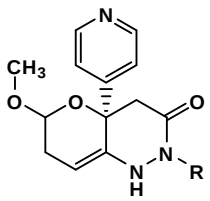
Ar'=



8a-c **8a**R=C_6H_5 **8b**R=2-furyl, **8c**R=2-Thienyl **9**

The polyfunctional tetrahydro-*2H*-pyrano[3,2-c]pyridazin-3(6H)-one derivatives were evaluated for anticancer agents. Compounds (**10** and **11**) were showed antiproliferative activity against the SK-BR-3 breast cancer cell line. Importantly compounds **10a** and **11b** were 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, **10a** and **10b** displayed about 295 fold less toxicity against normal breast cell line MCF10A compared to SKBR-3 breast cancer cells.[18]



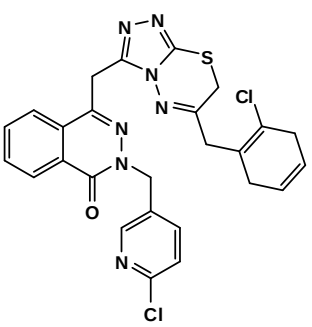


aR=2-indolyl **b**R=3,5-Dimethoxy-phenyl

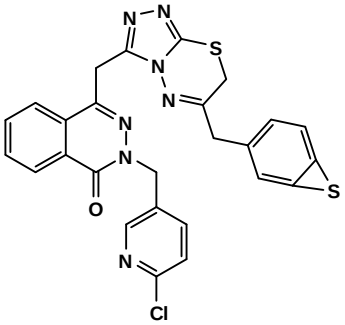
10 **11**

2.2 Antimicrobial activity

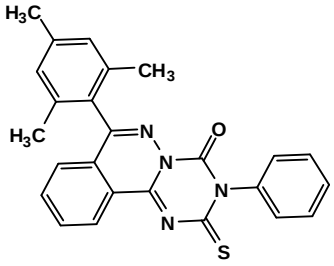
The 6-(chloropyridin-3-yl)methyl substituted phthalazine 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles were investigated for their antimicrobial activity. The derivatives substituents with 5-nitro-thiazole to triazolothiadiazole (**12a**) and methylthiophenyl to triazolo thiadiazines (**12b**) showed better activity compared to other derivatives.[19] The 3-substituted methyl 3-methoxy-2-(4-oxo-3,4-dihydrophthalazin-1-yl) acrylates phthalazine methoxyacrylate compounds substituted at C3 position with different functional groups starting from commercially available phthalic anhydride. Investigated their antimicrobial activity of compounds revealed that, compounds substituted methyl 2-{3-[(6-chloropyridin-3-yl)methyl]-4-oxo-3,4-dihydrophthalazin-1-yl}-3-methoxyacrylate(**12a**), methyl2-[3-(4,6-dimethoxy pyrimidin -2-yl)-4-oxo-3,4-dihydrophthalazin-1-yl]-3-methoxy acrylate (**12b**) showed better activity compared to other derivatives.[20] Some annelated phthalazine derivatives and acyclo Cnucleosides from 1-chloro-4-(2,4,6-trimethyl phenyl)phthalazine precursor and evaluated their antimicrobial activity, and found that 1,2,4-triazolo[3,4-a]phthalazine derivatives, 1,3,5-triazino[4,3-a]phthalazine **(13a),** and tetrazolo [5,1-a] phthalazine **(13b)** were the most active compounds.[21]



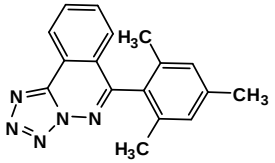
12a



12b

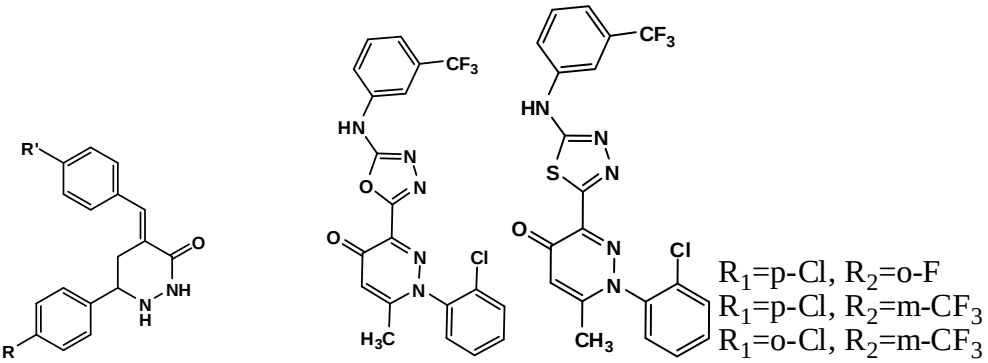


13a



13b

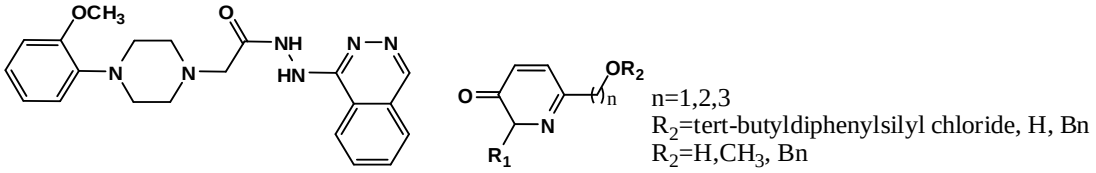
Some derivatives of pyridazinone were evaluated for anti-bacterial activity. The 6-phenyl-2,3,4,5-tetrahydro pyridazine-3-one which was then condensed with various aldehydes to form respective derivatives. The antimicrobial activity was performed on the compounds synthesized against *Staphylococcus aureus* (MTCC 737), *S. epidermis* (MTCC3615), *Pseudomonas aeruginosa* (MTCC 424) and *Escherichia coli* (MTCC1687). Compounds (**14a** and **14b**) were 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.[22] A series of 5-[1- aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxadiazoles (**15**), which was fungicidally active, based on bioisosterism and tested *in vivo* against wheat leaf rust, *Puccinia recondita.* 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 (**16**), 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.[23] Some 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-thiadiazoles were showed antifungal activity.[24]



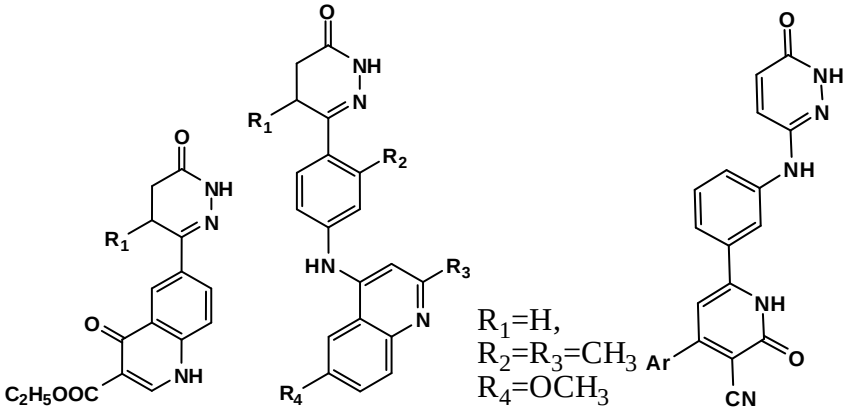
14a-b 14aR=H, R'=Cl **14b** R=Cl, R'OCH$_3$ **15** **16a-c**

2.3 Cardiovascular activities

Some new phthalazine derivatives and evaluated them for their vasorelaxant activity against nor-adrenaline- induced spam on thoracic rat aorta rings and compared to the reference drug prazosin. Several derivatives showed higher activity than standard drug, but derivatives 3-{4-(2-methoxyphenyl) piperain-1-yl)-N-phthalazin-1-yl} propane hydrazide (**17**) having an IC_{50}=0.10mM.[25] The 6-substituted and 2,6-disubstituted pyridazinone derivatives (**18**), 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] Three series of pyridazinones to identify potential vasodilatory cardiotonic lead compounds. Compounds with higher fit scores to the developed pharmacophore were namely; 6-(3-ethoxy carbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2H)-pyridazinones (**18**), 6-[4-(2,6-di-substituted-quinolin-4-ylamino)phenyl]-4,5-dihydropyridazin-3(2H)-ones (**19**), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino]-3(2H)pyridazinone (**20**). The vasodilator activity of the 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]



17 **18**

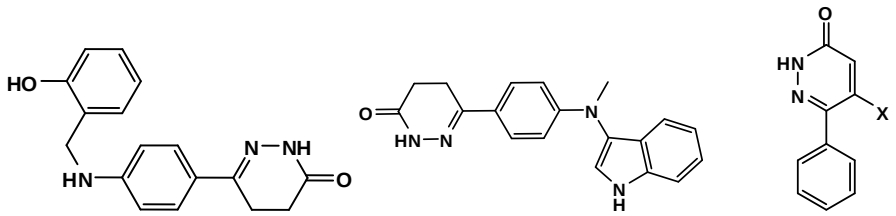


19 **20** **21**

2.4 Platelet aggregation inhibitory Activity

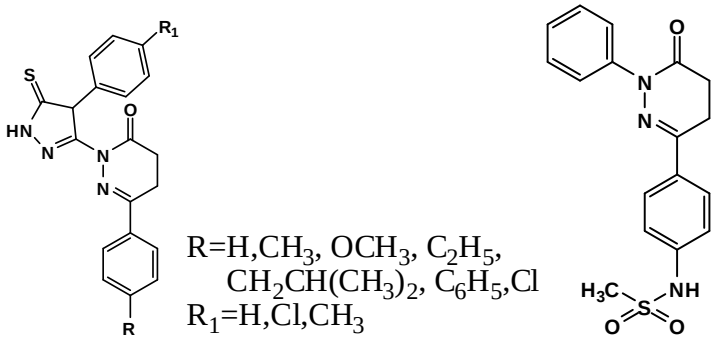
A series of 6-(4-(substituted-amino)phenyl)-4,5-dihydro-3(2H)-pyridazinones, were exhibited significant platelet aggregation inhibitory activity. The compounds (6-(4-(2-hydroxybenzyl amino)phenyl)-4,5-dihydropyridazin-3(2H)-one (**22**) and 6-(4-(1H-indol-3-ylmethyl amino) phenyl)-4,5-dihydropyridazin-3(2H)-one (**23**) 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] A series of 6-phenyl-3(2H)-pyridazinones with a diverse range of

substituents in the 5-position have been evaluated in the search for new antiplatelet agents. 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 (**24**) shows the highest efficacy as a platelet aggregation inhibitor and has an IC_{50} value in the micromolar range (15 mM).[29]



22 **23** **24** X=CH_2OH

The 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 (**25**) by a sequence of reactions starting from respective aryl hydrocarbons. Amongst these compounds, maximum antihypertensive activity exhibited by 6-(4-methylphenyl)-2-[4-(4-chloro-phenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]- 4,5-dihydropyridazin-3(2H)-one, 6-(4-methoxy-phenyl)-2-[4-(4-methylphenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl]-4,5-di-hydropyridazin-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-dihydro pyridazin-3(2H)-one. Therefore, 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.[30] The 2-substituted-6-(4-acylaminophenyl)-4,5-dihydropyridazin-3(2*H*)-ones exhibited potent inodilating activity. The pyridazinone derivatives were evaluated for cardiotonic activity using isolated rat atria and for vasorelaxant activity using descending thoracic aortic rings of Wistar rats precontracted with phenylephrine(10–6 mol/L). The 6-(4-Methanesulfonamidophenyl)-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one (**26**) was exhibited significant inodilatory properties and showed vasorelaxant activity in a nanomolar range (IC_{50}= 0.08 ± 0.01 mmol /L).[31]



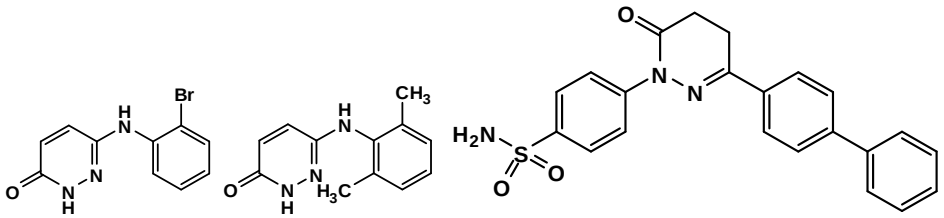
R=H,CH_3, OCH_3, C_2H_5, $CH_2CH(CH_3)_2$, C_6H_5,Cl

R_1=H,Cl,CH_3

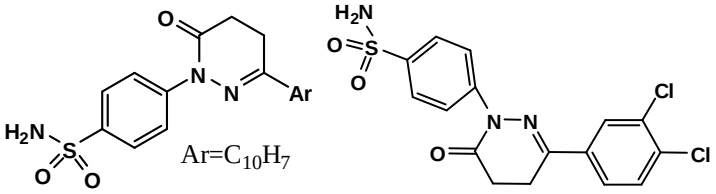
25 **26**

2.5 Anti-inflammatory Activity

A series of pyridazinone containing compounds as congeners for diclofenac. Some 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 (**27**) and 6-(2,6-dimethylphenylamino)pyridazin-3(2H)-one (**28**) exhibited 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 exhibited fewer numbers of ulcers and milder ulcer score than indomethacin in ulcerogenic screening 2,6-dimethyl group in (**9**) in the aromatic ring gave rise to an increased anti-inflammatory activity (74 and 75%), respectively. The substituting 2-chloropyridyl function at the 6-amino-pyridazinone seems preferable for obtaining an effective anti-inflammatory agent.[32] Some 6-aryl-2-(p-sulfamoylphenyl)-4,5-dihydropyridazin-3(2H)-ones by the condensation of appropriate aroylpropionic acid and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol. These compounds were tested for their anti-inflammatory activity in carrageenan-induced rat paw edema model. Compound **29** exhibited anti-inflammatory activity comparable to that of celecoxib (at 5h). Two other compounds **30** and **31** showed promising anti-inflammatory activity (edema reduction more than 80% at 5h).[33]

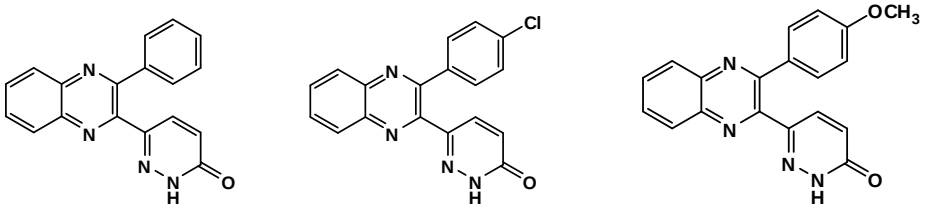


27 **28** **29**



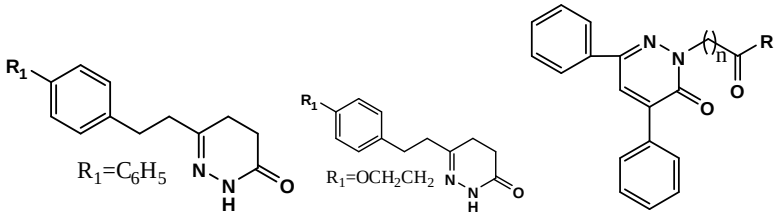
30 **31**

Compounds containing central bicyclic quinoxaline scaffold carrying only one phenyl ring and pyridazinone moiety as a replacement of sulfamylphenyl or sulfonylphenyl group. The benzene portion of the fused quinoxaline ring was used to cover the area occupied by the CF group of celecoxib. Bicyclic quinoxaline nucleus attached to pyridazinone and phenyl substituents formed potent anti-inflammatory novel structures especially chloro analogue (**32**). The *in vivo* high potency of compound (**32**) 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 (**32-34).[**34]



32 **33** **34**

The pharmacological activities of arylethenylpyridazinone and arylethylpyridazinone derivatives from the corresponding aryloxohexenoic and aryloxohexanoic acids respectively, a series of pyridazine derivatives linked at C(6) to aryl or biphenyl moieties through two carbon spacers. The compounds exhibited anti-inflammatory activity and superior gastrointestinal safety profile. The results of biological screening also revealed that compound (**35),** 6-[2-(Biphenyl-4-yl)ethyl]-4,5-dihydropyridazin-3(2H)-one and compound (**36**), 6-[2-(2,3-Dihydro-benzo [b][1,4] dioxin-6-yl)ethyl]-4,5-dihydropyridazin-3(2H)-one in which ethyl spacer between the dihydro pyridazinone 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.[35] The 4,6-diphenyl-3(2H)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonylalkyl moieties (**37**) on the nitrogen atom in the 2nd position of the pyridazinone ring and their analgesic and anti-inflammatory activity was investigated. All compounds showed significant analgesic activity at 100 mg/kg dose level in ratios from 55.6 to 82.7%. The more active compounds in terms of anti-inflammatory activity were found in acetamide derivatives in general. The 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.[36]

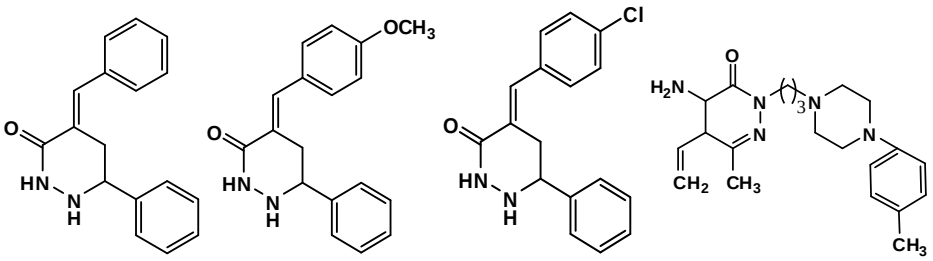


35 **36**

37R=Piperzin n=1,2

2.6 Analgesic Activity

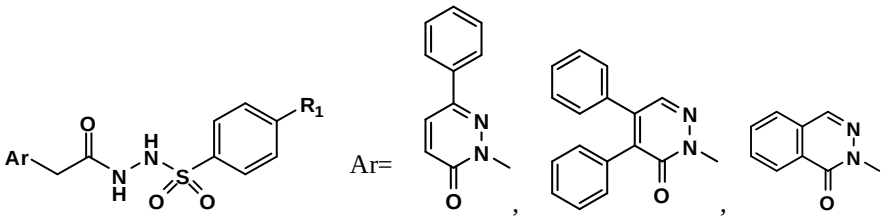
Three 6-Phenyl-4- Substituted Benzylidine tetrahydropyridazin-3(2H)-one derivatives (**38-40**) from 6-phenyl-4,5-dihydropyridazin-3(2H)-one. All three compounds (**38-40**) were exhibited significant analgesic activities when compared with control group by using hot plate model and less active than 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 (**39**) 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.[37] A 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. The compound 4-amino-6-methyl-2-[3-(4-p-tolylpiperazin-1-yl)propyl]-5-vinylpyridazin-3(*2H*)-one (**41**) as an exceptionally potent antinociceptive agent and showed an ED_{50}=3.5 µg, a value. about 3-fold higher with respect to morphine by the same route of administration.[38]



38 **39** **40** **41**

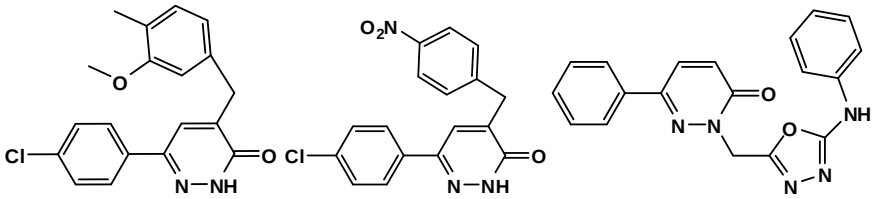
2.7 Antitubercular Activity

Various 3(2H)-pyridazinone and 1(2H)-phthalazinone derivatives were evaluated for their antibacterial activity against various gram-positive and gram-negative strains of bacteria and their clinical isolates and for their antitubercular activity against *M. tuberculosis* H37Rv. The results showed that the compounds were generally active against *B. subtilis* and its clinical isolate. Among the target compounds, compound (**42**) exhibited the best antibacterial activity, with a MIC value of 15.62*µ*g/mL against *B. subtilis.* Compound in Fig 42had the highest antitubercular activity.[39]



42 Ar= H,CH_3, Cl, OCH_3, $NHCOCH_3$

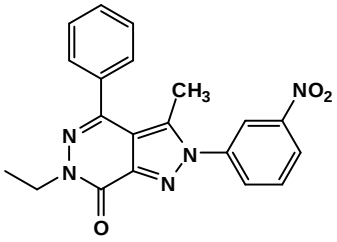
The pyridazinone derivatives were evaluated for anti-tubercular activities against *M. tuberculosis* H37Rv strain. The among the compounds, compound (**43**), 5-(4-hydroxy-3-methoxybenzyl)-3-(4-chloro-phenyl)-1,6-dihydro-6-pyridazinone emerged as a lead compound with good antitubercular activity. This compound showed best antitubercular activity among the synthesized compounds with *MIC*-12.5 µg/mL. Rests of the compounds showed MIC-values of 50µg/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.[40] A series of 5-{3'-oxo-6'-(substituted aryl)-2',3',4',5'-tetrahydropyridazin-2'-yl methyl}-2-substituted 1,3,4-oxadiazoles were tested for antitubercular activity at 6.25 µg/ml, result showed that percentage of inhibition ranging from 45 to 90%. The compound (**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.[41]



43 **44** **45**

2.8 Phosphodiesterase Inhibitory Activity

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 lM concentration. Most compounds showed more than 50% inhibition at this concentration. All the pyrazole derivatives were found to be inactive at the tested concentration being only 35% at 1μM. A number of pyrazolopyridazinones, amongst them the most potent compound (**46**).[42]



46

The literature review reveals pyridazines and phtalazines as a lead structure and as a part of central scaffold have diverse biological potential. In this review paper, try to discuss all about the reported activities of pyridazines and phtalazines by researcher. They have synthesized various derivatives with different substituents and evaluated for their divers pharmacological activities.[43-45]

From the review we can predict that pyridazines and phtalazines is one of the important biological active pharmacophore components in medicinal chemistry, who provides new ranges of safe and effective drugs for researchers.[46-50]

3. Conclusion

According to reported literature, pyridazinones and phtalazines have been reported to possess, anticonvulsant, cardio tonic, antimicrobial, antitumor, antihypertensive, antithrombotic, antidiabetic, antitrypanosomal, anti-inflammatory, vasorelaxant and other anticipated activities. By the present scenario it can be concluded that pyridazine and phthalazines have a great potential to be disclosed till date. Pyridazines and phthalazines 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 pyridazines and phthalazines containing agents. The incorporation of substituents in pyridazines and phthalazines 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 pyridazines and phthalazines resents much progress with regards to the old compounds.

Disclosure: No conflicts of interest.

References

[1] Nahed F, Ghaffar AE, Mona A, Ghanem HM, and HM Zaki. Synthesized and biochemical evaluation of some substituted phthalazines. *J Am Sci*, 2011; 7 (4): 771-781.

[2] Asif M. General study of pyridazine compounds against cyclooxygenase enzyme and their relation with analgesic, anti-inflammatory and anti-arthritic activities. *Chronicle s of Young Scientist*, 2010; 1: 3-9.

[3] Asif, M. Some recent approaches of biologically active substituted pyridazine and phthalazine drugs. *Curr. Med. Chem*. 2012; 19: 2984–2991.
[4] Asif M, Singh A, Siddiqui A.A. The effect of pyridazine compounds on the cardiovascular system. *Med. Chem. Res.* 2012, 21: 3336-3346.
[5] Seth S, Sharma A, Raj D. Pyridazinones: a wonder nucleus with scaffold of pharmacological activities. *Am J Biol & Pharm Res*, 2014; 1(3):105-116.
[6] Asif, M. Mini Review on Biological Activities of Pyridazinone Derivatives as Antiulcer, Antisecretory, antihistamine and Particularly against Histamine H3R. *Mini Rev Med Chem*, 2014; 14(13): 1093-1103.
[7] Murty MSR, Ramalingeswara Rao B. Synthesis and preliminary evaluation activity studies of novel 4-(aryl/ heteroaryl-2-ylmethyl)-6-phenyl-2-[3-(4-substituted-piperazine-1-yl) propyl] pyridazine-3(2H)-one derivatives as anticancer agents, *Med Chem Res*, 2012; 21: 3161-3169.
[8] Singh S, Kumar N. Importance of phthalazine moiety in pharmaceutical chemistry-a review. *World J Pharm & Pharm Sci*, 2014; 3(3): 729-736.
[9] Quan ZS, Sun XY, Guan LP. Synthesis and anticonvulsant activity of 6-alkoxy-[1,2,4] triazolo [3, 4-a] phthalazine. *Chem. Biol. Drug Des*, 2009; 73: 313-319.
[10] Sivakumar R, Kishore S, Ramachandran GS, Leonard JT. Pharmacological evaluation of some new 1-substituted-4-hydroxyphthalazines. *Eur J Med Chem*, 2002; 37: 793- 801.
[11] Asif M, Anita A. Anticonvulsant Activity of 4-(Substituted Benzylidene)-6-(3-nitro-phenyl)-4,5-dihydroPyridazin-3(*2H*)-ones Against Maximal Electro Shock Induced Seizure. *Middle-East J Sci Res*, 2011; 9(4): 481-485.
[12] Banarjee PS, Sharma PK, Nema RK. Synthesis and anticonvulsant activity of pyridazinone derivatives. *Inter J Chem Tech Res*, 2009; 1(3): 522-525.
[13] Kim JS, Lee HJ, Suh ME, Choo HYP. Synthesis and cytotoxicity of 1-substituted 2-methyl-1H- imidazo [4,5-g] phthalazine- 4, 9-dione derivatives. *Bioorg & Med Chem*, 2004; 12: 3683-3686.
[14] Gong P, Jing-Xion X, Yan-Fang Z, Juan L. Synthesis and anticancer activity of novel 1, 4- disubstituted phthalazines. *Molecules*, 2006; 11: 574-582.
[15] Gong P, Zhang YB, He L, Zhai X. Synthesis and *in vitro* cytotoxicity of novel 1,4-disubstituted phthalazines. *Chinese Chem Lett*, 2008; 19: 29-32.
[16] Mosaad SM, Goudah A, Abotaleb NA. Synthesis and anti-inflammatory evaluation of some condensed [4-(3, 4-dimethylphenyl)-1(2H)-oxo-phthalazin-2-yl] acetic acid hydrazide. *Eur J Med Chem*, 2010; 45: 1267-1277.
[17] Abd El-Ghaffar NF, Mohamed MK, Kadah MS, Radwan AM, Said GH, Abd el Al SN. Synthesis and anti-tumor activities of some new pyridazinones containing the 2-phenyl- 1H-indolyl moiety. *J Chem & Pharm Res*, 2011; 3(3): 248-259.
[18] Taleb H Al-Tel. Design and synthesis of novel tetrahydro-2H-Pyrano [3,2-c] Pyridazin-3(6H)-one derivatives as potential anticancer agents. *Eur J Med Chem*, 2010; 455724-5731.
[19] Sridhara AM, Venugopala Reddy KR, Prasad Y, Kumar GS, Vadiraja SG, Gouda SK, Peethambard SK. Synthesised phthalazine substituted 1,2,4-triazolo- [3,4-*b*]-1,3,4-thiadiazoles and 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and screened for their antimicrobial activity against variety of human pathogenic bacteria's. *Der Pharma Chemica*, 2010; 2 (5): 201-211.
[20] Sridhara AM, Reddy KRV, Keshavayya J, Vadiraj1 SG, Bose1 P, Ambika DS, Raju1 CK, Shashidhara S, Raju NH. Synthesised, antimicrobial and cytotoxicity studies of some novel phthalazine-methoxyacrylate derivatives. *J Pharm Res*, 2011; 4(2): 496-500.
[21] Maher AA, Youssef A, Essam I. Synthesis of some annelated phthalazine derivatives and acyclo C-nucleosides from 1-chloro-4-(2, 4, 6-trimethylphenyl) phthalazine precursor, and evaluated their antimicrobial activity. *Turk J Chem*, 2012; 36: 347 – 366.
[22] Alang G, Kaur R, Singh A, Budhlakoti P, Singh A. Synthesis, Characterization anti-bacterial activity of certain-2,3,4,5-Tetrahydropyridazinone analogues, *Turk J Pharm Sci*, 2011; 8(1), 71-80.
[23] Xia-Juan Z, Lu-Hua LAI, Gui-Yu JIN, Zu-Xing Z. Anti microbial Synthesis, Fungicidal Activity, and 3D-QSAR of pyridazinone-substituted-1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J Agric Food Chem*, 2002; 50(13): 3757-3760.

[24] Xia-Juan, Z, Gui-Yu, J. Synthesis of pyridazinonethiadiazoles as possible antifungal agents. *Chinese Chem Lett*, 2001; 12(5): 419- 420.
[25] Awadallah FM, Saleh DO, El-Eraky W. Synthesis vasorelaxant activity, and molecular modeling study of some new phthalazine derivatives. *Eur J Med Chem*, 2012; 52:14-21.
[26] Costas T, Besada P, Piras A, Acevedo L, Yañez M, Orallo F, Laguna R, Terán C. New pyridazinone derivatives with vasorelaxant and platelet antiaggregatory activities. *Bioorg & Med Chem Lett*, 2010; 20(22): 6624-6627.
[27] Abouzid K, Hakeem MA, Khalil O, Maklad Y. Pyridazinone derivatives: design, synthesis, and in vitro vasorelaxant activity. *Bioorg Med Chem*, 2008; 16: 382–389.
[28] Thota S, Ranju B. Synthesis of new pyridazinone derivatives as platelet aggregation inhibitors, *Med Chem Res*, 2010; 19: 808-816.
[29] Sotelo E, Fraiz N, Yanez M, Terrades V, Laguna R, Cano E, Ravina E. Pyridazines. Part XXIX: Synthesis and platelet aggregation inhibition activity of 5-substituted-6-phenyl-3(*2H*)pyridazinones novel aspects of their biological action. *Bioorg Med Chem*, 2002; 10: 2873- 2882.
[30] Siddiqui AA, Mishra R, Shaharyar M, Husain A, Rashid M, Pal P. Triazole incorporated pyridazinones as a new class of antihypertensive agents: Design, synthesis and in vivo screening. *Bioorg & Med Chem Lett*, 2011; 21: 1023–1026.
[31] Kumar D, Bansal R, Carron R, De La Calle C, Jindal DP. Synthesis and evaluation of 2-substituted-6-phenyl-4,5-dihydropyridazin-3(2H)-ones as potent inodilators. *Act Pharm*, 2008; 58: 393-405.
[32] Abouzid K, Khalil NA. Design, Synthesis, and evaluation of anti-inflammatory and ulcerogenecity of novel pyridazinone derivatives, *Med Chem Res*, 2012; 21: 3581-3590.
[33] Bashir R, Yaseen S, Ovais S, Ahmad S, Hamid H, Alam MS, Samim M, Javed K. Synthesis and biological evaluation of some novel sulfamoylphenyl-pyridazinone as anti-inflammatory agents (Part-II). *J Enzyme Inhib Med Chem*. 2012; 27(1): 92-6.
[34] Abouzid K. Structure-based molecular design, synthesis, and in vivo anti-inflammatory activity of pyridazinone derivatives as nonclassic COX-2 inhibitors, *Med Chem Res*, 2010; 19: 629-642.
[35] Abouzid K, Bekhit SA. Novel anti-inflammatory agents based on pyridazinone scaffold; design, synthesis and in vivo activity. *Bioorg & Med Chem*, 2008; 16: 5547-5556.
[36] Dogruer DS, Sahin MF, Kupeli E, Yesilada, E. Synthesis and analgesic and anti-inflammatory activity of new pyridazinones. *Turk J Chem*, 2003; 27: 727-738.
[37] Asif M, Deewan S, Singh A. Analgesic Activity of Some 6-Phenyl-4-Substituted Benzylidone TetrahydroPyridazin-3(2H)-ones, *Global J Pharmacol*, 2011; 5(1): 18-22.
[38] Biancalani C, Giovannoni MP, Pieretti S, Cesari N, Graziano A, Vergelli C, Cilibrizzi A, Di Gianuario A, Colucci M, Mangano G, Garrone B, Polenzani L, Dal Piaz V. Further studies on arylpiperazinyl alkyl pyridazinones: Discovery of an exceptionally potent, orally active, antinociceptive agent in thermally induced pain (dagger). *J Med Chem*, 2009; 52(23): 7397-409.
[39] Dogruer DS, Onkol T, Ozkan S, Ozgen S, Sahin MF. Synthesis and antimicrobial activity of some 3(*2H*)-pyridazinone and 1(*2H*)-phthalazinone derivatives. *Turk J Chem*, 2008; 32: 469-479.
[40] Husain A, Ahmad A, Bhandari A, Ram V. Synthesis and Antitubercular activity of pyridazinone derivatives, *J Chil Chem Soc*, 2011; 56: 778-786.
[41] Siddiqui AA, Islam M. Synthesis and antitubeculostic ac tivity of 5-{3-tetrahyro-pyridazin-2-yl}methyl-2-substituted 1,3,4-oxadiazole. *Der Pharm Lett*, 2010; 2(2), 319-327.
[42] Biagini P, Biancalani C, Graziano A, Cesari N, Giovannoni MP, Cilibrizzi A, Dal Piaz V, Vergelli C, Crocetti L, Delcanale M, Armani E, Rizzi A, Puccini P, Gallo PM, Spinabelli D, Caruso P. Functionalized pyrazoles and pyrazolo[3,4-d]pyridazinones: Synthesis and evaluation of their phosphodiesterase 4 inhibitory activity. *Bioorg Med Chem*, 2010; 18(10): 3506-17.
[43] Aziz MA, Youssef A, Essam I, Synthesised some annelated phthalazine derivatives and acyclo C-nucleosides from 1-chloro-4-(2, 4, 6-trimethylphenyl) phthalazine precursor, and evaluated their antimicrobial. *Turk. J. Chem*, 2012; 36: 347–366.
[44] Asif M. General study of pyridazine compounds against cyclooxygenase enzyme and their relation with analgesic, anti-inflammatory and anti-arthritic activities. *Chronicle s of Young Scientist*, 2010; 1: 3-9.

[45] Mantu, D., Antoci, V., Mangalagiu, I.I. Design, synthesis and antimycobacterial activity of some new pyridazine derivatives: Bis-pyridazine. Part IV. *Infectious Disorders-Drug Targets*, 2013; 13: 344-351.

[46] Asif M, Singh A. Exploring Potential, Synthetic Methods and General Chemistry of Pyridazine and Pyridazinone: A Brief Introduction. *Inter J Chem Tech Res*, 2010; 2(2): 1112-1128.

[47] Costas T, Besada P, Piras A, Acevedo L, Yañez M, Orallo F, Laguna R, Terán C. New pyridazinone derivatives with vasorelaxant and platelet antiaggregatory activities. *Bioorg & Med Chem Lett*., 2010; 20(22): 6624-6627.

[48] Mantu D, Cătălina Luca M, Moldoveanu C, Zbancioc G, Mangalagiu II. Synthesis and antituberculosis activity of some new pyridazine derivatives. Part II. *Eur J Med Chem*, 2010; 45(11): 5164-5168.

[49] Alan RJ, Alexander W. The tautomeric properties of 6-(2-pyrrolyl) pyridazin-3-one and 6-(2-pyrrolyl) pyridazin-3-thione. *Arkivoc*, 2007; (xi): 114-119.

[50] Cignarella G, Barlocco D, Pinna GA, Loriga M, Curzu M,Tofanetti O, Germini M, Cazzulani P, Cavalletti E. Synthesis and biological evaluations of substituted benzo[h]-cinnolinones and 3- benzo[6,7]cyclohepta[1,2-c]pyridazinones: higher homologues of the antihypertensive and antithrombotic 5H-indeno[1,2-c]pyridazinones. *J Med Chem*, 1989; 32: 2277-2282.