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Biologically Active Pyridazines and Pyridazinone Derivatives: A Scaffold for the Highly Functionalized Compounds

Mohd Imran[a] and Mohammad Asif[b, 1]

[a] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, PO Box 840, Rafha 91911 Saudi Arabia*

[b] *Department of Pharmacy, Himalayan Institute of Pharmacy and Research, Dehradun, (Uttarakhand), 248007 India*

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Abstract—Pyridazine and pyridazinone are heterocycles that contain two adjacent nitrogen atoms and shown wide range of pharmacological activities such as antimicrobial, antidepressant anti-hypertensive, anticancer, antiplatelet, antiulcer, herbicidal, antifeedant and various other anticipated biological activities. Pyridazine ring are present in some commercially available drugs and agrochemicals. Pyridazine based systems have been shown to have numerous practical applications.

Keywords: pyridazine, pyridazinone, biological activities, heterocyclic compounds

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INTRODUCTION

Heteroaromatic scaffolds such as pyridazine derivative have been shown to be 'privileged structures' in medicinal chemistry and many drug discovery programmes utilize a pyridazine (Fig. 1) as a core scaffold. However it should be noted that pyridazine based systems are less common in the literature than the other diazines (pyrimidine and pyrazine). Various pyridazine based scaffolds have been utilized in medicinal chemistry against a range of biological targets and physiological effects. Pyridazinone (Fig. 1) is the derivative of pyridazine which belong to an important group of heterocyclic compounds containing nitrogen atoms at 1 and 2 positions in a six membered ring and oxygen atom at 3 position of the ring. It is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities [1–5].Different structure form of pyridazinone that has been utilized as a part of various complex compounds and these compounds exhibited diversified pharmacological activities. Substantial numbers of pyridazines and pyridazinones containing the different moiety or substituent have been demonstrated to possess antipyretics, anti-inflammatory and analgesic, antiplatelet, anticancer, antidepressant, anxiolytic, antidiabetic, antihypertensive, anticonvulsant, bronchial asthma and allergy, antifungal, antibacterial, antitubercular and many other anticipated biological properties [6, 5].

[1] Corresponding author: e-mail: aasif321@gmail.com.

Pyridazine (1,2-diazine)pyridazin3(2H)-one Tetrahydropyridazin-3-one

Various pyridazinone derivatives are well known as agrochemicals also.The pharmaceutical industry has a continuing requirement for the synthesis of a diverse range of polysubstituted pyridazinone compounds bearing a varied range of ring substituents because many such compounds have been used as commercially drugs and agrochemicals. Examples anti-platelet agent Zardaverine, anti-inflammatory agent Emorfazone and herbicide agents Pyridaben and Norflurazon and various other therapeutically pyridazine and pyridazinone drugs [16–20].

Pyridazine and Related Compounds

The diazines are six membered ring containing 2 nitrogen atoms. Three isomeric diazinesare theoretically possible and all of them are known.Knorr coined the term pyridazine (Fig. 1) for 1,2-diazine ring system [21] however Fischer firstprepared substituted pyridazines in 1886 and later on by Tauber in 1895 [22]. Pyridazines have not been investigated as thoroughly as the other isomeric diazinesespecially pyrimidine because they are not known to occur in nature and are not easilyformed by nitrogen biochemical transformation. Some pyridazines have beenfound useful as growth inhibitors or medicinal compounds. Pyridazine has been assumed to be a planar molecule. Pyridazine is a resonance hybrid in which the greater contribution is made by the structure containing =N–N= configuration. The 1,2-diazine system that contains a carbonyl group in the ring is called

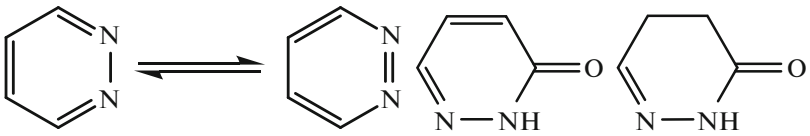


Fig. 1. Structure of pyridazie and pyridazinone ring.

pyridazinone. During last 2 decade numbers of pyridazines have been synthesized due to variety of biological activities specially related to cardiovascular system.

Properties of Pyridazine

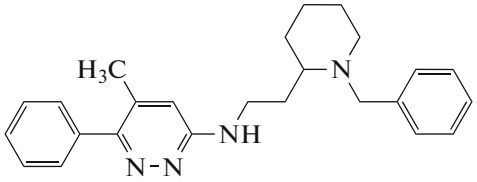
Pyridazine is a colorless liquid at roomtemperature with pyridine like odor and melting point (mp) of 8°C. Pyridazine is a weak base with boiling point (bp) 208°C. This unusually high boiling point compared tobenzene (bp 80°C) indicates the involvement at some hype of intermolecularassociation.Pyridazine derivatives are an important class of heterocycles found in various biologically active compounds. This class of compounds has confirmed a broad spectrum of activities and applications as pharmaceuticals and agrochemicals [21].

Biological Activities of Pyidazines and Pyridazinones

Various structural modifications were carried out in pyridazinone ring system. These structural changes resulted in some fruitful biological activities of the compounds some of these activities are mentioned here (Fig. 2).

Anticholinestrase Inhibitors

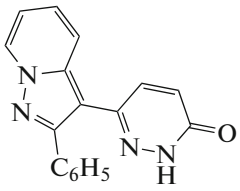
A series of different 4 and 5 substituted 6-aryl-3-benzyl-piperdinyl ethylaminopyridazines weretested for acetyl cholinesterase inhibitoractivity [23]. Among all these compounds 3-[2-(1-benzylpiperidine-4-yl)ethylamino]-5-methyl-6-phenyl pyridazine (**I**) was showed 100 times more selectively for inhibition towardshuman acetyl cholinesterase than reference drug Tacrine. Any substitution on the phenyl ring system attached at C-6 position does not affect the acetylcholinesterase inhibitory activity.



(I)

Diuretic Activity

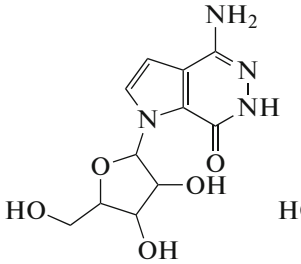
Some pyridazinones derivatives showed diuretic activity; compound (**II**) was showed marked increases in urine volume and Na ion output and strong diuretic activity [24].



(II)

Antiproliferative Activity

The 4-(substituted)-1-β-D-ribofuranosylpyrrolo(2,3-d)-pyridazin-7(6H)-3-one derivatives were tested for anti proliferative activity against human tumor cell lines. The 4-amino derivative (**III**) was found to be most potent in this series while 4 amino-5-chloro derivative (**IV**) was found to be most potent against human cytomegalovirus [25].



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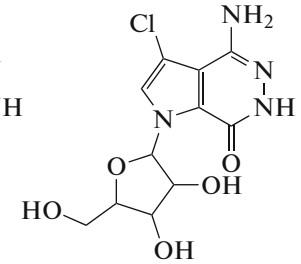
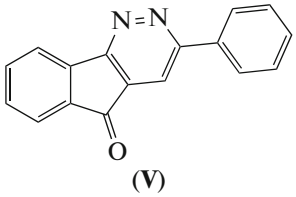


(IV)

Mono Amino Oxidase Inhibitors (MAOIs)

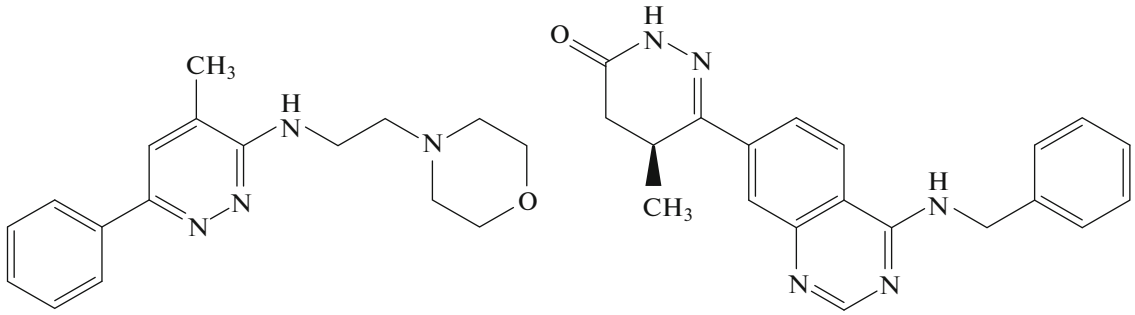
Some pyridazine derivatives were tested for their MAO-A and MAO-B activity, compound (**V**) was showed prominent reversible inhibitory activity on MAO-B and this activity was found to be the function of lipophilicity of the compound [26].



(V)

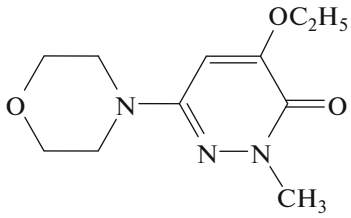
Antidiabetic Agents

Increased glucose flux through sorbitol pathway and the high intracellular accumalation of sorbitol are likely to be involved in etiology of late onset diabetic

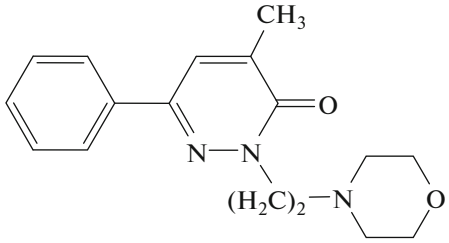


Minaprine (Psychotropic drug)

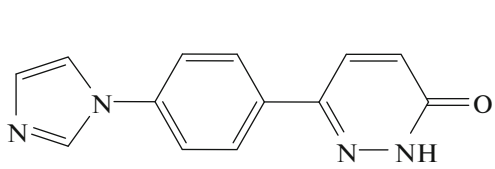
KF 15232 (Congestive Heart Failure)



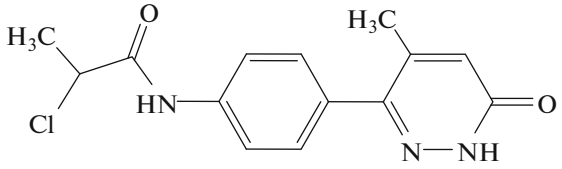
Emorfazone (Analgesic)



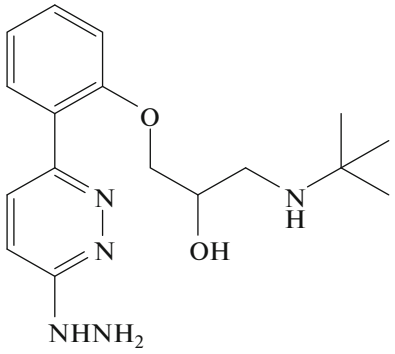
Ag246 (Analgesic)



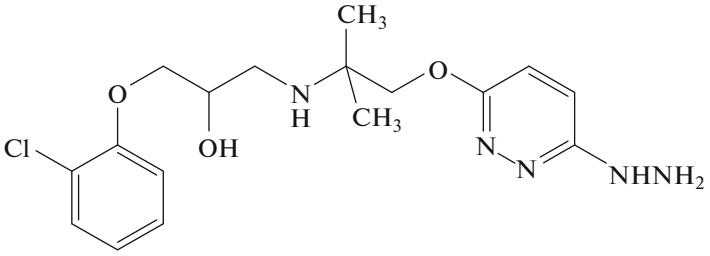
Imazodan (Cardiotonic)



Amipizone (Antithrombotic drug)



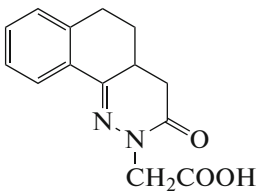
Prizidilol (antihypertensive)



TLC 1370 (hypotensive)

Fig. 2. Some pharmacologically active pyridazine compounds and their uses.

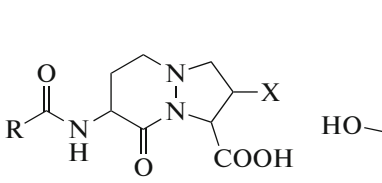
complication likes neuropathy, nephropathy, retinopathy and cataract. Aldose reductase is the first enzyme in "Polyol Pathway" which converts glucose to sorbitol and then to fructose. The tricyclic pyridazinones were tested to inhibit aldose reductase enzyme. The compound **(VI)** which has N-acetyl substitution was found to inhibit the enzyme and act as antidiabetic drug [27].



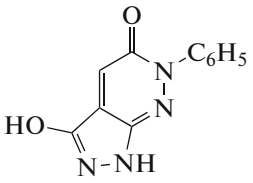
(VI)

Antibacterial Activity

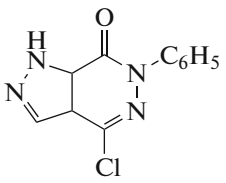
Bicyclic tetrahydropyridaziones where X is strong electron withdrawing group were tested for antibacterial activity. Bulky nature of the compound (**VII**) was responsible for ineffective alignment of compound with receptor and was found to be less active [28].Various substituted 5,6-dihydro-3-hydroxy-lH-pyrazolo-(4,3-c)pyridazinone were tested for their antibacterial activity. Few compounds like (**VIII**) were found to be active against *S. aureus*, *E. coli*, *B. subtilis*, and *S. cemsiae* at a concentration of 2 mg/mL and 5 mg/mL. Electron withdrawing group on phenyl ring at N-2 in pyridazinone ring reduced the antibacterial activity in this series [29]. The pyrazole fused pyridazinone derivative (**IX**) and found to have bacteriostatic activity [30]. The diaryl pyrazolo-(3,4-d) pyridazine-4(5H)-ones (**X**–**XIV**) have acquired pharmacological importance owing to their antimicrobial activity [31].



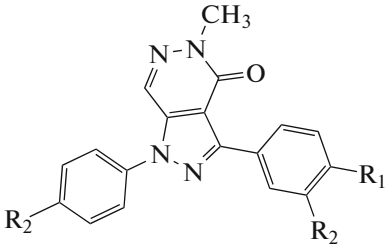
(VII)



(VIII)



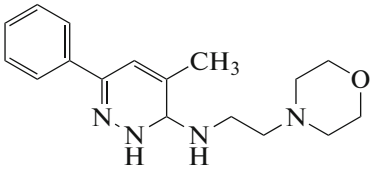
(IX)



(**X**) $R_1 = H$, $R_2 = H$, $R_3 = H$;
(**XI**) $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$;
(**XII**) $R_1 = CH_3$, $R_2 = H$, $R_3 = H$;
(**XIII**) $R_1 = H$, $R_2 = OCH_3$, $R_3 = H$;
(**XIV**) $R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = H$

Antidepressant Activity

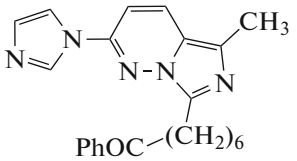
Varioussubstituted analogues of Minaprine were tested for their antidepressant, serotonergic and dopaminergic activities [12]. The compound (**XV**) was found to be more active as serotonergic but least active as dopaminergic. Serotonergic activity appears to be correlated mainly with substituent at C-4 position of pyridazine ring whereas dopaminergic activity appears to be dependent on the presence of/or in the formation of p-hydroxylated aryl ring in the gamma position of pyridazine [32].



(XV)

Anti-HIV Drugs

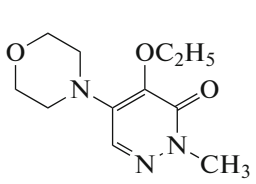
The imidazo-[l,5-b] pyridazines (**XVI**) were tested them for inhibitory activity against reverse transcriptase of HIV-1 and ability to inhibited the growth of infected MT-4 cells. Exceptionally activity against RT-HIV-1 was obtained with compound (**XVI**). Substitution on imidazole ring system attached to pyridazinones however, decreased the activity of these compounds against reverse transcriptase enzyme [33].



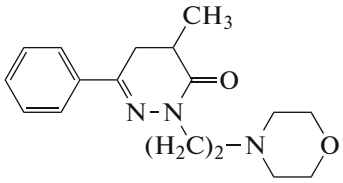
(XVI)

Analgesic, Antipyretic and Anti-Inflaminatory Activities

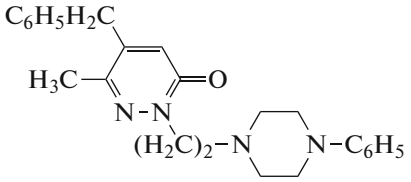
Pyridazinones like Emorfazone (**XVII**) and Ag 246 (**XVIII**) have been shown to possess analgesic activity [34]. Emarphazone was marketed in Japan as analgesic and antinflammatory drug in last decade. The structural modification of Emorfazone having an aryl piperaznyl moiety appeared to be most active on the antinociceptive property. Among the different derivatives, the compounds (**XIX**) and (**XX**) were found to be potent antinociceptive agents. The antinociceptive activity shown by 3(2H)-pyridazinone derivative (**XXI**) [35], a series of 2 substituted 4,5-functionalized 6-phenyl-3(2H) pyridazinones were tested for antinociceptive activities. Single dose studies showed that compounds (**XXII**–**XXIV**) were promising compounds [36].



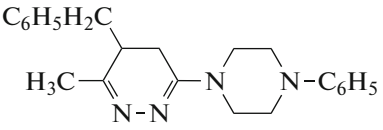
(**XVII**)



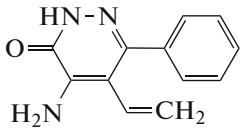
(**XVIII**)



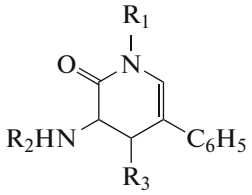
(**XIX**)

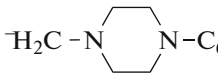
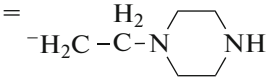


(**XX**)

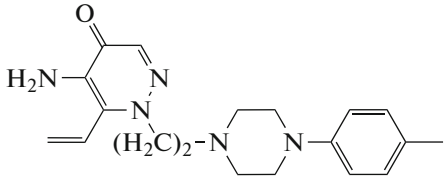


(**XXI**)

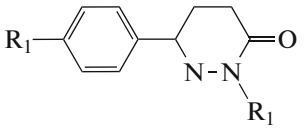


(**XXII**) R_1 =  ,
R_2 = H, R_3 = $COCH_3$;
(**XXIII**) R_1 = CH_3, R_2 = H, R_3 = –CH=CH_2;
(**XXIV**) R_1 = CH_3, R_2 = 
R_3 = $COCH_3$

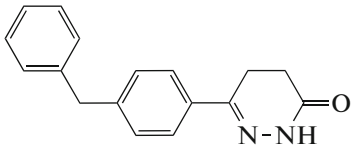
Some 4-amino-3(2H)-pyridazinones, substituted at C-2 position with aryl piperazinylalkyl groups were tested for antinociceptive effect. The compound (**XXV**) was found to be most potent than the Emorfazone [37]. Various 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones (**XXVI**) were tested for their anti-inflammatory activity. Most of the compounds were showed dose dependent response of anti inflammatory activity. Substitutionof the amide hydrogen by a phenyl moiety reported to decrease the activity considerably *p*-substitution in the aryl ring system at C-6 position of the pyridazinone ring by *p*-methoxy, *p*-isobutyl, *p*-benzyl, *p*-phenyl are found to increase the activity. The compound (**XXVII**) showed maximum activity [38]. Some 4-nitro and 4-amino, 5-acyl, 6-aryl-3(2H)-pyridazinones were tested for anti inflammatory activity [39]. The 4-amino derivative (**XXVIII**) was used orally and found to be more potent antiinflammatory agent than aspirin. Some compounds like 5-acyl-N-methyl derivative (**XXIX**) when tested in vivo on lipopolysaccharide stimulated rat peritoneal macrophages, were seen to be active in inhibition of prostaglandin E2 and interleukin activity. The NSAIDs Emorfazone, 4-chloro-5-(2-hydroxy-ethylamino)-3-(2H)-pyridazjnone were converted to novel fused ring compound 3,4-dihydro-2H-pyridazino[4,5-b]-l,4-oxazin-8(7H)-ones [40]. It resulted in the potent analgesic compounds (**XXX**–**XXXI**) and anti-inflammatory compound (**XXXII**) and (**XXXIII**).



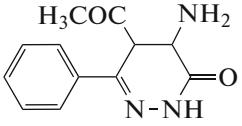
(**XXV**)



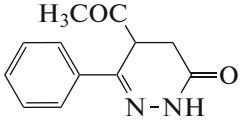
(**XXVI**) R_1 = H, C_6H_5–,
R_2 = C_6H_5–, $C_6H_5CH_2$–,
C_6H_5O–, OCH_3 · P-isobutyl



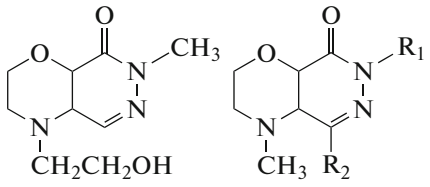
(**XXVII**)



(**XXVIII**)



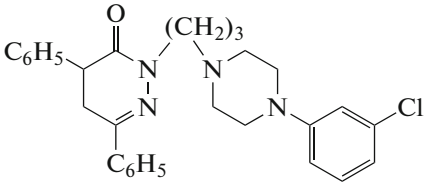
(**XXIX**)



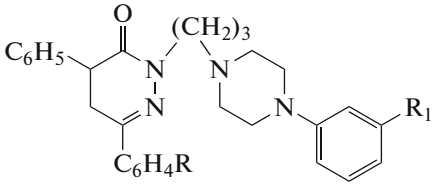
(**XXX**)

(**XXXI**) $R_1 = -(CH_2)_2-C_6H_5$, $R_2 = H$;
(**XXXII**) $R_1 = -CH_2-C_6H_5$, $R_2 = H$;
(**XXXIII**) $R_1 = -CH_3$, $R_2 = NH_2$

A series of 4,6-diaryl pyridazinones, chemically related to trazodone were tested for analgesic activity [41]. Most of the compounds like (**XXXIV**) were reported several times more potent than standard acetaaminophen and noramidopyrine. Substitution on either phenyl ring system or pyridazinone does not affect activity. The potential pharmacological interest of 3(2H)-pyridazinone derivative, a series of pyridazinone derivatives bearing two aryl group in the C-4 and C-6 positions and various substitutents at C-2 position was developed [42]. The compound (**XXXV**) with phenyl or 3-trifluro phenyl piperazino-methyl group exhibited significant anti-inflammatory activity. The compound (**XXXVI**) gave better protection to animals than noramido-pyridine and showed potency equivalent to morphine and proved to be promising analgesic. The compound (**XXXVII**) was found significantly effective against yeast induced fever and also produced a good level of anti inflammatory activity.

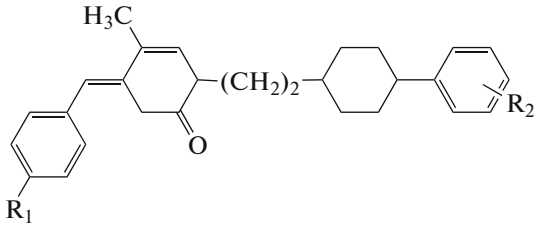


(**XXXIV**)

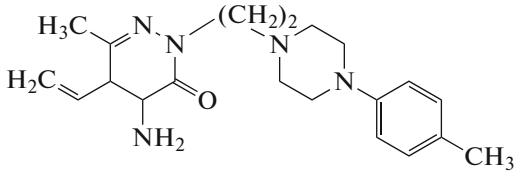


(**XXXV**) R = H, R_1 = H;
(**XXXVI**) R = H, $R_1 = CF_3$;
(**XXXVII**) R = F, R = H

Various 5-arylidenepyridazin-3-one substituted at C-2 position by an arylpiperazinoalkyl moiety were exhibited analgesic activity [43]. The compounds (**XXXVIII**) and (**XXXIX**) were found potent and produced higher level of analgesic than aspirin and noramidopyridine. These compounds were significantly effective and much more active against yeast induced fever in mice and proved to be promising antipyretic activity. The arylidene moiely as such and substituents contributed to lipophilicity. The presence and nature of substituent posses by the phenyl nucleus attached to piperazinyl moiely seemed to be essential for potent analgesic activity, in continuation explored 40 fold more potent 4-amino-3(2H)-pyridazinone (**XL**) possessing antinociceptive effect than structurally related einorfazone in mouse abdominal constriction model [44].

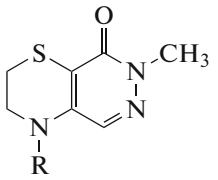


(**XXXVIII**) R_1 = H, R_2 = 3-CF_3;
(**XXXIX**) R_1 = F, R_2 = 3-Cl

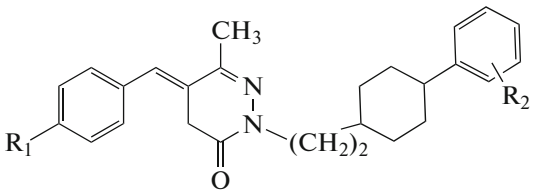


(**XL**)

The two fused ring system made up of 1,4 thiazine and 3(2H) pyridazinone. The 3,4-dihydro-7-methyl-2H-pyridazino[4,5-b]-1,4-thiazin-8(7H)-one was prepared from intramolecular cyclisation of 4-chloro-5-[2-chloroethyl-amino]-2-methyl-3(2H)-pyridaziones with sodium sulphide. The compounds (**XLI**) and (**XLII**) were found to have significant anti-inflammatory activity [45]. A series of 5-arylidene pyridazin-3-ones substituted at the C-2 position by an aryl piperazino alkyl Moiety [46]. These compounds were evaluated for analgesic activity. Among these, the compounds (**XLIII**–**LII**) were found to be potent.

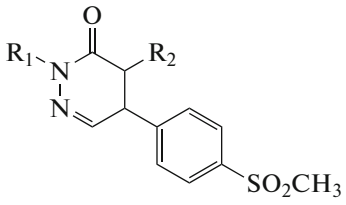


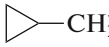
(**XLI**) R = H;
(**XLII**) R = CH_3



(**XLIII**) R_1 = H, R_2 = H; (**XLIV**) R_1 = F, R = H; (**XLV**) R_1 = CH_3, R_2 = H; (**XLVI**) R_1 = H, R_2 = 3-CF_3; (**XLVII**) R_1 = F, R_2 = 3-CF_3; (**XLVIII**) R_1 = CH_3, R_2 = 3-CF_3; (**XLIX**) R_1 = H, R_2 = 3-Cl; (**L**) R_1 = F, R_2 = 3-Cl; (**LI**) R_1 = CH_3, R_2 = 3-Cl; (**LII**) R_1 = H, R_2 = 4-F

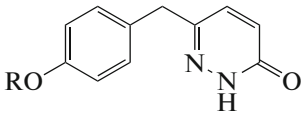
Two potent selective and orally active COX-2 inhibitors that possess pyridazinones moiety (**LIII**) and (**LIV**) [47].



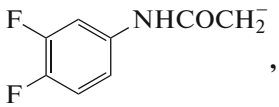
(**LIII**) R_1 = C_6H_5-CH_2–, R_2 = $(CH_3)_2CHO$;
(**LIV**) R_1 =  , R_2 = *p*-F-C_6H_4–

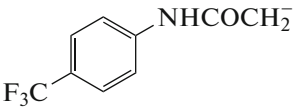
Cyclooxygenase-2-Lnhibitors

Cyclooxygenase (COX) inhibitory activity and COX-2 selectivity exhibited by 3-*o*-substituted benzyl pyridazinone compounds (**LVa**–**c**) [47].

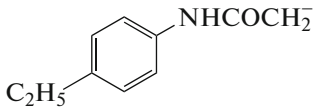


(**LVa**)

R =  ,



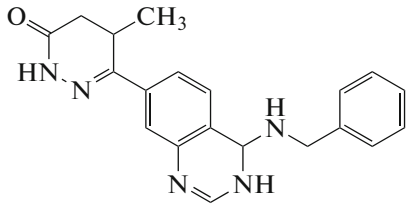
(**LVb**),



(**LVc**)

Calcium Sensitizers

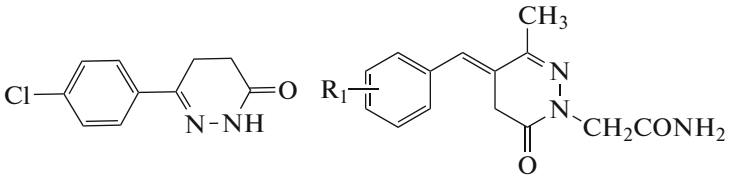
The 6-4(benzylamino)-7-quinazolinyl)-4,5-dinydro-5-methyl-3(2H)-pyridazinone (**LVI**) was showed potent cardiotonic activity with strong myofibriilar Ca^{2+} sensitizing effect [48]. This compound was compared with trifluroperazine for Ca^{2+} sensitizing effect and was found to be most potent. The phosphodiestrase (PDE) inhibitory activity of compound plays an important role in cardiotonic activity. When recemic mixture of the compound was tested, results indicated that R configuration might be essential for the inhibition of PDE-III. Structural requirement for cardiotonic activity were different from those for the myofibrillar Ca^{2+} sensitizing effect.



(**LVI**)

Anticonvulsant Activity

The anticonvulsant activity of 6-(substituted aryl)-2,3,4,5-tetrahydro-3-pyridazinones [49]. The *p*-chloro phenyl substituted pyridazinone (**LVII**) was showed better anticonvulsant activity. A series of 3-oxo-5-substituted benzylidenes 6-methyl-(4H)2-pyridazinyl acetamides and 2-pyridazinyl acetyl hydrazides were evaluated for anticonvulsant activity against electrically and chemically induced seizures [50]. The compound (**LVIII**) and (**LIX**) showed significant anticonvulsant properties at doses that did not produce ataxia or sedation.

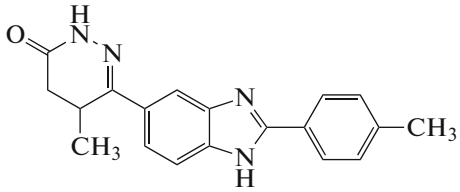


(**LVII**)

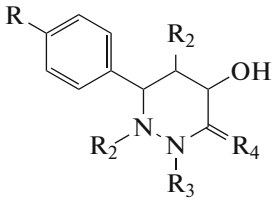
(**LVIII**) R = H; (**LIX**) R_1 = *o*-Cl

Cardiotonic Activity

The cardiovascular profile of pimobendan, benzimidcizole pyridazinone derivative (**LX**) with vasodilating and inotropic properties. This improves cardiac output with severe myocardial ischemia. The cardiovascular effect of pimobenden excludes the involvement of adrenoreceptor mechanism [51]. Based on pyridazinones, several l,2-dinydro-5-(substituted phenyl)-2(1H)-pyridinones were evaluated for inotropic activity [52]. The 1,2 dihydro-5-[4-(1H-imidazo-l-yl)phenyl]-6-methyl-2-oxo-3-pyridinecarbonitrile (**LXI**) and the corresponding unsubstituted analogue (**LXII**) were the most potent ionotropic agents.

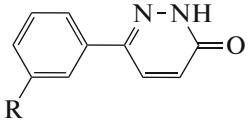


(**LX**)

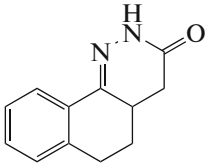


(**LXI**) R = 1-imidazolyl,
$R_1 = CH_3$, $R_2 = R_3 = H$, R_4 = -CN;
(**LXII**) R = 1-imidazolyl,
$R_1 = R_2 = R_3 = R_4 = H$

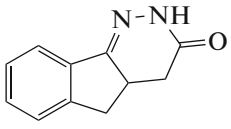
The conformationally constrained congeners of 6-aryl-4,5-dihydro-3(2H)-pyridazinones active on the cardiovascular system. Unsubstituted phenyl pyridazinones (**LXIII**), (**LXIV**) and their tricyclic analogues arylpyridazinone (**LXV**), benzocinnolinone (**LXVI**) and benzocyclohepta-pyridazinone (**LXVII**) were submitted to relate the cardiovascular activity [53].



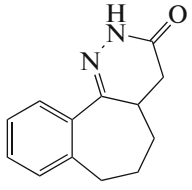
(**LXIII**) R = H;
(**LXIV**) R = CH_3



(**LXV**)



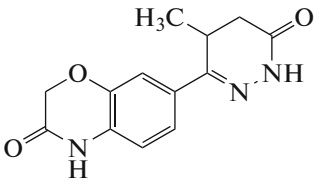
(**LXVI**)



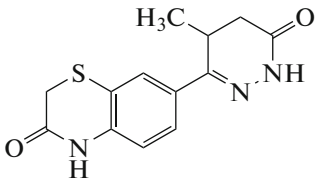
(**LXVII**)

A series of close analogues of the potent long acting cardiotonic, bemoradan (**LVIII**) [54], replacement of oxygen atom in the benzoxazine ring of bemoradan with sulfur gave the compound (**LXIX**). Lack of a het-

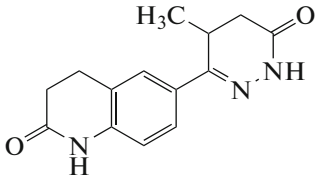
eroatom at the 1 position afforded a compound (**LXX**) with activity and potency very similar to those of bemordan while the compound (**LXXI**) gave a much less potent.



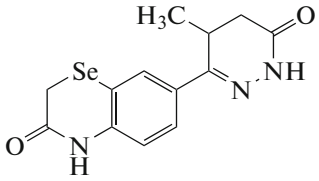
(**LXVIII**)



(**LXIX**)

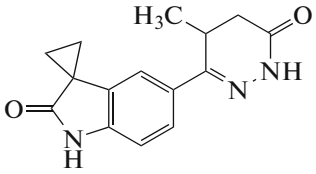


(**LXXX**)

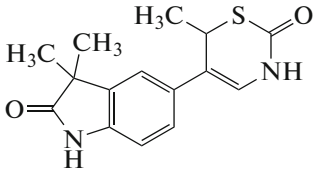


(**LXXI**)

The 1,3-dihydro-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2H-indol-2-ones as cardiotonic that a spirocyclo alkyl ring may be annealed to the C-3 position of the indoline moeity while retaining inotropic activity [55]. The compound (**LXXII**) was found to be most potent. The dipyridazinone or thidadiozionone cardiotonic agents with the chiral center The PDE inhibitory and myofibriliar calcium sensitization action was found in different enantiomers of the compound (**LXXIII**) [56].

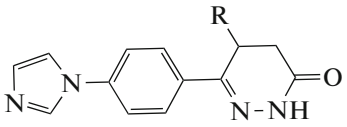


(**LXXII**)

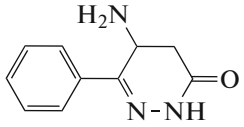


(**LXXIII**)

Two potent positive inotropic agents have developed for the treatment of CHF namely 4,5- dihydro-6-[4-(1H-imidazo-1-yl) phenyl]-3(2H)-pyridazinone (**LXXIV**) (CI-914) and 4,5-dihydro-6-[4-(lH-imidazol-l-yl)phenyl]-5-methyl-3(2H)pyridizinone (**LXXV**) (CI-930) [57]. The substituted 4-aryl-2,5-dioxo-8-phenylpyrido-[2,3-d]pyridazines compounds (**LXXVII**–**LXXXII**) from the corresponding arylidene substituted meldruin acid and 5-amino-6-phenyl-3(2H)-pyridazinone (**LXXVI**). All these compounds exhibiting cardiotonic effect [58].



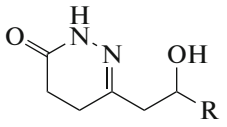
(**LXXIV**) R = H
(CI-914, Imazodan);
(**LXXV**) R = H (CI-930)



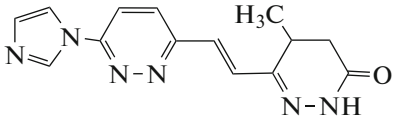
(**LXXVII**) R = 2-NO_2-C_6H_5-;
(**LXXVIII**) R = 2-Cl, 6-F-C_6H_3-;
(**LXXIX**) R = 2,6-diCl-C_6H_3-;
(**LXXX**) **81** R = 2,4-diNO_2-C_6H_3-;
(**LXXXI**) R = 2-Cl, 5-NO_2-C_6H_3-;
(**LXXXII**) R = 4-Cl, 3-NO_2-C_6H_3-

Pharmaceutically important 6-substituted-4,5-dihydro-3(2H)-pyridazinones, the ionotropic and chronotropic effects of compound (**LXXXIII**–**LXXXV**) on isolated cardiac preparation from guinea pig hearts

[59]. A series of (E) 4,5-dihydro-6-[2-[4-(1H-imidazo-I-yl)phenyl]ethienyl]-3(2H)-pyridazinone with various substituent in imazodan (**LXXV**) [60] were tested for hemodynamic, cAMP-PDE inhibitory, platelet aggregation inhibitory activities. The insertion of the ethenyl moiety between the phenyl and dihydropyridazinone ring produced a compounds that retained the potent inotropic or and vasodilator activity of the parent imazodan. The compound (**LXXXVI**) was found most potent in this series.

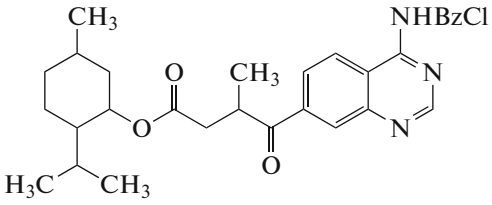


(**LXXIII**) R = *n*-C_4H_9;
(**LXXXIV**) R = *n*-$C_{11}H_{23}$;
(**LXXXV**) R = $CH_2C_6H_3$;

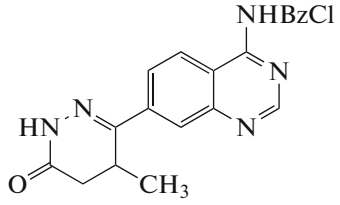


(**LXXXVI**)

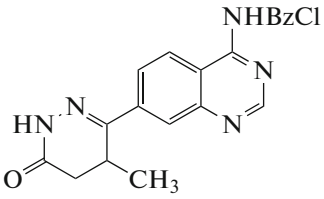
The optically active 1±-4-(4-(benzylamino)-7-quinazolinyl)3-methyl-4-oxobutyric acid (–) menthyl ester (**LXXXVII**). The dextro compound (**LXXXVIII**) was showed only weak cardiotonic and vasodilating eactivity. The recemic and levo (–) isomers (**LXXXIX**) was used in congestive heart failure (CHF) [61]. The compound T-ZC-5665 (**XC**) exhibited cardiac and hemodynamic effects [62]. The potent cardiotonic action of pyridazinones (**CI-914**) (**LXXIV**) **75** and (**CI-930**) (**LXXV**) along with amrinone (**XCI**) and milrinone (**XCII**) [63].



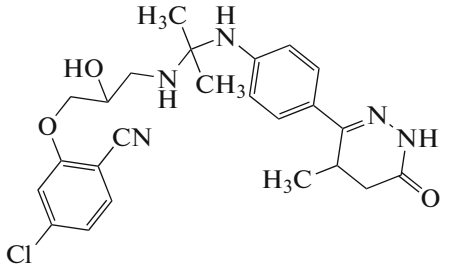
(**LXXXVII**)



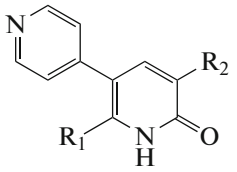
(**LXXXVIII**)



(**LXXXIX**)



(**XC**)

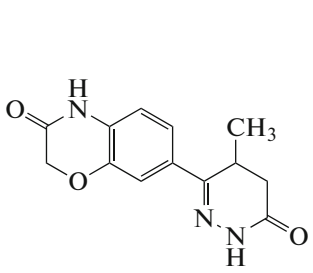


(**XCI**) R = H, $R_2 = NH_2$;
(**XCII**) R = CH_3, R_2 = CN

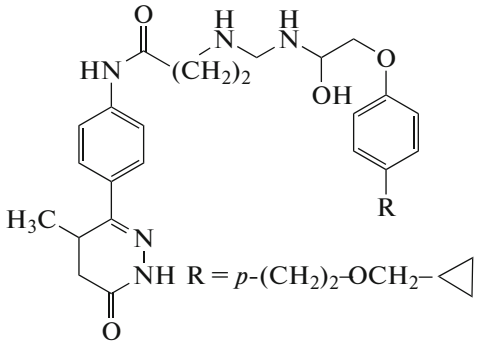
Phosphodiestrase Inhibitor and Vasodilator

A series of 6-benzoxacinyl pyradazin-3-ones was tested for inhibition of cardiac phosphodiestrase-III (PDE-III) fraction in vitro andfor the inotropic activity in vivo 6-[3,4-dihydro-3-oxo-l,4-(2H)-benzooxazin-4-yl]-2,3,4,5-tetrahydro-5-methyl pyradazin-3-one (**XCIII**) was found to be very potent and selective inhibitor of canine PDE-III fraction and long acting potent, orally active inotropic, vasodilator agent. The most active and potent compound contains a methyl group at C-5 position of the pyridazinone ring. Substitution as either of free nitrogen atoms reduces in vivo activity [64]. To determine selective inhibitors of certain cyclic nucleotides PDE families CI-930, PDE-III inhibitor and rolipram PDE-IV inhibitors effect human coronary allergy smooth muscle cell proliferation [65]. A series of 6-[4-[[aryloxy)acyl]amino]phenyl]-4,5-dihydropyridaziones have been evaluated as combined vasodilator and adrenoceptor antagonist and potential antihypertensive agents [66]. All of these compounds were vasodilators but the 5-methyl pyridazine derivative showed

constantly greater antihypertensive activity than their lower homologue. The pharmacological study led to the selection of 6-[4-[[z-hydroxy-3-[4-[2-cyclopropylmethoxy)ethyl]phenoxy]propyl]amino] propionamido]phenyl]5-methyl-4,5-dihydro-3(2H)-pyridazinone (**XCIV**).

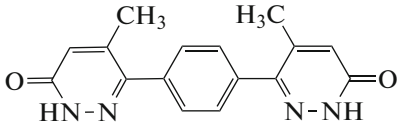


(XCIII)

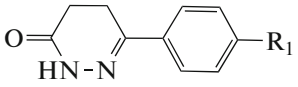


(XCIV)

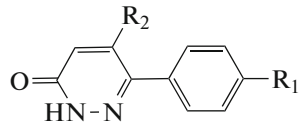
The 1,4-bis(3-oxo-2,3-dihydropyridazine-6-yl)benzene and a series of related bis(azinone) compounds were tested [67]. The most potent PDE-III inhibitor of the series was 6-[4-(5-methyl-3-oxo-2,3,4,5-tetraliydro pyridazin-6-yl)phenyl]pyridazin-3(2H)-one (**XCV**). A methyl group at the C-5 position of dihydropyridazinone ring leads to enhanced potency. The inotropic and vasodilator properties of substituted 6-phenyl-pyridazin-3(2H)-ones are well recognized. Activity is retained by the phenyl pyridazinone derivatives (**XCVI**, **XCVII**) and (**XCVIII–CI**) where R_1 is a small, heteroatom containing substituent and compound in which R_1 is acetamido or 1H-imidazol-1-yl are particularly potent [68].



(XCV)



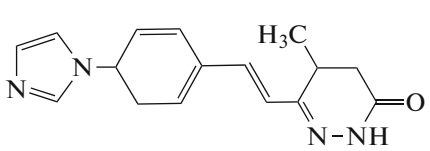
(XCVI) R_1 = NHCOCH$_3$
(XCVII) R_1 = 1-imidazolyl



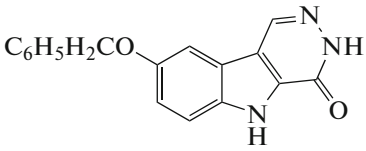
(XCVIII) R_1 = NHCOCH$_3$, R_2 = CH$_3$;
(XCIX) R_1 = NHCOCH$_3$,
(C) R_2 = R_1 = 1-imidazolyl, R_2 = H;
(CI) R_1 = l-imidazolyl, R_2 = CH$_3$,

Anti-Thrombotic Activity

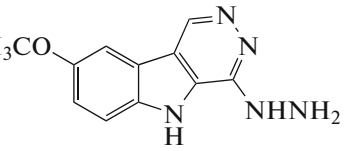
A series of analogues of (E)-4,5-dihydro-6-[2-[4(lH-imidazol-1-yl) phenyl]ethynyl]2(2H)-pyridazinone was tested for hemodynamic, cAMP-PDE inhibitory activity and platelet aggregation inhibitory activity. The compound (**CII**) was found to be most potent inhibitor for platelet aggregation [69]. For any antithrombotic drug a more effective approach may be the selective inhibition of thromboxane synthetase. Thromboxane (TxA) is rapidly hydrolysed into TxB2, which is a potent vasoconstrictor and platelet aggregating agent. A series of 4-hydrazino-5H-pyridazino [4,5-b]indole and 4-hydrazine[4,5-a]indole derivatives were tested for their thromboxane synthetare inhibitor activity. The compound (**CIII**) and (**CIV**) were not only found potent as anti-thrombotic but also showed antihypertensive activity similar to that of hydralazine and 2.2 times less toxicity in mice [70].



(**CII**)

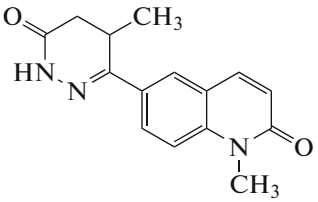


(**CIII**)

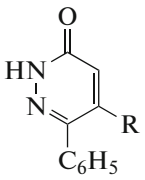


(**CIV**)

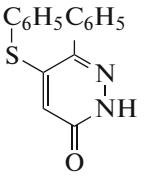
The effect of 6-{2,3,4,5-tetrahydro-5-methyl-3-pyridazine-6-yl)-1,2,3,4-tetraliydro-1-methyl quinolin-2-one (**CV**) (Y-590) on platelet phosphodiestrase. The compound Y-590 potently inhibited cAMP-PDE but its inhibitory effect on c-GMP-PDE was less potent. Y-590 is a selective inhibitor of CAMP-PDE which exerts antiplalelet activity by inhibiting cAMP degradation in platelets [71]. Some 6 aryl 5-oxygenated substituted pyridazinones have been evaluated in vitro for inhibition of platelet aggregation induced by adenosine 5-disphosphate (ADP), thrombin and collagen [72]. The inhibition of platelet aggregation of compound was dependent on the level of oxidation of the function at the C-5 position, with the order of IC_{50} values being R–OH (**CVI**) < R–CHO (**CVII**) ⋘ R–COOH (**CVIII**). The group present at the C-5 position of 6-aryl-5-substituted pyridazinones determines the platelet aggregation inhibitory activity. A series of 6-phenyl-3(2H)pyridazinones with diverse range of substituents at C-5 position have been teted in the search of better antiplatelets agent. The compound (**CIX**) was found to have highest efficacy [73]. Most of the compounds were showed antiaggregation activity in the micromolar or submicromolar range; the most active compounds were (**CX**–**CXI**) [74].



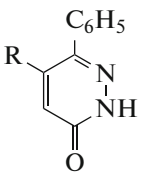
(**CV**)



(**CVI**) R = CH_2OH;
(**CVII**) R = CHO;
(**CVIII**) R = COOH

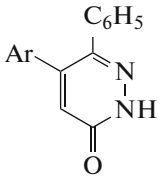


(**CIX**)

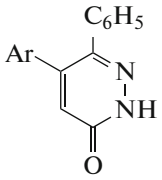


(**CX**) R = CH=CH-C_6H_5;
(**CXI**) R = CH=CH-C_2H_5

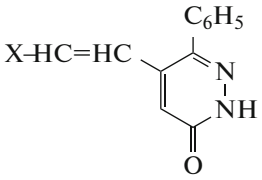
A series of 5-substituted-6-phenyl-3(2H)pyridazlnones as potential anti platelets drugs [75]. The most active compounds were those that contain 3-phenyl-3-oxo-propenyl group or a phenylthio group at C-5 position. Two compounds (**CXII**) and (**CXIII**) were interesting. Various 5-substituted 6-phenyl-3(2H)-pyridazinone were tested for their antiplatelet activity. A significance dependence of the substituent on the inhibitory effect has been observed. These compounds confirms that modification of chemical group at C-5 position influences both variation in the antiplatelet activity [76]. The most active compounds were (**CXIV**) and (**CXV**) but not better than compound (**CIX**). Some 6-phenyl-3(2H)-pyridazinones (**CXVI**) and (**CXIX**) bearing alkenyl groups at C-5 position have antitplatelets drugs [77].



(**CXII**) Ar = *p*-$CH_3C_6H_5$;
(**CXIII**) Ar = 2-Fury1



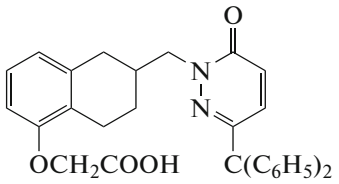
(**CXIV**) Ar = $CH_2OC_6H_5$;
(**CXV**) Ar = OC_6H_5



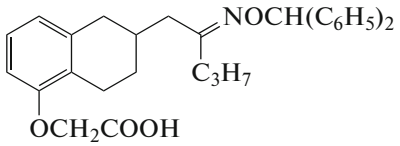
(**CXVI**) X = COOEt;
(**CXVIII**) X = CN;
(**CXVII**) X = COOMe;
(**CXIX**) X = C_6H_5

Anoptically pure pyridaziznone derivatives were recognized as a non prostanoid PGI2 agonist [78]. The compound (**CXX**) (FR181877) was exhibited potent nonprostanoid PGI2 activity in human plate-

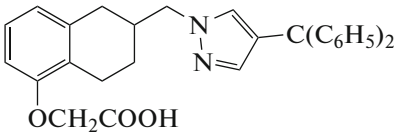
lets and has high oral bioavailability in rats. The pyridazinone functional group was alternative to the oxime group of compound (**CXXI**) (AP227) or pyrazole group of compound (**CXXII**) (AP437).



(**CXX**)

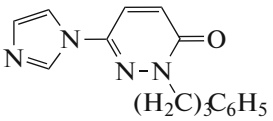


(**CXXI**)

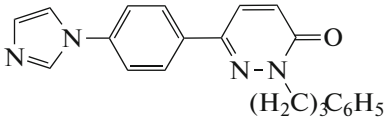


(**CXXII**)

Compounds (**CXXIII**–**CXXIV**) exhibited thromboxane synthetase inhibiting activity. These compounds inhibited platelet aggregation induced by arachidonic acid (AA), ADP, collagen and simultaneously suppressed the synthesis of TXA2 and increased the production of PGE2 [79].

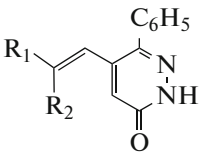


(**CXXIII**)

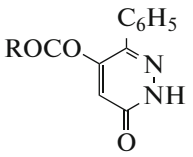


(**CXXIV**)

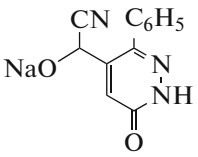
The antiplatelet effects of several 5-alkylidene-6-phenyl-3(2H)-pyridazinones, the most potent compounds are those that contain oxygenated functional groups like compounds (**CXXV**–**CXXVII**) [80]. The highly efficient pharmacologically useful 4-cyano-6-phenyl-5-substituted-3(2H)-pyridazinones, the direct cyanide addition offers a pharmacologically useful 4,5-clifunctionalized 6-phenyl-3(2H)pyridazinones. The compounds (**CXXVIII**–**CXXXI**) were showed encouragingly antiplatelet activity [81].



(**CXXV**) R_1 = COMe, R_2 = COOMe;
(**CXXVI**) R_1 = COOMe, R_2 = COOMe;
(**CXXVII**) R_1 = COEt, R_2 = COOEt

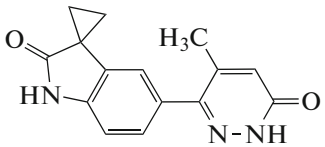


(**CXXVIII**) R = CH_3;
(**CXXIX**) R = C_2H_5;
(**CXXX**) R = $CH(CH_3)_2$



(**CXXXI**)

Spirocyclopropane indole pyridazinone were tested for inotropic activity. A spirocycloaikyl ring annealed to the indole-3-position retains inotropic activity and an inverse relationship was found between spiroalkyl ring size and inotropic activity. The compound (**CXXXII**) was found to be most potent non catecholamine and non glycoside positive inotrope [60].



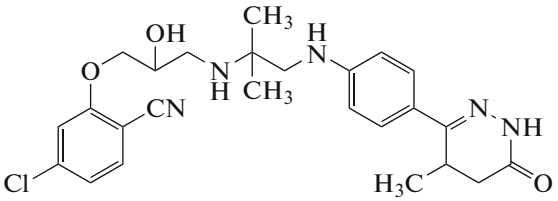
(**CXXXII**)

The 5-methyl substitution in the dihydropyridazinone ring (β to pyridazinone carbonyl) leads to enhance

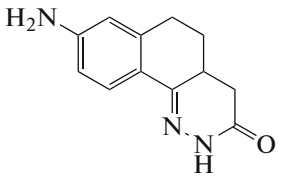
in inotropic potency of this series and tends to generate a greater decrease in mean arterial blood pressure (B.P) than the other congeners. When cycloalkyl ring size is four or five carbon atoms, inotropic potency is sustained or decrease relative to unsubstituted derivative whereas a ring size of three carbon atoms results in 10 fold enhance in potency.

Antihypertensive Activity

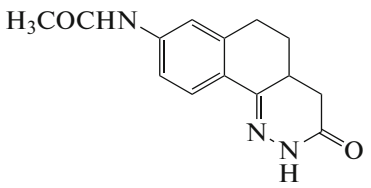
A series of pyridazinone derivatives having a phenoxypropanol amine moiety were tested for hypotensive and β-blocking activities [82]. Among them 5-chloro-2-cyano-2-cyanophenoxy compound (**CXXXIII**) and its mono ethyl maleate salt were posses most promising β-adrengic receptor blocking activity and use in the treatment of congestive heart failure (CHF). Several substituted 3H-benzo[6,7]-cyclohepta[1,2-c]pyridazinones were tested for anti hypertensive and inotropic activity [83]. The 8-amino and 8-acetylamino derivatives (**CXXXIV**) and (**CXXXV**) respectively together with the 4,4a-dihydro analogue were possess most potent and long lasting antihypertensive activity. A series of 4-hydrazino-5H-pyridazino[4,5-b]indoles and their melabolites 3,4-dihydro-4-oxo-5H-pyridazino[4,5-b]indoles (**CXXXVI**) were tested for antihypertensive activity [84]. The compound (**CXXXVI**) was found to be active at a dose of 25 mg/kg i.p Bulky substitution on nitrogen atom of indole ring reduced the activity considerably. The 3-hydrazino-cycloheptyl[1,2-c]pyridazinone and its hydrazone derivative were tested against genetic DOCA induced hypertension and was found to be at less potent than hydralazine [63]. The vaso-relaxation of rat aorta caused by compound (**CXXXVII**) and they have antihypertensive activity due to direct relaxation of vascular smooth muscles.



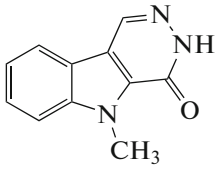
(**CXXXIII**)



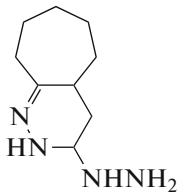
(**CXXXIV**)



(**CXXXV**)

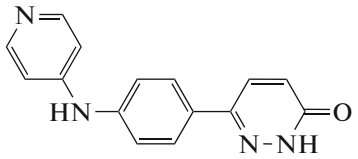


(**CXXXVI**)

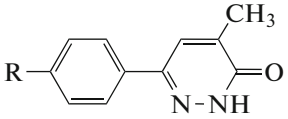


(**CXXXVII**)

The compound (**CXXXVIII**) was tested for contractile properties of skinned rabbit skeletal muscle fibers showed that the drug in cardiac muscles potentiated isometric tension and improved isometric tension during full Ca^{++} activation. Hence, drug is MCI-154 used for the treatment of CHF [85]. The hypotensive activity of some 6-(substituted aryl)-4methyl-2,3-dihydropyridazionones-3-ones, compounds (**CXXXIX–CXLII**) were showed satisfactory hypotensive activity at a dose of 100 mg/kg body weight in normotensive rats. The result indicated that the compounds with bulky substitution at C ~ 5 position add to the hypotensive activity appreciably [86].



(**CXXXVIII**)



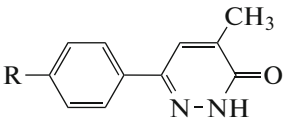
(**CXXXIX**) R = $C_6H_5CH_2$;

(**CXL**) **146** R = $C_6H_5CH_2O$;

(**CXLI**) R = C_6H_5;

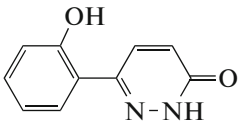
(**CXLII**) R = 6-methoxy-2-naphthyl

The antihypertensive properties of 6-{substitutedphenyl)-5-substituted4,5-dihydro-3(2H)-pyridazinones, consistent antihypertensive activity of the 6-(alkyl amino phenyl) compound and their acyl derivatives (**CXLIII–CLI**) were confirmed [87].

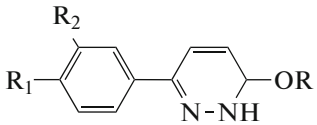


(**CXLIII**) R = *m*-CH_3NH, R_1= CH_3, R_2 = H;
(**CXLIV**) R = *p*-$N(CH_3)COCH_3$, R_1 = CH_3, R_2 = H;
(**CXLV**) R = *p*-$N(C_2H_5)COCH_3$, R_1 = H, R_2 = H;
(**CXLVI**) R = *m*-NO_2, R_1 = CH_3, R_2 = CH_3;
(**CXLVII**) R = *p*-CN, R_1 = CH_3, R_2 = CH_3;
(**CXLVIII**) R = *m*-Br, R_1 = CH_3, R_2 = H;
(**CXLIX**) R = *p*-F, R_1 = CH_3, R_2 = H;
(**CL**) R = *m*-CONH, R_1 = CH_3, R_2 = H;
(**CLI**) R = *p*-CONH, R_1 = CH_3, R_2 = H

The 6-(2-hydroxy-phenyl)-3-pyridazinone (**CLII**) was found to be quiet promising [88].The acid base behavior for some 6-disubs£ituted phenyl 4,5-dihydro-3(2H)-pyridazinones (**CLIII–CLVI**) with potential antihypertensive effects [89].



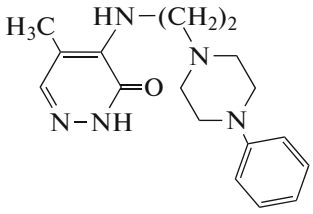
(**CLII**)



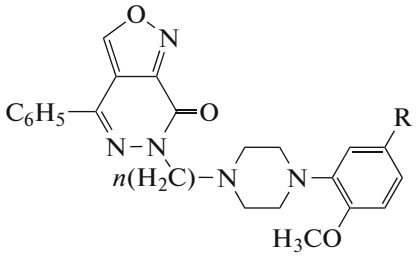
(**CLIII**) R = H, R_1 = Cl, R_2 = C1;
(**CLIV**) R = H, R_1 = Cl, R_2 = Br;
(**CLV**) **161** R = CH_3, R_1 = H, R_2 = H;
(**CLVI**) R = CH_3, R_1 = H, R_2 = CH_3

Adrenoreceptor Antagonist Activity

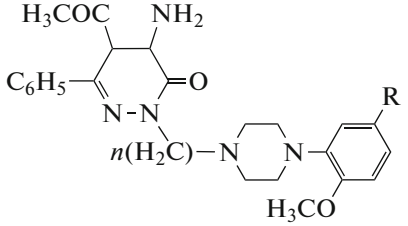
Phenyl piperazinyl alkyl amino substituted pyridazinones were tested for their α_1-adrenoreceptor antagonistic activity. Compound (**CLVII**) selectively acted upon α_1-adrenoreceptor at a dose of 25 mg/kg [90]. A series of phenyl piperazinyl alkyl moieties were attached to monocyclic or bicyclic substituted pyridazinones and the compounds tested for their affinity towards α_1-adenoreceptor and its α_1a, α_1b and α_1d subtypes as well as erotonin $5HT_1$a receptor. Several compounds (**CLVIII–CLXI**) were showed significant potency and selectivity towards α_1a and α_1d and with respect to α_1b subtype [71].



(**CLVII**)



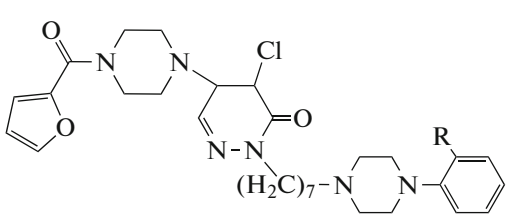
(**CLVIII**) *n* = 2 R = H;
(**CLIX**) *n* = 2 R = Cl



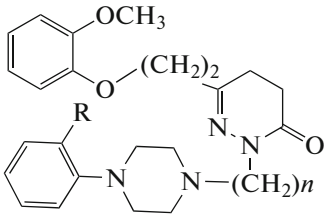
(**CLX**) *n* = 2 R = H; (**CLXI**) *n* = a R = Cl

A series of 3(2H)-pyridazinones were tested for their affinity in vitro towards α_1–α_2 adreno-receptor by radio-ligand receptor binding assay. A gradual increase in affinity was found by increasing the polymethylene chain length up to maximum of 6 to 7 carbon atoms between furoyl-piperazinyl-pyridazinone and aryl-piperazine moiety. The compounds (**CLXII–CLXIII**) were found to potent [92]. In the series, a gradual increase in affinity was found by promoting

the polymethylene chain upto 6–7 carbon atoms, when the fragment 4-{2-(2-methoxy phenoxy) ethyl}-1-piperazine is linked at C-5 position of the 3(2H)-pyridazinone. The compounds (**CLIV–CLVII**) showed affinity in vitro towards α_1–α_2 adrenoreceptor [93].



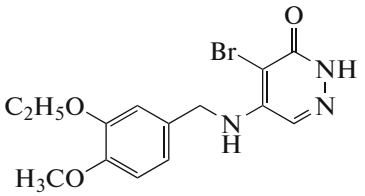
(**CLXII**) R = CH_3O;
(**CLXIII**) R = C_2H_5O



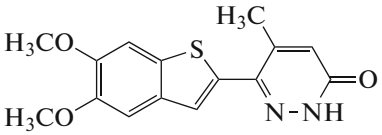
(**CLIV**) *n* = 6 R = OCH_3;
(**CLVI**) *n* = 6 R = Cl;
(**CLV**) *n* = 7 R = OCH_3;
(**CLVII**) *n* = 7 R = Cl

Antihistaminic Agents

The effect of pyridazinone compound (**CLVIII**) **173** (NZ-107) and two known antiastmatic drugs, amiexone and disodium cromoglycate on antigen, histamine and leukotriene CT4 induced constriction of isolated tracheal muscle and histamine release from human lung tissue. All of them found toinhibit the antigen induced release of histamine and LTC4 from human lung tissue [94–96]. The effects of selective phosphodiestrase inhibitors rolipram (PDE-IV selective), pyridazinone derivative (**CLIX**) (Org 9935, PDE-III selective) administered by inhalation in approximately equipotent bronchodilator effects [97].



(**CLVIII**)



(**CLIX**)

Table 1. Pyridazinone moiety containing pharmacological drugs

S. no.	Drug name	Uses	S. no.	Drug name	Uses
1	Azelastine	Bronchodilator	12	Bemorandan	Cardiotonic
2	Emorfazon	Analgesic	13	Chloridazon	Herbicide
3	Ag 246	Analgesic	14	Norflurazon	Herbicide
4	Imazodan	Cardiotonic	15	BAS 44521 OR SAN 9789	Herbicide
5	Amipizon	Antithrombotic	16	Pyridaben	Insecticide and acaricide
6	CI 930	Phosphodiestrase inhibitor	17	Phthalazin-1-one	Antifungal
7	Indolidan	Cardiotonic	18	Brompyrazon	Herbicide
8	Zardaverine	Phosphodiestrase III/IV inhibitor	19	Metflurazon	Herbicide
9	Pimobendan	Cardiotonic	20	Flufenpyr	Herbicide
10	Zopolrestat	Antidiabetic	21	Oxapyrazon	Herbicide
11	KK 505	Antiasthmatic			

CONCLUSION

The derivatives of pyridazine are expected to have diverse biological activities. Pyridazines are important class of heterocycles present in various biologically active molecules and have broad applications as pharmaceuticals and agrochemicals, dyes, biodiagnostics etc. They have exert antitubercular, anti-inflammatory, analgesic, antihistaminic, antidepressant, antihypertensive, antimicrobial, antianxiety, antifungal, antitumor, phosphodiesterase inhibitors, insecticidal, pesticidal and acaricidal activities. Pyridazinone ring has been extensively studied in the search for new and selective drugs molecules. The efforts to synthesize of pyridazine derivatives from readily available starting materials for the synthesis of new pyridazine compounds in order to explore their desired biological activities.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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