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Diverse Biologically Active Pyridazine Analogs: A Scaffold for the Highly Functionalized Heterocyclic Compounds[1]

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Abstract—Nitrogen atom containing heterocycles showed diverse biological properties are important structural feature of many physiologically active compounds. Pyridazines and phthalazines hold considerable interest relative to the preparation of physiologically active compounds. The pyridazine compounds also show antifeeedant, insecticidal, herbicidal, molluscicidal, plant growth regulatory and other agrochemical activities. The various pyridazine drugs are selective PDE-III inhibitors possessed positive inotropic effect combined with vasodilation. These agents are effective in different cardiovascular diseases like acute and chronic heart failure, myocardial infarction, angina, arrhythmia, and hypertension. Pyridazines and phthalazines further focus our attention because of their easy functionalization at various ring positions, which makes them attractive synthetic compounds for designing and development of the novel pyridazines and phthalazines drugs in future. Various substituted pyridazine derivatives were also reported to show antibacterial, antifungal, and antiviral properties. We considered some compounds bearing pyridazine in their molecular framework.

Keywords: Biological activities, drugs, phthalazines, pyridazines, pyridazinone, structural feature, antifeedant, fungicides, herbicidal, plant growth regulator

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1. INTRODUCTION

The use of aromatic heterocycles has become ubiquitous in recent years in a variety of applications, ranging from pharmaceuticals to materials and, as a result, the chemistry of heteroaromatic systems has been studied in detail. Consequently, this chapter will offer a general introduction to heteroaromatic

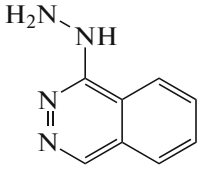
[1] The article is published in the original.

chemistry, before a more detailed discussion of pyridazine chemistry and corresponding fluorinated systems. The structures of the three diazines (pyridazine, pyrimidine and pyrazine) consist of two nitrogen atoms in a six membered aromatic ring. The basicity of the diazines is reduced, relative to pyridine, due to the electron withdrawing effect of the second ring nitrogen destabilising the protonated cation. Pyridazine based systems have been shown to have numerous practical applications and the forthcoming section will outline some of these. There is a great desire for the synthesis of new heteroaromatic compounds, which have a range of applications from pharmaceuticals. These industries require large numbers of heterocyclic derivatives for their screening programmes, however many common routes for the synthesis of aromatic heterocycles do not allow for the flexible introduction of a diverse range of substituents. Our approach involves the use of pyridazine as a scaffold for the synthesis of a diverse range of heteroaromatic systems. Heteroaromatic compounds, such as pyridazine, are highly reactive towards displacements by nucleophilic species. Sequential nucleophilic aromatic substitution reactions of pyridazine have been studied and a range of polysubstituted systems synthesised. Similarly, reactions of pyridazine with dinucleophiles have been utilised to yield ring-fused products, many of which are rare heterocyclic substructures. This approach has allowed the synthesis of a small library of compounds based on the pyridazine ring system with moderate skeletal and substituent diversity. Pyridazine, their oxygenated derivative-pyridazinone and benzfused pyridazine or phthalazine are heterocyclic compounds that contain two adjacent nitrogen atoms (1,2-diazine) in the ring structure. They show a wide range of pharmacological activities and are found in a lot of natural compounds having different biological activities [1–7].

2. BIOLOGICAL ACTIVITIES

Many heterocyclic compounds derived from synthetic as well as natural sources, commonly in practice contain one or more nitrogen in the heterocyclic ring system. Pyridazine and phthalazine (1,2-diazines) is an important membered heterocylic ring. Recently, much attention has been focused on pyridazine and phthalazine derivatives for their broad-spectrum biological activities. Various structural modifications were carried out in pyridazine and phthalazine ring system. These structural changes resulted in some fruitful biological activities of the pyridazine and phthalazine compounds [8–12].

Heteroaromatic scaffolds, such as pyridazine derivatives, have been shown to be "privileged structures" in medicinal chemistry, and many drug discovery programmes utilise a pyridazine as a core scaffold. Examples are far too numerous to give more than a flavour of the chemistry reported in the literature in this section, however it should be noted that pyridazine based systems are less common in the literature than those based on pyridine or the other diazines. Commercially available pharmaceutical pyridazines include **hydralazine**, an antihypertensive which acts as a vasodilator, azelastine, a bronchodilator used in the treatment of asthma, and minaprine, an antidepressant which acts as an acetylcholinesterase inhibitor [13–15]. Various pyridazine based heterocyclic scaffolds have been utilised in recent medicinal chemistry programmes against a range of biological targets and physiological effects. The pharmaceutical industry has a continuing requirement for the synthesis of a diverse range of polysubstituted pyridazin-3(2*H*)-ones bearing a varied range of ring substituents because many such compounds have been utilised as commercially available drugs and agrochemicals. Examples include the anti-platelet clotting agent Zardaverine, the anti-inflammatory Emorfazone and herbicides Pyridaben and Norflurazon [16–20].

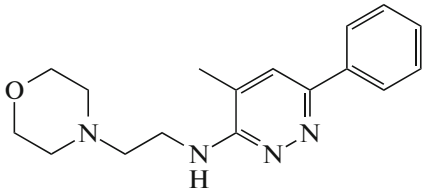


Hydralazine

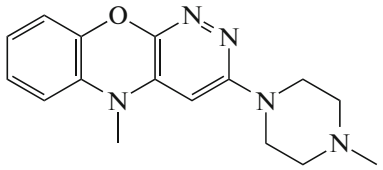
2.1. Pyridazines and Pyridazinones

Pyridazine and pyridazinone are six-membered heterocycles that contain two adjacent nitrogen atoms. They show a wide range of pharmacological activity and are found in a lot of natural compounds having a biological activity. Pyridazines have antimicrobial, anti-hypertensive and anticancer activity. In addition, pyridazinones are used for the treatment of platelet aggregation and ulcer [21, 22]. Pyridazine deriv-

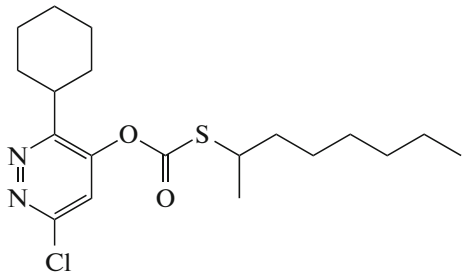
atives are found in skeleton of some commercially available drugs. For instance, Apresoline contains hydralazine as a pyridazine derivative that is used to treat hypertension for pregnant. Brantur is other drug which is used for the treatment of depression and it includes **minaprine** as an active compound. Azaphen is another medicine including pyridazine ring. It has **pipofezine** structure which is tricyclic anti-depressant having a sedative effect. Pyridazine derivatives are also widely used in agriculture as herbicides. For example, **pyridate** has thiocarbonate composition, **credazine** kill pests and unwanted plants. Comprises the ether linkage and **pyridafol** consists of alcohol unit. Pyridazinones hold considerable interest relative to the preparation of organic intermediates and physiologically active compounds.



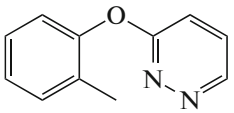
Minaprine



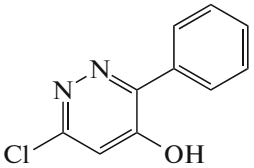
Pipofezine



Pyridate

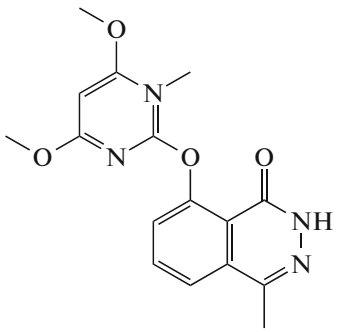


Credazine

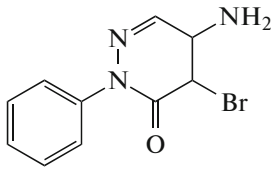


Pyridafol

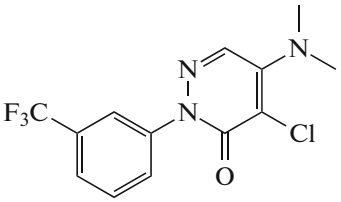
They are used as 5-HT agonists, which play an important role in emesis, mood, sexuality, sleep and appetite [13–15]. Moreover, pyridazinones exhibit bronchodilator activity on the cardiovascular system. They inhibit the blood platelet aggregation. Another pharmacological properties of pyridazinone derivatives is the reduction of blood pressure. Pyridazinone derivatives are also found as an inhibitor, such as **methylphthalazin-1-one** which is the inhibitor of acetohydroxyacid synthase (AHAS), an enzyme that speeds up the biosynthesis of branched-chain amino acids including leucine and valine. For the case, in the structure of AHAS inhibitor, **methylphthalazin-1-one**, pyridazinone ring is fused to benzene ring, which is called phthalazinone [15]. Some herbicides including pyridazinone ring in their structure have various functional groups on the pyridazinone ring. For example, **brompyrazon** and **metflurazon** have amine group in their skeleton and also they have halides such as bromine and chlorine, respectively.



Methylphthalazin-1-one

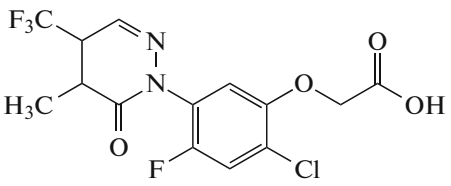


Brompyrazon

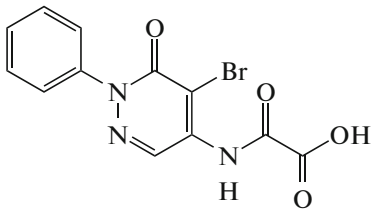


Metflurazon

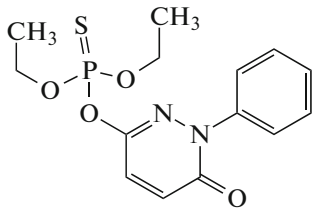
Several pyridazinone herbicides contain carboxylic acid as a functional group, such as **flufenpyr** and **oxapyrazon** [19]. Another important pyridazinone herbicide is **pyridaphenthion**, which comprises both sulphur and phosphorus. Furopyridazinone and utilized in the inhibition of thromboxane A synthetase and it showed bronchodilating activity [21–25].



Flufenpyr



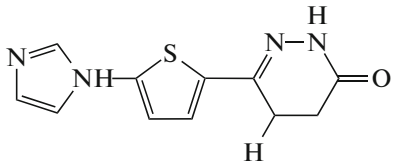
Ozapyrazon



Pyridaphenthion

Various pyridazinones have been reported as cardio-tonic and other cardiovascular activities [22, 24, 26]. These biological diversity in their biological activities are due to various structural modifications in the pyridazinone ring [26–28].

Large number of pyridazinone derivatives having various cardiovascular activities such as antiplateletes, antihypertensive, antianginal, antiarrthmic, cardiotonics and other anticipated activities [29, 30]. Traditional approach to the treatment of heart failure (HF) is the enhancement of myocardial contractility by the use of inotropic drugs to improve depressed cardiac function [31]. Pyridazinone based cardiotonics exhibited activity against CHF, however, different derivatives have shown difference in inotropic responses [32]. Aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones such as **imazodan** were showed ionotropic properties comparable to inotropic drugs like milrinone and amrinone. Pyridazinone compounds showed also other uses in cardiac activities such as cardiac diagnosis [33, 34].



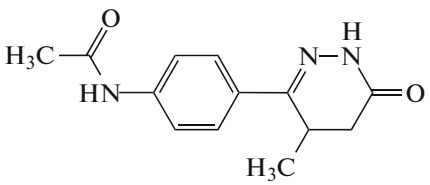
Imazodan

2.1.1. Pyridazine compounds. Substantial number of pyridazines have been reported to possess various biological activities such as antimicrobial, antitubercular, antifungal [35, 36], potent analgesic and anti-inflammatory [37, 38], Phosphodiesterase inhibitors [39], potent and selective cyclooxygenase inhibitors [40], antipyretic, antidiabetic [41], antifeedant, insecticidal [42], antihypertensive [29], antiplatelet [28], anticancer [43, 44], anticovulsant [45, 46], inhibitory activity against the reverse transecripatase of HIV-1, inhibitor of bronchial asthma and allergy [47], molluscicidal, insect antifeedant, herbicidal [48–51], gastric anti-secretory, anti-ulcer activities [52, 53], insect and their larval growth regulator, on armyworm, *Pseudaletia separata* [54], neurological activity, anti anxiety and depressant [55], aldose reductase inhibitory activity [56] and intermediates for drugs. Some pyridazinone compounds have activity toward both α_1- and α_2-adrenoceptors [57] and analogues of the neurotransmitters GABA and glutamate [27], adenosine A_1 receptor antagonist [58], used in brain imaging in rats myocardial imaging agent [59, 60], agrochemicals and other anticipated biological [61] properties. Large numbers of pyridazinone derivatives are well known as therapeutic agents. The diverse biological activities of various functional derivatives of substituted phtahlazines are well known. Some of the phtahlazines derivatives have clinical medicine value such as antipyretic, analgesic, cardiovascular, vasodialator and antihypertensive properties [62–64]. Phtahlazines bearing a substitution represent the synthesis of various compounds with interesting biological properties. Phtahlazines have selective phosphodiesterase (PDE) inhibitor or the thromboxane synthetase inhibitor and bronchodilator activities [65–68]. The development of potentially bioactive phthalazine derivatives is important [69–73]. The structural modifications of the parent system which have been carried out in order to optimize the biological activity of phthalazine-derived drugs can be seen as a variation of the substitution pattern at position 1, 2, and 4 [74].

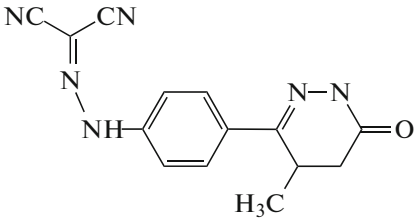
3. PYRIDAZINE AND PHTHALAZINE DRUGS

Pyridazine and phthalazine derivatives are found in skeleton of some commercially available drugs. For instance, apresoline contains **hydralazine** as a pyridazine derivative that is used to treat hypertension for pregnant [75]. Brantur is other drug which is used as antidepression [76] and it includes **minaprine** as an active compound. It has **pipofezine** which is tricyclic anti-depressant having a sedative effect [77]. Pyridazine derivatives, **pyridate** has thiocarbonate composition, **credazine** comprises the ether linkage and **pyridafol** consists of alcohol unit [78, 79]. They are used as 5-HT2c agonists, which play role in emesis, mood, sexuality, sleep and appetite. Pyridazinones exhibit bronchodilator activity on the cardiovascular system and also act as antiplatelet [80]. Other biological activity of pyridazinones is antihypertensive activity. Pyridazinones are also used as an inhibitor, such as **methylphthalazin-1-one** which is the inhibitor of acetohydroxy acid synthase (AHAS), an enzyme that speeds up the biosynthesis of branched-chain amino acids including leucine and valine [81]. The AHAS inhibitor, **methylphthalazin-1-one** is called phthalazinone.

Pyridazinones like **SK&F-93741,** its nor-methyl derivative and **levosimendan**, possess a substituted amino group at *para*-position of 6-phenyl ring and have potent cardiotonic agents with dual inotropic and vasodilatory activity [30].

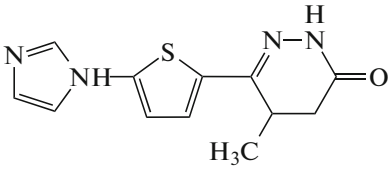


SK&F-93741

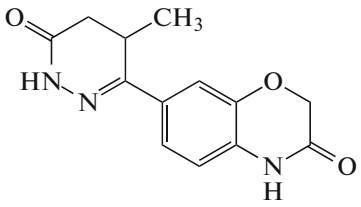


Levosimendan

These pyridazinone derivatives have good activity against congestive heart failure (CHF). Besides, aryl-substituted 4,5-dihydro-3(2*H*)-pyridazinones such as **imazodan** and **Cl 930** show ionotropic activity [82]. These pyridazine drugs have relatively selective inhibitors of cardiac cyclic nucleotide phosphodiesterase (PDE) activity. A series of 6-benzoxazinylpyridazin-3-ones were inhibited cardiac PDE-III and exhibited positive inotropic activity. The 6-(3,4-dihydro-3-oxo-1,4-(2*H*)-benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methyl pyridazin-3-one (**bemoradan**) was potent and selective inhibitor of PDE-III [83] and a long-acting, potent inotropic vasodilator and treatment of CHF.



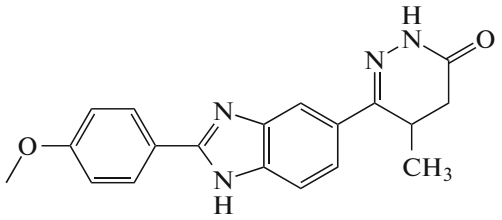
Cl 930



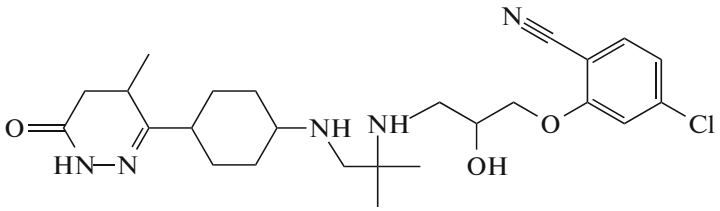
Bemordan

Some benzothiazolyl, imidazobenzothiazolyl, benzothienyl, benzothienopyrimidinyl and quinazolinyl 4,5-dihydro-3(2*H*)-pyridazinones exhibited cardiotonic activity, and 6-(4-(benzylamino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (KF15232) showed potent cardiotonic activity with Ca^{2+}-sensitizing effect [84]. A series of (E)-4,5-dihydro-6-(2-(4-(1*H*-imidazol-1-yl) phenyl) ethenyl)-3(2*H*)-pyridazinones as a variation on the **imazodan** series were tested for hemodynamic activity, cyclic AMP-PDE inhibitory activity, and antiplatelet activity. The 4,5-dihydro-6-(2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl)methyl-3(2*H*)-pyridazone exhibited positive inotropic effect. The calcium antagonist pyridazinone derivative, **pimobendan** is a PDE inhibitor with vasodilating, antihypertension and positive inotropic properties. The 6-(4-(2-(3-(5-chloro-2-cyanophenoxy)-2-hydroxypropylamino)-2-methylpropyl-

amino) phenyl)-4,5-dihydro-5-methyl-3(2*H*)pyridazinone monoethyl maleate **TZC-5665** showed negative chronotropic and inotropic effects, **TZC-5665** showed a non-selective β-adrenoceptor blocking activity comparable to that of propranolol. In enzyme preparations, **TZC-5665** was more potent and selective inhibitors of PDE-III. Combination of β-adrenoceptor blocking effect of **TZC-5665** and positive inotropic effect could be useful in the treatment of CHF [85, 86].



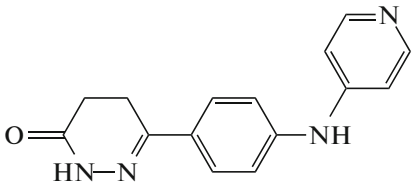
Pimobendan



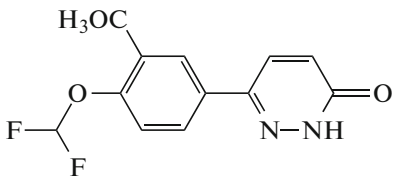
TZC-5665

A potent Ca^{2+}-sensitizer, the effects of the pyridazinone derivative **pimobendan**, increased force of contraction by sensitizing of the contractile proteins towards Ca^{2+} and by inhibition of PDE-III isoenzymes [87]. **Levosimendan** is a pyridazinone-dinitrile derivative is a cardiac inotropic drugs, Ca^{2+} sensitizers, as a vasodilator. The lowering of Ca^{2+} by **levosimendan** consistent with opening of potassium channels and a relaxation that is independent of Ca^{2+} [88]. **Pimobendan** is a benzimidazole-pyridazinone derivative with calcium-sensitizing properties that increases myocardial contractile force without increasing intracellular calcium. The **pimobendan** is useful in heart failure [89].

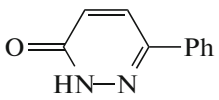
The Ca^{2+} sensitizers, a class of cardiotonic agents, have exerts positive inotropic effects without increasing intracellular Ca^{2+} transient. They avoid Ca^{2+} overload that leads to arrhythmias. Therefore, Ca^{2+} sensitizers is useful for the treatment of heart failure. The **MCI-154**, 6-(4-(4'-pyridylamino) phenyl)-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride trihydrate, is a calcium sensitizer that has more potent positive inotropic effect than that of pimobendan and adibendan. The effect of a cardiotonic agent, **MCI-154**, showed little Ca^{2+}-sensitizing effect. The **MCI-154** acts directly on skeletal actomyosin and inhibits ATPase cycle later than the force-generating event [90]. The **MCI-154**, is a Ca^{2+} sensitizer that has more potent positive inotropic effect than that of pimobendan and adibendan [90]. **Levosimendan** increases myocardial contractility and vasodilator [91]. The pyridazinone derivative, **zardaverine** is a selective inhibitor of PDE isozymes as a potent bronchodilator, positive inotropic action and ADP-induced aggregation of human platelets. **Zardaverine** inhibited the cyclic GMP-inhibitable PDE III from human platelets. It affected the calmodulin-stimulated PDE I and the cyclic GMP-stimulated PDE II. Again, this effect was increased by activators of adenylate cyclase. **Zardaverine** is a selective inhibitor of PDE III and PDE IV isozymes. A series of 6-phenyl-3 (2*H*)-pyridazinones with different substituents in the 5-position of pyridazinone ring showed antiplatelet-activity [92]. A series of 6-phenyl-3(2*H*)-pyridazinones with different substituents in the 5-position of the ring were showed antiplatelet activity [93]. The **PC-09** is significantly increased the cyclic AMP level through inhibiting cyclic AMP PDE activity. The **PC-09** is reduced platelet aggregation and intracellular calcium mobilization.



MSI-154

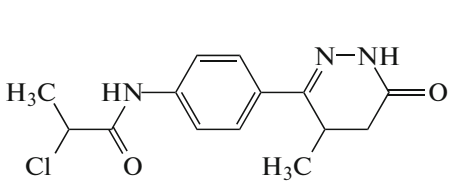


Zardaverina

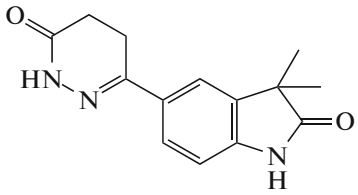


PC-09

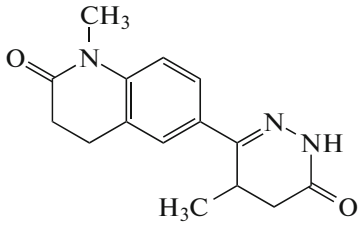
The positive inotropic drug 4,5-dihydro-6-(2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl)methyl-3(2*H*)-pyridazinone (**Pimobendan**) enhances calcium induced contraction from cardiac muscle. **Pimobendan** is a cardiotonic vasodilator that increases myocardial contractility and relaxation of vascular smooth muscle, probably due to PDE inhibition [94]. Various different pyridazine derivatives such as **amipizone**, **indolidan**, **Y-590**, **motapizone** and other also used in treatment of cardiac vascular diseases. The phthalazine derivative **azelastine** is an antihistamine used in allergic rhinitis. It is more selective inhibitors of the cGMP-inhibited PDE, like phthalazine derivatives **MY5445** [95].



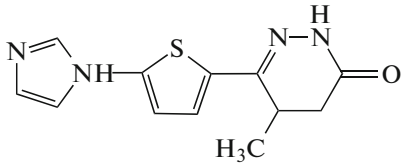
Amipizone



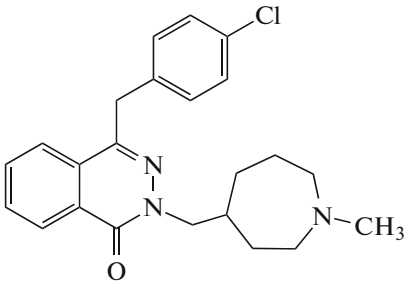
Indolidan



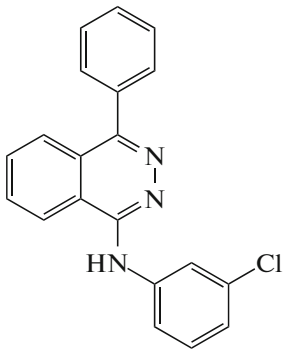
Y 590



Motapizone

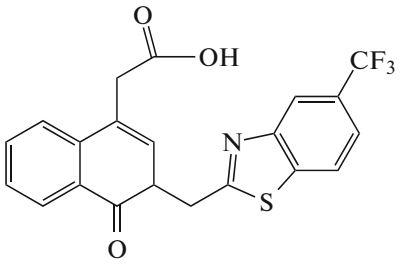


Azelastine

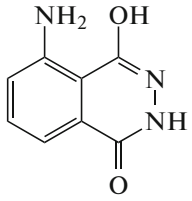


My5445

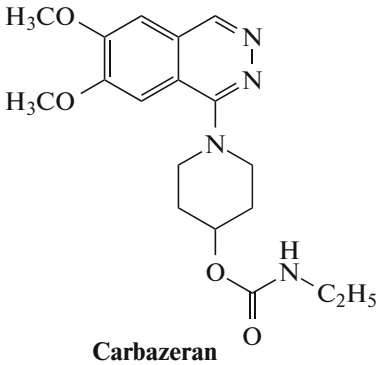
Zopolrestat is a phthalazinone derivative inhibits aldose reductase and use in the prevention of retinopathy, neuropathy, and cataract formation in diabetes. The chemiluminescence reactions of **luminol** and related phthalazines, in biological systems where the inherent signal strength and low signal noise ratio contribute to sensitivity [96–98]. The potentially bioactive derivatives are important for the development of newer drugs. Phthalazine derivatives such as **carbazeran** and **phthalazinol** are used in treatment of various diseases [15]. Phthalazine derivatives are applied as therapeutic agents due to their anticonvulsant, cardiotonic, vasorelaxant, antimicrobial and anti-inflammatory properties [99–101]. The 3-amino-6-methyl-pyridazine-4-thiol (**ES-1007**) marketed in Germany is used as an analgesic and anti-inflammatory drug [102].



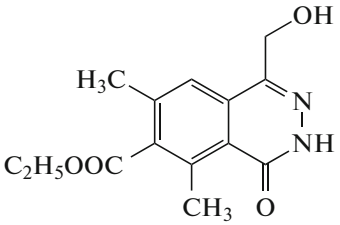
Zopolrestat



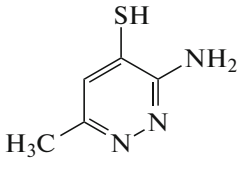
Luminol



Carbazeran

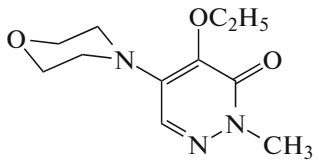


Phthalazinol

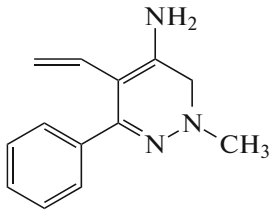


ES-1007

The pyridazinones are characterized to possess good analgesic and anti-inflammatory activities and also very low ulcerogenicity [103]. Among the various pyridazinones, 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**emorfazone**) is marketed in Japan as an analgesic and anti-inflammatory drug. Moreover, 4-amino-2-methyl-6-phenyl-5-vinyl 3(2*H*)-pyridazinone (**I**) was seven-fold more potent than **emorfazone** [104] in analgesic and anti-inflammatory action. The 2-substituted 4,5-dihalo-3(2*H*)-pyridazinone derivatives with high analgesic activity and with no ulcerogenic side effects. The 2-substituted 4,5-functionalized 6-phenyl-3(2*H*)-pyridazinone derivatives have potent analgesic activity with negligible general side effects as currently used NSAIDs [105]. The 3-*O*-substituted benzyl pyridazinone derivatives were exhibit potent anti-inflammatory activity [106].

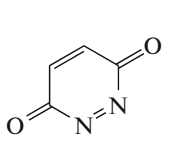


Emorfazone

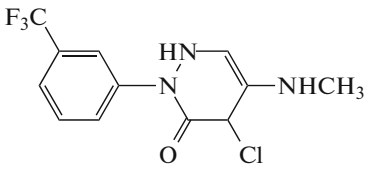


I

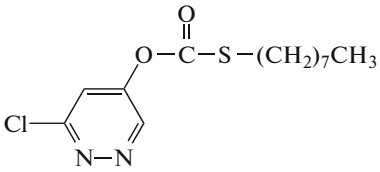
The pyridazine derivatives are also used in agriculture as plant growth hormone like **maleic hydrazide**, herbicides such as **norflurazon pyridazine-pyridate, pyrazon** or **pyramin, NC-170** and **NC-184**.



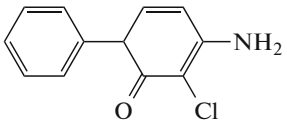
Maleic hydrazide



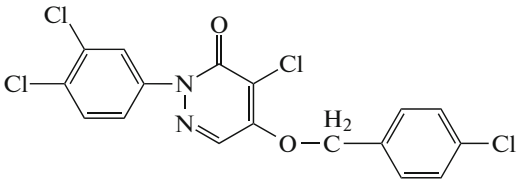
Norflurazon



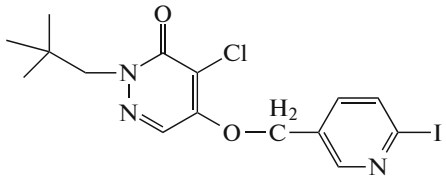
Pyridazine-pyridate



Pyrazon (pyramin)



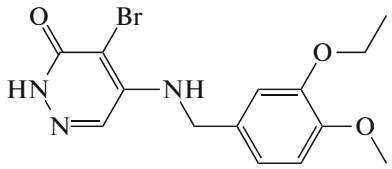
NC-170



NC-184

The **brompyrazon** and **metflurazon** have amine group in their skeleton and also they have halides such as bromine and chlorine, respectively. Some pyridazinone herbicides contain carboxylic acid as a functional group, like **flufenpyr** and **oxapyrazon**. Another pyridazinone herbicide is **pyridaphenthion**, which comprises both sulphur and phosphorus. The combination of two or more heterocyclic and non heterocyclic systems enhances the biological profile many-fold than its parent nuclei [19].

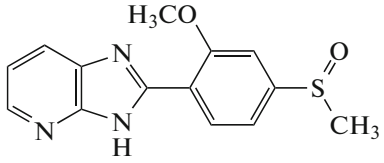
The pyridazinone derivative, 4-bromo-5-(3-ethoxy-4-methoxy benzylamino)-3(2*H*)-pyridazinone (**NZ-107** has potent anti-allergic effects based on the inhibition of antigen-induced histamine- and leukotriene-C4 (LT-C4)-induced contraction of tracheal muscle. **NZ-107** also inhibited antigen-induced histamine release from atopic human leukocytes [107].



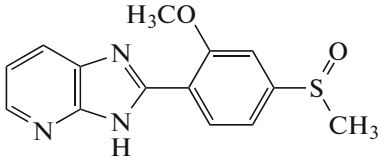
NZ-107

3.1. Calcium Sensitizers

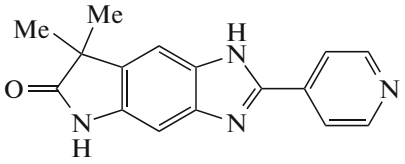
Ca^{2+} sensitizers, a new class of cardiotonic agents, have been shown to exert positive inotropic effects without increasing intracellular Ca^{2+} transient. There are several drugs with reported calcium sensitizing properties (**sulmazole**, **isomazole**, **adibendan**, **meribendan**, and **MCI-154**), but most of the data come from two compounds: **pimobendan** and **levosimendan**. **Pimobendan** is a Ca^{2+} sensitizer with PDE-III inhibitor properties. In comparison with captopril, **pimobendan** appeared to be a stronger arterio-venodilator [108–112]. Although **pimobendan** improved exercise duration, a trend towards increased mortality was seen in the **pimobendan** group and this effect was more pronounced among patients receiving concomitant digoxin [113].



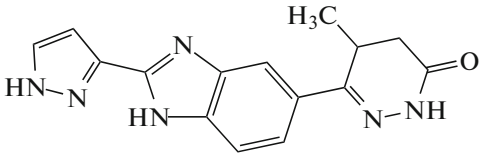
Sulmazole



Isomazole



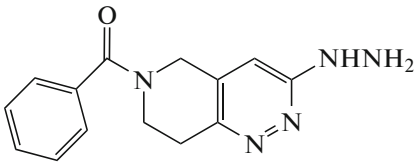
Adibendan



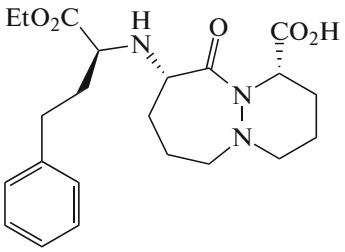
Meribendan

3.2. Cardiovascular Activities

The Ca^{2+} sensitizer **pimobendan** increases the affinity of troponin-C (TnC). **Pimobendan** is a very weak Ca^{2+} sensitizing agent and therefore in clinical use does not reach concentrations high enough to cause Ca^{2+} sensitization [114, 115]. The Ca^{2+} sensitizer, EMD 53998, acts beyond troponin in the contraction cascade. Thus, the target protein of EMD 53998 is not directly affected by Ca^{2+} and prolongs relaxation despite its potent PDE III inhibitory activity [116]. The 4,5-dihydro-3(2*H*)pyridazinones such as CI-914, CI-930, and **pimobendan** along with tetrahydro-pyridopyridazine (**endralazine**) and perhydropyridazinodiazepine (**cilazopril**) used as potent positive inotropes, antihypertensives, and antiplatelet.



Endralazine

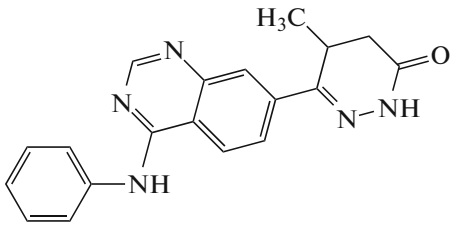


Cilazapril

The 4,5-dihydro-3(2*H*)pyridazinones showed positive inotropic effect. Some compounds showed hypotensive effect and few compounds showed antiplatelet activity [117]. The i.v. **levosimendan**, 1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl.-phenylxhydrazonoxpropane dinitrile, is uses in stable patients with less severe HF [118]. **Levosimendan** was found to reduce mayocardial infarction (MI) size, suggesting cardioprotective effects [119] and simendan (racemic **levosimendan**) improved survival in rats with healed MI [120, 121]. Pyridazinones as potential vasodilator-cardiotonic lead compounds as a set of potent cyclic nucleotide PDE-III, cAMP PDE III inhibitors, 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2*H*)-pyridazinones, 6-(4-(2,6-disubstituted-quinolin-4-ylamino) phenyl)-4,5-dihydropyridazin-3(2*H*)-ones, and 6-(3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino)-3(2*H*)pyridazinone. Some compounds showed moderate vasorelaxant activity compared with milrinone [122]. A series of 6-benzoxazinylpyridazin-3-ones were showed inhibition of cardiac PDE-III and positive inotropic activ-

ity. The 6-(3,4-Dihydro-3-oxo-1,4-(2*H*)-benzoxazin-7-yl)-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (**bemoradan**) was an extremely potent and selective inhibitor PDE-III and a long-acting, potent inotropic and vasodilator agent. **Bemoradan** was developed as a cardiotonic agent for use in the management of CHF [123].

Several 4,5-dihydro-3(2*H*)-pyridazinones were exhibited cardiotonic activity in dogs, and 6-(4-(benzylamino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (**KF15232**) was showed potent cardiotonic activity with a strong myofibrillar Ca^{2+}-sensitizing effect [124]. Analogues of (E)-4,5-dihydro-6-(2-(4-(1*H*-imidazol-1-yl) phenyl) ethenyl)-3(2*H*)-pyridazinone as a variation on the imazodan series were exhibited hemodynamic activity, cAMP-PDE inhibitory activity and antiplatelets activity. A series of 6-(4-(((aryloxy)acyl)amino)phenyl)-4,5-dihydropyridazinones were exhibited combined vasodilator and potential antihypertensive activity by β-adrenoceptor antagonists action.



4KF 15232

A potent Ca^{2+}-sensitizer, **pimobendan**, a positive inotropic responses were examined in electrically driven human LV papillary muscle strips from terminally failing hearts and non failing donor hearts. **Pimobendan** increased force of contraction (FOC) in a concentration-dependent manner. **Pimobendan** increased Ca^{2+}-sensitivity significantly increases FOC in human myocardium via sensitizing of the contractile proteins towards Ca^{2+} and by inhibition of PDE-III isoenzymes [87]. The **pimobendan**, changes in heart rate, left ventricular systolic pressure, left ventricular filling pressure but had only a minor effect on the maximum rate of rise of left ventricular pressure. **Pimobendan** clearly increased cardiac output and it is usefulness in the treatment of CHF. The 4,5-dihydro-6-(2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl)methyl-3(2*H*)-pyridazone exhibited positive inotropic effect. The acute systemic hemodynamic effects of Ca^{2+}antagonist nisoldipine and pimobendan, a PDE-III inhibitor was exhibited vasodilating and positive inotropic properties. Both nisoldipine and pimobendan normalized cardiac output and exhibited a similar cardiac profile. For both drugs, the vasodilatory and positive inotropic properties shifted more in favor of the vasodilatory actions during CHF.

Vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2*H*)-pyridazinone were exhibited vasodilatory potential. An effect of substitution at 2-position of pyridazinone ring on vasodilatory potential has also been explored. Compound 6-(4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)phenyl)-2-(4-fluorophenyl)-4,5-dihydropyridazin-3(2*H*)-one exhibited vasodilating activity in nanomolar range [125]. A series of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone derivatives were studied on isolated perfused toad heart and compared with the activity of **levosimendan**. Some compounds were showed potential cardiotonic activity [126]. A series of pyridazinone derivatives having a phenoxypropanolamine moiety, were exhibited hypotensive and β-blocking activities in rats. Among them, the 5-chloro-2-cyanophenoxy derivative showed the promising dual activities [127].

Levosimendan, is a Ca^{2+} sensitizer in cardiac muscle that produces enhanced myocardial contractility. At therapeutic concentrations it induced enhanced myofilament contractility mainly via its Ca^{2+} sensitizing actions by binding to cardiac troponin C in a Ca^{2+} dependent manner. It does not affect intracellular free Ca^{2+} and cAMP levels and should, therefore, possess no arrhythmogenic potential. This mechanism of action appears to differ from that seen with other Ca^{2+} sensitizers such as **pimobendan** and EMD 53998 [128–130]. The cardiac target protein of **levosimendan**, troponin C, is a Ca^{2+}-binding protein. This raises the possibility that **levosimendan** may also interact with smooth muscle proteins, such as, calmodulin, the regulatory myosin light chains. The mechanism might involve the direct effect of **levosimendan** on the smooth muscle contractile or regulatory proteins themselves [88]. The positive-inotropic and vasodilatating drug **Pimobendan** (racemate), and its enantiomers were investigated to their cardiotoxicity in female Beagle dogs. Reduction of the BP occurred already at low dosages of the racemate and the eutomer, but only in high dose distomer-treated animals. A tendency to tachycardia developed only in high dose for females receiving the racemate. Racemate is equivalent to the eutomer. The cardiotoxicity by **Pimobendan** in dogs resulted from the exaggerated pharmacodynamic effect [131, 132]. The UD-CG 115 is a cardiotonic vasodilator that increases myocardial contractility through Ca^{2+} sensitization and relaxation of vascular smooth muscle, probably due to PDE inhibition. In man, pimobendan is *O*-demethylated to UD-

CG 212. This latter is metabolized to *O*- and *N*-glucuronides. **Pimobendan** itself is also glucuronidated to a *N*-glucuronide [94]. **Pimobendan** with Ca^{2+}-sensitizing properties increased myocardial contractile force without increasing (Ca^{2+}). Pimobendan (**UD-CG 115 BS**) enhances Ca^{+2} induced contraction of cardiac muscle probably by increasing the Ca^{+2} sensitivity of troponin.

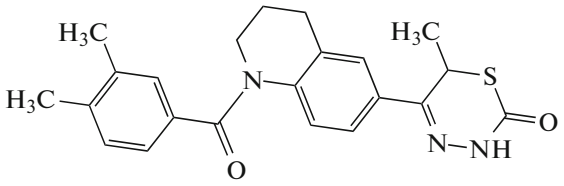
The 5-methyl-6-*p*-cyanophenyl-4,5-dihydro-3(2*H*)-pyridazinone is a antihypertensive agent. The benzimidazolo-pyridazinones showed inotropic activity with calcium sensitizing effects. The 5-methyl-6-(2-(3-pyrazolyl)-5-benzimidazolyl)-2,3,4,5-tetraahydro-pyridazinone hydrochloride (**meribendan**) is a positive inotrope [133]. The 2-substituted-6-(4-acylaminophenyl)-4,5-dihydro pyridazin-3(2*H*)-ones and 6-(4-methanesulfonamido phenyl)-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one exhibited significant inodilatory properties in rats. Cardiotonic activities of a variety of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinone derivatives: 2,3-dichloro-*N*-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)phenyl)benzamide, 4-amino-3-methyl-*N*-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl)benzamide, 3-methyl-4-nitro-*N*-(4-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl)phenyl)benzamide and 4-amino-3-methyl-*N*-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide were compared with 3(2*H*)-pyridazinone derivative of **levosimendan** [56]. Some 2-nonsubstituted/2-methyl-/2-(2-acetyloxyethyl)-6-(4-(substitutedpyrrol-1-yl)phenyl)-4,5-dihydro-3(2*H*)-pyridazinone derivatives exhibited antihypertensive activities [10]. The Ca^{2+} sensitizers may be useful for the treatment of CHF. **MCI-154**, 6-(4-(4'-pyridylamino)phenyl)-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride trihydrate, is a Ca^{2+} sensitizer that has more potent positive inotropic effect than that of pimobendan, adibendan and sulmazole. **MCI-154** has improves not only cardiac systolic function but also diastolic relaxation in CHF [134]. The **MCI-154** possessed more potent positive inotropic effect than that of **pimobendan**, **adibendan**, and **sulmazole**. Ca^{2+} sensitizers have exerted positive inotropic effects without increasing intracellular Ca^{2+} transient. They avoid Ca^{2+} overload that leads to arrhythmias and myocyte injury, and do not increase the energy consumption for handling Ca^{2+}. Therefore, Ca^{2+} sensitizers may be useful for the treatment of CHF. However, most of the Ca^{2+} sensitizers may impair cardiac diastolic function as a result of increased Ca^{2+} sensitivity of the myofilaments. A series of (4-(substituted-amino)phenyl)pyridazinones and (4-(substituted-methyl)amino)phenyl)pyridazinones exhibited inotropic and cardio hemodynamic effects. The **MCI-154** and 6-(4-(4-pyridylamino)phenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride showed extremely potent inotropic activity along with vasodilating activity. The cardiovascular effects of 6-(4-(2-(3-(5-chloro-2-cyanophenoxy)-2-hydroxypropyl-amino)-2-methylpropylamino)phenyl)-4,5-dihydro-5-methyl-3(2*H*)pyridazinone monoethyl maleate (**TZC-5665)** and its main metabolite in human, M-2, were examined in isolated atrial and ventricular muscles of guinea pigs and dogs. **TZC-5665** showed negative chronotropic and inotropic effects, whereas M-2 showed a potent positive inotropic effect with a slight positive chronotropic effect. The positive inotropic effect of M-2 was not modified by phentolamine, propranolol and cimetidine, but completely depressed by carbachol. **TZC-5665** showed a non-selective β-adrenoceptor blocking activity comparable to that of propranolol. **TZC-5665** and M-2 were more potent and selective PDE-III inhibitor than milrinone. Combination of β-adrenoceptor blocking effect of **TZC-5665** and positive inotropic effect of M-2 could be useful in the treatment of CHF [85, 86].

The pyridazinone derivative zardaverine is a selective inhibitor of PDE-isozymes as a potent bronchodilator. In addition, it exerts a positive inotropic action on heart muscle in vitro. **Zardaverine** inhibited the cGMP-inhibitable PDE-III from human platelets and the rolipram-inhibitable PDE-IV from canine trachea and human polymorphonuclear (PMN) cells, respectively. The pyridazinone derivative affected the calmodulin-stimulated PDE-I, the cGMP-stimulated PDE-II and the cGMP-specific PDE-V only marginally at concentrations. **Zardaverine** inhibits the ADP-induced aggregation of human platelets. **Zardaverine** is a selective inhibitor of PDE-III and PDE-IV isozymes [45]. Several 4,5-dihydropyridazinone ring open analogues of imazodan (Cl-914) were exhibited inotropic activity in an anesthetized dogs. The PC-09 is a pyridazinone derivative, has antiplatelet activity and ATP release induced by arachidonic acid (AA), collagen or thrombin. The TX formation caused by collagen or thrombin was markedly inhibited by PC-09, but there was no alteration in that caused by AA. The PC-09 significantly increased the cAMP level through inhibiting cAMP-PDE activity. The PC-09 is an inhibitor of platelet aggregation and (Ca^{+2})i mobilization. The 6-(α,α-diphenyl acetyl piperazinyl)phenyl-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone inhibited archidonic acid, adenosine di-phosphate and platelet activating factor-induced rabbit platelet aggregation. This compound depressed thromboxane-B2 (TXB2) content and increased cAMP levels in rabbit platelets [135]. The 2-(2-dimethylaminoethyl)-5-benzylidene-6-methyl (2*H*,4*H*)-3-pyridazinones reduced the TXA_2 synthesize activity of heart tissue.

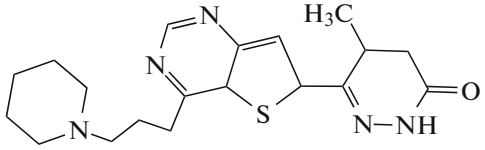
The tetrahydro pyridazinones may be able to provide suitable candidates because quite a few new drugs belonging to this class of drugs were designed as PDE inhibitor [133]. Adrenolytic effect of 6-piperazinyl-

3(2*H*)-pyridazinones consist in blocking pre- and postsynaptic α-adrenoreceptors of rats was determined. It was stated that 2-methoxyphenoxyethyl and phenoxyethyl groups in benzodioxanes are indispensable for α-blocking activity. Several 6-substituted 1*H*-imidazol-4(5)-yl)-3(2*H*)-pyridazinones were exhibited positive inotropic activity. The 1*H*-imidazol-4-yl substituted regioisomers of 4,5-dihydro-6-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)-3(2*H*)-pyridazinone and 6-(1-methyl-2-phenyl-1*H*-imidazol-4-yl)-3(2*H*)-pyridazinone were stated as ionotropic inhibitors of cardiac PDE-III.

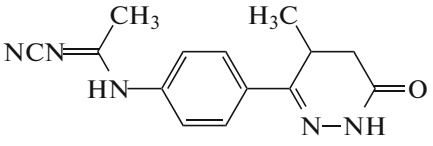
The inotropic Ca^{2+}-sensitizing agent claimed to be completely devoid of PDE inhibitory activity or any other known inotropic mechanism is 5-methyl-6-phenyl-1,3,5,6-tetrahydro-3,6-methano-1,5-benzodiazocine-2,4-dione BA 41899 (especially its (+)-isomer CGP 48506). Different activity ratios (PDE inhibition vs Ca^{2+} sensitization) were found for the enantiomers of **sulmazole**, **pimobendan**, **meribendan**, **EMD 53 998**, **KF 15232**, **ORG 20494**, **siguazodan**, and **simendan**. The (*R*)-configuration may be essential for the Ca^{2+}-sensitizing effect. The stereoselectivity between these isomers is less significant and a single (−)-isomer was found to be more potent on both enzymatic activities. The low influence of a chiral centre more distant from the pyridazinone/thiadiazinone cycle is fully compatible with the topographical model of the cardiac cAMP-PDE receptor [136]. The selected 4-(4-(phenoxyethyl)-1-piperazinyl)-3(2*H*)-pyridazinones and alkane-bridged dimers of 6-(4-(phenoxyethyl)-1-piperazinyl)-3(2*H*)-pyridazinones possessed the blocking activity on the pre- and postsynaptic rats α-adrenoreceptors. These adrenoreceptor antagonists were investigated in parallel with the development of postsynaptically selective α-adrenoreceptor antagonists due to their importance in the treatment of hypertension and prostatic hypertrophy [137]. A series of pyridazin-3(2*H*)-one derivatives was studied for affinity at adenosine receptors in bovine brain cortical membranes as well as in bovine brain striatal ones. None of the compounds shows any affinity towards the receptor while compounds in which the 6-chloro-pyridazin-3(2*H*)-one or 6-phenyl-pyridazin-3(2*H*)-one fragment is linked through a chain of two carbon atoms with the 6 position of the adenosine showed good affinity towards adenosine receptor, particularly compound in which a phenyl-pyridazinone group is present shows highest affinity. The 3(2*H*)-pyridazinone derivatives show many pharmacological activities, reduction of BP [138]. The cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2*H*-indol-2-one (**LY195115**) is a potent, competitive inhibitor of SR derived PDE. The compound is a potent inotropic agent. These involved the geminal methyl groups at the indol-2-one moiety and the C5' methylene unit of the dihydropyridazinone ring. Methyl group at the 4-position of the dihydropyridazinone and pyridazinone rings provided disparate results. The 4-methyl analogue of **LY195115** was 2-fold more potent than **LY195115**, and the methyl substituent probably caused only minor perturbations in overall molecular topology.



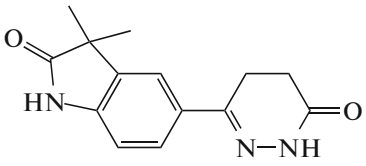
EMD 53998



5ORG 20494

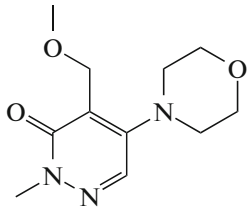


Siguazodan



LY195115

Biological actions of 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**M73101**) as a non-steroidal anti-inflammatory drug (NSAID) produced a slight transient fall in BP, as well as increase in heart rate and respiratory stimulation. The contraction induced by epinephrine in the isolated ear vessels of rabbits relaxed by **M73101**. The **M73101** showed no significant activities on the blood sugar level, blood coagulation, platelet aggregation, methemoglobin formation and local irritation.



M73101

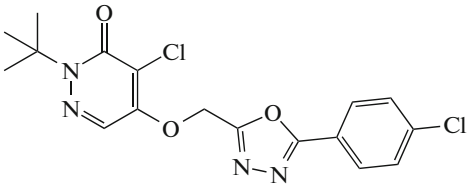
Theophylline as PDE-inhibitor is used in the treatment of asthma. Derivatives of theophylline–(6-(7-theophylline)-3(2*H*)-pyridazinone) and other purine analogs—were tested as PDE-inhibitors and cardiac stimulants. Some of them were found several times more active than theophylline. A variety of 4,5-dihydro-6-phenyl-3(2*H*)-pyridazinone derivatives are PDE-inhibitors like CI-914 which produced a cardiotonic effect accompanied by only slight decreases in BP and moderate increases in heart rate. Some 6-phenyl-3(2*H*)-pyridazinones showed a bronchospasmolytic effect more significant than that of xanthenes [139]. The cardiovascular effects of RG W-2938—6-(6-(3,4-dihydro-3-methyl-2(1*H*)-2-oxoquinazolinyl))-4,5-dihydro-3-(2*H*)-pyridazinone—a nonglycoside noncatecholamine cardiotonic vasodilator agent were founf for anesthetized and conscious dogs and in isolated guinea pig hearts; in the latter RG W-2938 in 5 nmol–5 μmol concentration increased contractility in a dose-related fashion. Doses of 30–300 mg/kg of RG W-2938 were responsible for increased contractile force, arterial pressure decreasing and total peripheral resistance of anesthetized dogs. Heart rate was only slightly increased, and aortic flow was not appreciably altered. A single oral 0.3 mg/kg dose of RG W-2938 is caused in 15–240 min period after treatm increase in contractility with only slightly increasing HR of the tested dogs. The effect of 30–300 μg/kg dose of RG W-2938 30–300 μg/kg was studied in a mecamylamine-propranolol-induced model of heart failure. RG W-2938 effectively reversed the drug-induced heart failure by increasing myocardial contractility and decreasing arterial pressure while only slightly affecting HR. RG W-2938 is an orally effective positive inotropic/vasodilator agent [140]. The intrinsic positive inotropic activity were found for 5,7-dihydro-7,7-dimethylpyrrolo(2,3-f)benzimidazol-6(1*H*)-one. The structural features that impart optimal inotropic activity are stated and compared with those of the 4,5-dihydro-3(2*H*)-pyridazinone series. A series of analogues of (E)-4,5-dihydro-6-(2-(4-(1*H*-imidazol-1-yl) phenyl)ethenyl)-3(2*H*)-pyridazinone was synthesized as a variation on the **imazodan** series. The compounds were evaluated for hemodynamic activity, cAMP-PDE inhibitory activity (human platelets and guinea pig heart tissue), and platelet aggregation inhibitory activity. The insertion of the ethenyl moiety between the phenyl and dihydropyridazinone rings produced novel compounds that retained the potent inotropic/vasodilator activity of the parent **imazodan** series and enhanced the antiplatelet activity. A series of 6-phenyl-3(2*H*)-pyridazinones bearing different substituents at the 5-position of the pyridazinone ring showed antiplatelet activity. The 5-acetyl-2-methyl-4-methylsulfinyl-6-phenyl-3(2*H*)-pyridazinone5-acetyl-2-methyl-methylsulfinyl-6-phenyl-3(2*H*)-pyridazinone exhibited antiplatelet activity [141]. The effects of 2-(2-dimethylaminoethyl)5-benzylidene-6-methyl-(2*H*,4*H*)-3-pyridazinone (**II**) were studied on the biosynthesis of TXA_2 and PGI_2 in vitro the TXA_2 and PGI_2 synthetase activity of heart tissue. Biosyntheses of TXA_2 and PGI_2 were carried out using arachidonic acid as a substrate and horse platelet and aorta microsomes as sources of TXA_2 and PGI_2 synthetases respectively. TXB_2 and 6-keto PGF_1 alpha were determined by RIA. **II** does not significantly modify either the biosynthesis of PGI_2 in vitro or the PGI_2 synthetase activity of heart tissue and does not inhibit TXA_2 biosynthesis in vitro but markedly reduced the TXA_2 synthetase activity of heart tissue. Thus **II** possessed a specific inhibitor of the TXA_2 synthetase activity of heart tissue and could have a beneficial use in therapeutics. The Y-590 (a pyridazinone derivative) is a potent anti-thrombotic agent by inhibition of platelet PDE.

Pyridazine derivatives have been reported to possess wide variety of activities against microbial organisms and act as anti-microbial, fungicidal, herbicidal, and molluscicidal, etc [142]. A number of pyridazines are used commercially in agriculture as herbicides in order to kill pests and unwanted plants, as drugs, drugs intermediates and for other industrial purposes. These compounds have different functionalities in their structures [13, 14, 26]. Pyridazines are widely used as pesticides, such as herbicides and insecticides. They have structure diversity, for example **pyridate** involves thiocarbonate group, **credazine** comprises of the ether linkage and **pyridafol** has alcohol unit. Some herbicides including pyridazine ring in their structure have various functional groups on the pyridazine ring. For example, **brompyrazon** and **metflurazon** have both halide and amine group in their skeleton, respectively. Several pyridazinone herbicides contain carboxylic acid as a functional group, such as **flufenpyr** and **oxapyrazon**. Another important pyridazine herbicide is **pyridaphenthion**, which comprises of both sulphur and phosphorus [143]. Herbicides that inhibit photosystem-II are represented by several herbicide families including the symmetrical

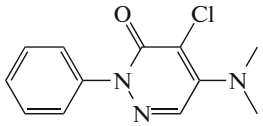
triazines, triazinones (triazines), substituted ureas, uracils, pyridazinones, phenyl carbamates, nitriles, benzothiadiazoles, phenyl pyridazines, and acid amides. The pyridazines families of herbicides also have specific herbicide effect. Compounds with phenyl ring bonded to the 2-position of pyridazine ring as well as other pyridazines and norflurazon inhibit carotenoid biosynthesis. Phenyl pyridazines, pyridate are only herbicides in this family [15, 143]. In contrast to the photosynthesis inhibiting herbicides, the pyridazinone herbicide norflurazon is a pigment inhibitor. Other pyridazinones and pyrazons did not inhibit the photosynthesis at PS-II (pigment synthesis/inhibition of phytoene desaturase). In contrast to **norflurazon**, the pyridazinone herbicide pyrazon is a photosynthesis inhibitor. 4,5-Dichloro-2-phenyl-3-(2*H*)-pyridazinone (PCC) is an intermediate product during the preparing of the selective herbicide known as **pyrazon**. Other 4,5-substituted 2-phenyl-3(2*H*)-pyridazinones is reduced at more positive potentials. Herbicide used for controls grasses, sedges, and broad leaf weeds. Various pyridazines are used commercially, in particular **maleic hydrazide** is used as a selective plant growth regulator.

4. INSECTICIDAL AND ANTIFEEDANT ACTIVITIES

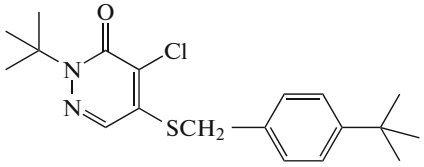
Insect growth regulators control insect population, being known primarily as regulators of moulting, metamorphosis, physiological and developmental processes [144, 145]. Oxadiazolyl 3(2*H*)-pyridazinone, 2-*tert*-butyl-4-chloro-5-(5'-(4'-chlorophenyl)-2'-(1',3',4'-oxadiazolyl) methoxy)-3(2*H*)-pyridazinone (**ODP**), act as a growth inhibitor that possessed inhibitory activity on weight gain of lepidopterans such as *Ostrinia furnacalis*, *Plutella xylostella*, *Pieris rapae*, *Bombyx mori*, and *Pseudaletia separata* [146–148]. The effect of **ODP** on the process of growth of larvae of the armyworm *P. separata* Walker (Lepidoptera: Noctuidae) was studied in comparison with toosendanin—a tetranortriterpenoid extracted from the bark of *Melia toosendan*. It was found the multiple modes of action of **ODP** on insects as a feeding deterrent and an insect-growth regulator that disrupts the moulting process. In mammals it acts as a pre-synaptic blocker at the neuromuscular junction [149–151]. The toxic and anti-feedant activity of 2*H*-pyridazin-3-one-substituted 1,3,4-oxadiazoles against the armyworms and other insects and mites was studied. 1,3,4-oxadiazoles containing a 2*H*-pyridazin-3-one compounds were possess considerable activity in retarding the development of larvae of Lepidoptera, but they were all inactive against *Homoptera*, *Diptera*, and *Acarina*. The compounds have powerful anti-feedant activity comparable with azadirachtin. Treatment of wheat (*Triticum aestivum*) plants with **BASF 13-338** (4-chloro-5-(dimethylamino)-2-phenyl-3(2*H*)-pyridazinone) completely inhibits accumulation of linolenic acid in the roots during the hardening period and acquisition of frost resistance [152, 153]. The 2,5-disubstituted-1,3,4-oxadiazoles inhibited chitin synthesis in *Drosophila* and *Musca domestica* [154]. Some oxadiazoles showed good solubility and insecticidal activity [155–157]. Pyridazinones have been used in numerous applications in the fungal, weed, and insect control sectors of agriculture. Four commercial products for insect control, **NC-129** (acaricide), **NC-170**, **NC-184** were developed. For example, **NC-129** is a acaricide which causes excellent control of mites and some insects including whiteflies, aphids, and thrips; **NC-170** is a highly selective juvenoid, and it strongly inhibits metamorphosis in planthopper when topically applied to midpenultimate larvae [158, 159].



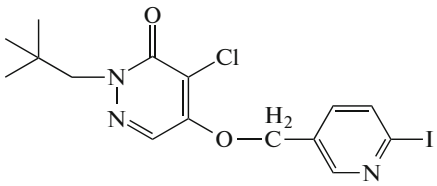
ODP



BASF 13-338



NC-129

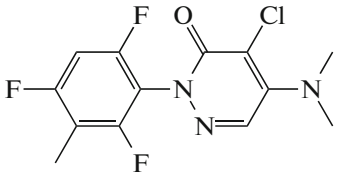


NC-184

The oxadiazolyl moiety attached to 3(2*H*)-pyridazinones enhance the solubility of the 1,3,4-oxadiazoles in polar solvents and improve the activity of the pyridazinones [160]. Some compounds exhibited good antifeedant activity on the Asiatic corn borer *Ostrinia furnacalis* (Guenee). The substitution of sulfur for oxygen in the heterocyclic ring represents an example of an approach that is commonly known as bio-

isosterism. The 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. Pyridazinone-substituted 1,3,4-thiadiazole exhibited highly fungicidal activity against wheat leaf rust, *Puccinia recondite* [161, 162]. The 1,3,4-oxadiazoles exhibit a broad spectrum of biological activity [163–166]. The di-heterocyclic compound containing both pyridazinone and 1,3,4-oxadiazole moieties possessed better biological activity. The pyridazinone substituted 1,3,4-oxadiazoles exhibited fungicidal activity against wheat leaf rust, *Puccinia recondita,* as well as pyridazinonesubstituted 1,3,4-thiadiazoles. The pyridazinone-substituted 1,3,4-thiadiazoles and 1,3,4-oxadiazoles have a common core structure but differ from each other by the heterocyclic ring and the phenyl substituents. The digestive physiological properties of **ODP** on insects were investigated by feeding them maize leaves dipped in this compound [167].

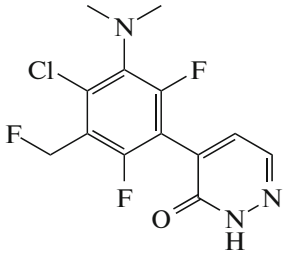
The influence of two pyridazinone herbicides **6706-3197** (4-chloro-5-(dimethylamino)-2-trifluoromethyl-3-tolyl-3(2*H*)-pyridazinone) and **BASF 13-338** on growth and aflatoxin release from aflatoxigenic strains of *A. flavus* and *A. parasiticus* were systematically studied. The influence of pyridazinone herbicides on aflatoxin production is expressed in terms of the level of aflatoxin released in relation to the amount of mycelial growth.



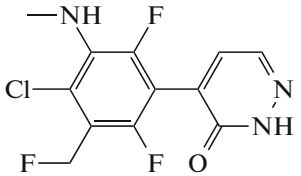
6706-3197

5. PHOTOSENSITIZING ACTIVITIES

Dibenzoxazoles, pyridazinones, and especially a dibenzthiazole derivatives of hypericin demonstrated an efficient singlet oxygen yield and intracellular uptake, and concomitantly a potent photocytotoxic effect under white-light conditions. These results indicate that it is possible to synthesize bathochromically-shifted compounds based on hypericin chemistry which maintain their PDT potential. However, the data also show that the present derivatives are only poor photosensitizers when used under red-light conditions [169]. Pyridazinone herbicides such as (4-chloro-5-(dimethylamino)-2-(α,α,α-trifluoro-*m*-tolyl-3-(2*H*) pyridazinone) (**SAN 6706**) and (4-chloro-5-(methylamino)-2-(α,α, α-trifluoro-*m*-tolyl-3-(2*H*) pyridazinone) (**SAN 9789**) are known to inhibit chlorophyll and carotenoid biosynthesis and thereby bleach the cells.



SAN 6706



SAN 9789

SAN 9785 is one of the substituted pyridazinones that can significantly change the fatty acid composition of chloroplast membrane and pigment content. It has been shown that wheat seedlings grown in the presence of 100 μM SAN 9785 did not show any change in pigment content. Wheat seedlings grown in the presence of 500 μM SAN 9785 showed a 20% decrease in chlorophyll content. *Chlorella protothecoides* cells were grown in the presence of various concentrations of the **SAN 9785** with time varying and it was observed decrease in carotenoid content prompted us to examine the formation of carotenes and xanthophylls from their precursors. The inhibition of carotenogenesis has been considered as a possible mechanism of action of several herbicides. Effects of substituted pyridazinones on photosynthetic electron transport have been studied by various authors and the herbicides are known to inhibit photosystem II (PS II) electron transport. Variation exists in the literature regarding the I_{50} values for the inhibitory effect of pyridazinone herbicides on photosynthetic electron transport with respect to plant species and the nature of substitution. In barley chloroplasts the I_{50} value of **SAN 9785** for the inhibition of PS II is 14 μM as compared to that in wheat chloroplasts (10 μM). The I_{50} value of **SAN 9789** for the inhibition of PS II in the whole cells of *Scenedesmus* was found to be 350 μM.

6. ANTIMICROBIAL AND MOLLUSCICIDAL ACTIVITIES

Some pyridazinones showed antibacterial activity [170]. Compound (4-cyano-3-oxido-1-β-D-ribofuranosylpyridazinium) is an example of a mesoionic analogue of a pyrimidine nucleoside. Compound have gram-negative antibacterial activity against a systemic *E. coli* infection in mice with an ED_{50} of 25–50 mg/kg. The 4-substituted 3-oxidopyridazinium ribonucleosides have several times more active than 4-cyano-3-oxido-1-β-D-ribofuranosylpyridazinium against *E. coli*. 2-(5-Chloro-1,3-diphenyl-1*H*-pyrazol-4-ylmethylene)-malononitrile reacts with the pyridazinone derivative to afford the phthalazinone. The compounds showed a moderate molluscicidal activity towards *Biomphalaria alexandrina* snails [50]. Some oxadiazolyl 3(2*H*)-pyridazinones were exhibited insect antifeedant activities against Asiatic corn borer *Ostrinia furnacalis* (Guenee) compared with commercial azadirachtin [42]. The oxadiazolyl-3(2*H*)-pyridazinone, a potent effective insect growth regulator affected the process of growth of *P. separata* larvae. The anti-feeding effect of oxadiazolyl-3(2*H*)-pyridazinone attributed its interfering action on many kinds of enzymes such as trypsine-like, chymotrypsin-like enzyme, and alpha amylase in the guts of insects. The disruption of larval growth physiology could also be caused by an effect on gustatory receptors. Since inhibitors of digestive enzymes could be used to protect plants against insects, oxadiazolyl (2*H*)-pyridazinone could be a pro-insecticide for the development of novel pesticides [54].

7. DISCUSSION

The nitrogen heteroatom containing aromatic compounds are very popular in the area of research. Pyridazines and phthalazines compounds exhibited diverse biological activities such as anti-inflammatory, analgesic, antimalarial, antipsychotropic, antimicrobial, antitubercular, anticancer, anticonvulsant, insecticidal, herbicidal and plant growth regulator, antivirus, anti AIDs activities, etc. [171, 172]. Pyridazines and phthalazines are inexpensive and easily synthesized and therefore have been examined for different biological activities. A slight variation in the substitution pattern on the pyridazine and phthalazine nucleus often causes a marked difference in activities and therefore pyridazines and phthalazines with various substituents are being synthesized and evaluated for biological activities in search of better medicinal drug and great interest has arisen in the design and synthesis of new pyridazines and phthalazine compounds to explore their potent activities against various disorders. The pyridazines and phthalazines nucleus, which has a useful structure for further molecular exploration for the development of new derivatives with different biological activities has received much attention in recent years [173–176]. Positive inotropic agents are an efficacious and incomparable tool in the short-term treatment of patients with severe left ventricular dysfunction. The positive inotropy by Ca^{2+} sensitization and PDE-III should be considered as a developing approach for the treatment of CHF and MI. The pyridazines have diverse biological potential and taken attention of the researchers to explore its multiple potential against cardiac disorders. Some pyridazinone derivatives possessed antifeedent activities. Though some of the compounds possess only modest biological activity, we hope to find a potent simple structural antifeedant agent which can mimic the activity of the complex azadirachtin through structural modifications of compounds. The substituted pyridazinones has shown a wide spectrum of biological activities. The biological profile of these new generations of pyridazinones presents much progress with regards to the old compounds. Pyridazinone have a great potential which remain to be disclosed till date. A considerable number of pyridazinone derivatives bear different biological activities [15–20]. In order to further explore chemical space available for pharmaceutical applications, there is a continued demand for the development of new pyridazine heterocyclic core scaffolds that have novel structures and bear functionality and subsequent hit-to-lead medicinal chemistry development. The chemistry of pyridazine derivatives is of significant current interest, particularly to pharmaceutical and materials chemists who require the efficient synthesis of a diverse range of heteroaromatic derivatives for screening programmes. For this purpose, various compounds incorporating a pyridazinone ring have been synthesized and theirs biological activities have been reported.

8. CONCLUSION

The pyridazines and phthalazines which may be easily functionalized at various positions of their rings are of considerable interest for chemists and biologists as wide variety of bio-active compounds. These ring system became interesting in search of new and more potent drugs with lesser side effect. There is an increasing need to prepare pyridazinones and phthalazines bearing various substituents at the ring system. The cardiotonic activities are one of the most encouraging activities. By the present scenario it can be concluded that pyridazinone have a great potentials which remain to be disclosed till date. The biological pro-

file of pyridazines represents much progress with this regards. The researchers have taken attention on pyridazine and phthalazine compounds due to its diverse biological potentials.

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