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Review Article

Calcium Sensitizing and Phosphodiesterase-III Inhibitory Activity of Pyridazine Compounds: A Review

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Abstract: Congestive heart disease is one of the main causes of death in the globe, affecting more than 1% of the world population. Various remedial agents are used for the treatment of cardiac diseases such as inotropics and vasodilators. Sympathomimetic drugs play an important role, but they unfortunately undergo severely from oral ineffectiveness and tachyphylaxis due to receptor desensitization. Recently, several cardiac phasphodiestrase-III (PDE-III) inhibitors have been developed with improved ventricular performance and exercise tolerances. Theoretically, PDE-inhibitors combine positive inotropy and vasodilation (known as zinodilator) action and these exceptional features make them very attractive. Various pyridazine drugs act as selective PDE-III inhibitor and characterized by a positive inotropic effect combined with vasodilatory effects. The pyridazine is an important heterocyclic structure with various biologically active compounds with diverse pharmacological activities. Pyridazine hold considerable interest relative to the physiologically active cardiac compounds such as Ca^{+2} sensitizing and PDE-III inhibitor activity. However, some pyridazine compounds have been reported as effective agents in the treatment of several cardiovascular diseases including, acute and chronic heart failure, myocardial infarction, angina, arrhythmia, and hypertension. Pyridazinone nucleus has focus attention because of new pyridazinone compounds will design and development of novel Ca^{+2} sensitizing and PDE-III inhibitors as cardio tonic agents in future.

Key words: Ca^{+2} sensitizer, phosphodiesterase-III, cardio tonic, pyridazinone.

Biography:

- **Mohammad Asif** was born in India. He studied **Bachelor of Pharmacy (**Pharmaceutical Chemistry) from IFTM, Moradabad, affiliated with Rohilkhand University Bareilly (U.P) in year **2003**. and received the Master degree in Pharmaceutical Chemistry at Bundelkhand University Jhansi (U.P) in **2006** and the Ph.D degree also in Pharmaceutical Chemistry at Uttarakhand Technical University, Dehradun in year **2015**. He focused his doctoral thesis on the Synthesis and biological evaluation of some new pyridazine-3(2H)-one derivatives. His research interests focus on the Medicinal Chemistry, Inorganic Chemistry, Organic Chemistry, Chemistry of Natural Products, Pharmaceutical Analysis and Physical Chemistry.

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1. introduction

Recently, great attention has been focused on the pyridazine compounds due to their broad-spectrum of pharmacological activities. Several substituted pyridazinone compounds have been

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reported as cardio-tonic and other cardiovascular agents [1-3]. In particular, a large number of pyridazinone derivatives are having various cardiovascular activities such as antiplateletes, antihypertensive, antianginal, antiarrthmic, and cardiotonics. Various pyridazinone compounds are also used as agrochemicals [4, 5]. These biological diversities of the pyridazinone derivatives are due to various structural modifications on the pyridazinone ring by different type atoms or groups. Conventional approach to the treatment of heart failure (HF) is the improvement of myocardial contractility by the use of inotropic drugs that improve depressed cardiac function. Importance of the vasodilator therapy reduces the preload and impedance as an additional and/or adjunct therapy. The first generation of non-glycoside, non-catecholamine cardiotonics with mixed inotropic and vasodilator activities are amrinone, milrinone, imazodan, CI-930, enoximone, and piroximone. Although these inotropics can stimulate the failing ventricle and improve the hemodynamics, their influence on the heart failure is not clear yet. Positive inotropic drugs, especially PDE-III inhibitors and adrenergic agonists such as dobutamine, may be linked with increasing myocardial oxygen demand and the potential to induce myocardial ischemia (MI) or malignant arrhythmias [6]. Pyridazinone based cardiotonic agents exhibited activity against CHF. However, different pyridazinone derivatives have shown difference in inotropic responses [7]. Aryl-substituted-4,5-dihydro-3(2*H*)-pyrida-zinones such as imazodan were showed ionotropic activities equivalent to inotropic drugs like milrinone and amrinone [8]. Pyridazinone compounds were also showed other cardiac activities such as cardiac diagnosis [9, 10].

2. Phosphodiesterase inhibitors

Phosphodiesterase-III (PDE-III) inhibiting drugs (like amrinone, milrinone and enoximone) increase contractility of heart muscle by reducing the degradation of cAMP. They reduce both the preload and afterload via vasodilation. The haemodynamic consequences of this action are reduced left ventricular (LV) after load, increased cardiac output (CO) and reduced total peripheral resistance (PR). Unlike the sympathomimetic amines, PDE-III inhibitors produce no tolerance and have the distinctive advantage of directly decreasing pulmonary vascular resistance (PVR) [11]. Another drug (vesnarinone), a mixed PDE inhibitor and ion-channel modifier that has reserved, dose-dependent, positive inotropic activity, but minimal negative chronotropic activity, has improved haemodynamics and quality of life in small experimental trials [5, 12].

3. Calcium sensitizers

The calcium (Ca^{2+})-sensitizers is a new class of cardiotonic agents and exert positive inotropic effects without increasing intracellular Ca^{2+} transient. They avoid of 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 congestive heart failure (CHF). However, the majority of the Ca^{2+} sensitizers may impair cardiac diastolic function as a result of increased Ca^{2+} sensitivity of the myofilaments. The positive inotropic agents act by increasing the sensitivity of troponin C or some other part of the myofibrillar Ca^{2+} binding apparatus to ionized calcium. There are several drugs act as calcium sensitizing agents (sulmazole, isomazole, adibendan, meribendan, and MCI-154), but the majority of the information 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 [13-15]. The pimobendan increased exercise duration, peak oxygen uptake and improved quality of life [16, 17]. Although pimobendan improved exercise duration, a trend towards increased mortality was seen in the pimobendan group and this effect was more obvious among patients receiving simultaneous digoxin [5, 18]. In contrast, pimobendan considerably lowered morbidity and improved the physical activity of patients. Therefore, pimobendan in the treatment of HF remains to be clarified and effectively powered prospective.

4. Cardiovascular activities of pyridazine derivatives

The cardiotonic drug sulmazole enhance myofibrillar Calcium (Ca^{2+}) sensitivity, jointly with other properties, is a potent cardiotonic drug for the treatment of CHF acting selectively. The inotropic effects of α_1-adrenergic stimulants and PDE-III inhibitors are poor or slight compared to

seen in a healthy heart, Ca^{2+} sensitization has become an attractive option. In addition, to be effective this mechanism does not require enhance in free Ca^{2+} concentration. It should avoid the risk of Ca^{2+} overload and potentially the connected arrhythmias. The contractions evoked by Ca^{2+} sensitizing drugs are produced more efficiently than adrenergic drugs or PDE inhibitory agents. This mode of action might be more suitable for the CHF. All of the first generation CHF drugs claimed to be Ca^{2+} sensitizers have additional properties, PDE-inhibition is the major effect and Ca^{2+} sensitization is of secondary importance. The Ca^{2+} sensitization of contractile proteins has become a capable approach to raise contractile force in the failing heart muscle. Advantage of this mechanism is that it does not increase intracellular $[Ca^{2+}]i$ whereby arrhythmias due to impulsive release of Ca^{2+} from over loaded $[Ca^{2+}]i$ stores may be avoided. Since the amount of Ca^{2+} required for the contraction force is lower during Ca^{2+} sensitization, the energy needed for Ca^{2+} handling is reduced. A chief disadvantage of Ca^{2+} sensitization may be to prolonged relaxation [19]. To balance the impaired relaxation, attempts to accelerate $[Ca^{2+}]i$ handling by another mechanism have been included as a biological property for some Ca^{2+} sensitize drugs. The Ca^{2+} sensitizer, pimobendan increases the affinity of troponin-C (TnC). Pimobendan is a very weak Ca^{2+} sensitizing drug and in clinical use does not reach concentrations high enough to cause Ca^{2+} sensitization. This makes it impossible to the balance between the increased Ca^{2+} affinity of TnC and accelerated Ca^{2+} handling would be in practice. In pimobendan therapy, the potent metabolite, UDCG 212Cl, further complicates the evaluation [20, 21]. 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 the compound prolongs relaxation despite its potent PDE III inhibitory property [22]. The 4,5-dihydro-3(2H)pyridazinones, CI-914, CI-930 and pimobendan along with tetra hydropyrido-pyridazine (endralazine) and perhydro pyridazinodiazepine (cilazopril) were used as effective positive inotropic, antihypertensive and platelet aggregation inhibitor agents. The 4,5-dihydro-3(2H)pyridazinones showed positive inotropic effect in isolated rabbit heart in comparison to digoxin glycoside. Most pyridazinone compounds were exhibited higher activity than digoxin and some compounds showed less activity. Some compounds also showed marked hypotensive effect and few compounds showed platelet aggregation inhibition activity. Correlation of cardiotonic and hypotensive activities with structures of compounds pharmacophore models were computed to get useful approach onto the crucial structural features necessary for inhibiting PDE-III in the cardiac muscles and blood vessels [23].

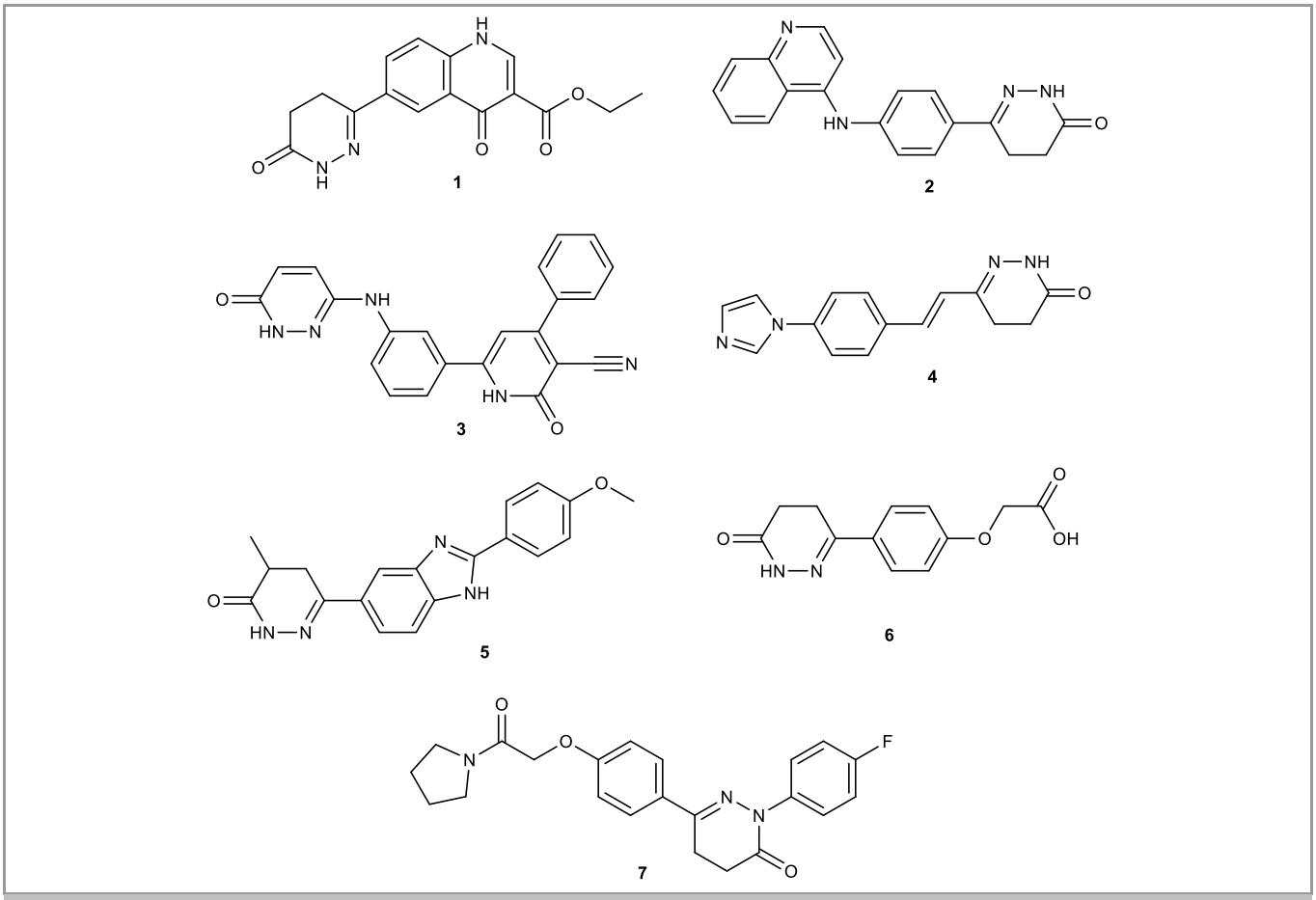
Inotropic drug with a dual mechanism of action: sensitisation of the cardiac myofilament to Ca^{2+}, enhancing cardiac contractility and vasodilation of vascular smooth muscle. The i.v. levosimendan, 1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl.-phenylxhydrazonoxpropane dinitrile is well absorbed orally and its uses in stable patients with less severe HF are in progress [24]. The patients with left ventricular failure (LVF) complicating an acute MI to receive levosimendan at different level of doses, patients experienced lower risk of death. In a dog study, levosimendan was found to reduce MI size, suggesting cardioprotective effects [25]. In another study, racemic simendan improved survival in rats with healed MI [26, 27]. The PDE-III inhibitor and Ca^{2+} sensitization in the cardiac actions of levosimendan and milrinone increased the LV systolic peak pressure almost to the same extent. The cardiac effect of levosimendan at its relevant concentration and its positive inotropy is most probably due to the reported TnC-mediated Ca^{2+} sensitization of contractile proteins [28, 29]. The potent Ca^{2+} sensitizer levosimendan does not increase the affinity of cTnC for Ca^{2+} but stabilizes the Ca^{2+} induced conformation of this protein. The binding of levosimendan itself to cTnC occurs in a Ca^{2+} dependent manner and the Ca^{2+} sensitization does not prolong relaxation. However, levosimendan is a potent PDE-III inhibitor and it important to evaluate the role of PDE-III inhibition in its cardiac actions. The different types of Ca^{2+} sensitizers show that the proportions of Ca^{2+} sensitization and PDE-III inhibition cannot be accurately evaluated by analyzing the relaxation of cardiac muscle. The muscarinic receptor agonists, carbachol and adenosine, are the pharmacological tools most frequently used in the evaluation of PDE inhibition [30-32]. These agents may not only

counteract the contribution of PDE inhibition to the positive inotropic effect of Ca^{2+}sensitizers, but they may also abolish the Ca^{2+} sensitizing mechanism as well by altering the phosphorylation state of contractile proteins [33]. Levosimendan, little effect on myocardial oxygen demand, is better tolerated by patients with ischemic cardiomyopathy, in patients with acute MI [34, 35].

Some pyridazinone compounds act as potential vasodilator-cardiotonic compounds as a set of potent cyclic nucleotide PDE-III, cAMP PDE III inhibitors, such as 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-4,5-dihydro-3(2H)-pyridazinones (**1**), 6-[4-(2,6-disubstituted-quinolin-4-ylamino) phenyl]-4,5-dihydropyridazin-3(2H)-ones (**2**), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino]-3(2H)pyridazinone (**3**). Some of these compounds showed moderate vasorelaxant activity compared with the reference drug, milrinone [4]. A series of 6-benzoxazinylpyridazin-3-ones were showed inhibition of cardiac PDE-III and positive inotropic activity. 6-[3,4-Dihydro-3-oxo-1,4-(2H)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methyl pyridazin -3-one (bemoradan) was an very potent and selective inhibitor PDE-III and a long-acting, potent, orally active inotropic and vasodilator agent in various canine models. Bemoradan is a cardiotonic agent used to manage the CHF [36, 37]. Several 4,5-dihydro-3(2H)-pyridazinones were exhibited cardiotonic activity in dogs, like 6-(4-(benzylamino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2H)-pyridazinone (KF15232) and showed potent cardiotonic activity with a strong myofibrillar Ca^{2+}-sensitizing effect [38]. Analogues of (E)-4,5-dihydro-6-[2-[4-(1H-imidazol-1-yl) phenyl] ethenyl]-3(2H)-pyridazinone (**4**) as a variation on the imazodan series were exhibited hemodynamic, cAMP-PDE inhibitory and antiplatelets activities [39,40]. 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 [41]. A effective Ca^{2+}-sensitizer, pimobendan is a positive inotropic agent was 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 dose-dependent manner. Pimobendan increased Ca^{2+}-sensitivity appreciably increases FOC in human myocardium via sensitizing of the contractile proteins towards Ca^{2+} and inhibit of PDE-III isoenzymes activity [42]. The pimobendan is a benzimidazole-pyridazinone derivative, changes in heart rate (HR), left ventricular systolic pressure (LVP), left ventricular filling pressure (LVFP) but had only a minor effect on the maximum rate of rise of LVP. The decrease in mean arterial BP was primarily due to systemic vasodilation. Peripheral resistance and cardiac output was decreased respectively. Myocardial O_2 consumption was not affected despite the increase in heart rate. Pimobendan clearly increased cardiac output (CO). Vasodilator and positive inotropic property of pimobendan improves cardiac output in animals with severe MI and useful in the treatment of CHF [43]. The 4,5-dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-5-yl]methyl-3(2H)-pyridazone (**5**) 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 CO and exhibited similar cardiac profile. For both drugs, the vasodilatory and positive inotropic properties moved more in favor of the vasodilatory effects during CHF [44]. Vasodilatory action of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone (**6**) were exhibited vasodilatory potential. Compound 6-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)phenyl]-2-(4-fluorophenyl)-4,5-dihydropyridazin-3(2H)-one (**7**) exhibited vasodilating activity in nanomolar range [45]. Effect of a series of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives on isolated perfused toad heart and compared with the activity of levosimendan (CAS 141505-33-1). Some compounds showed potential cardiotonic activity [46]. Pyridazinone derivatives having a phenoxypropanolamine moiety, were exhibited hypotensive and β-blocking activities in rats. Among them, 5-chloro-2-cyanophenoxy derivative showed the promising dual activities [47].

Levosimendan is a novel inotropic agent and used i.v. in the treatment of acute CHF. Levosimendan exhibits linear pharmacokinetics, approximately

97–98% drug bound to plasma proteins and its elimination half-life of approximately one hour and it appears to be completely metabolized. The active metabolites of levosimendan have longer half-lives and may report for the prolonged haemodynamic effects, which occasionally persist for up to one week. Impaired renal function does not considerably alter plasma concentrations, although the elimination of the active metabolites may be affected. In contrast, the elimination of levosimendan may be a little prolonged in the presence of hepatic impairment [5]. Levosimendan has an essential secondary action–vasodilation of vascular smooth muscle. It acts upon the ATP-sensitive K^+ channels in the myocardium, peripheral blood vessels and coronary arteries. This extensive vasodilation has the beneficial effect in the failing heart, improving coronary flow, reducing ischaemia and improving the renal blood flow. Levosimendan has been appraised clinically in more patients than any other i.v. inotropic drug. Since coronary artery disease (CAD) is the principal cause of CHF, new inotropic agents need to be widely evaluated in this group. A high proportion of the patients included in trials with levosimendan had CHD [48]. Levosimendan produces enhanced myocardial contractility [49].



Scheme 1. Structure some pyridazine compounds with calcium sensitizing and phosphodiesterase-III inhibitory activity.

At therapeutic concentrations, it induces improved myofilament contractility mainly via its Ca^{2+} sensitizing actions by binding to cardiac troponin C in a Ca^{2+} dependent manner [26, 30]. It does not affect intracellular free Ca^{2+} and cAMP levels and possess no arrhythmogenic potential. This mechanism of action appears to differ from that seen with other Ca^{2+} sensitizers like pimobendan and EMD 53998 [50-52]. Levosimendan is a pyridazinone-dinitrile derivative, a class of cardiac inotropic or Ca^{2+} sensitizer agents. It is a vasodilator but its mechanism is not clearly known. The cardiac target protein of levosimendan, troponin C, is a Ca^{2+}-binding protein, it raises the possibility that levosimendan may interact with smooth muscle proteins, like, calmodulin, the regulatory myosin light chains. Levosimendan relaxes coronary arteries and lowers $[Ca^{2+}]i$ by mechanisms different than milrinone. The reduction of $[Ca^{2+}]i$ by

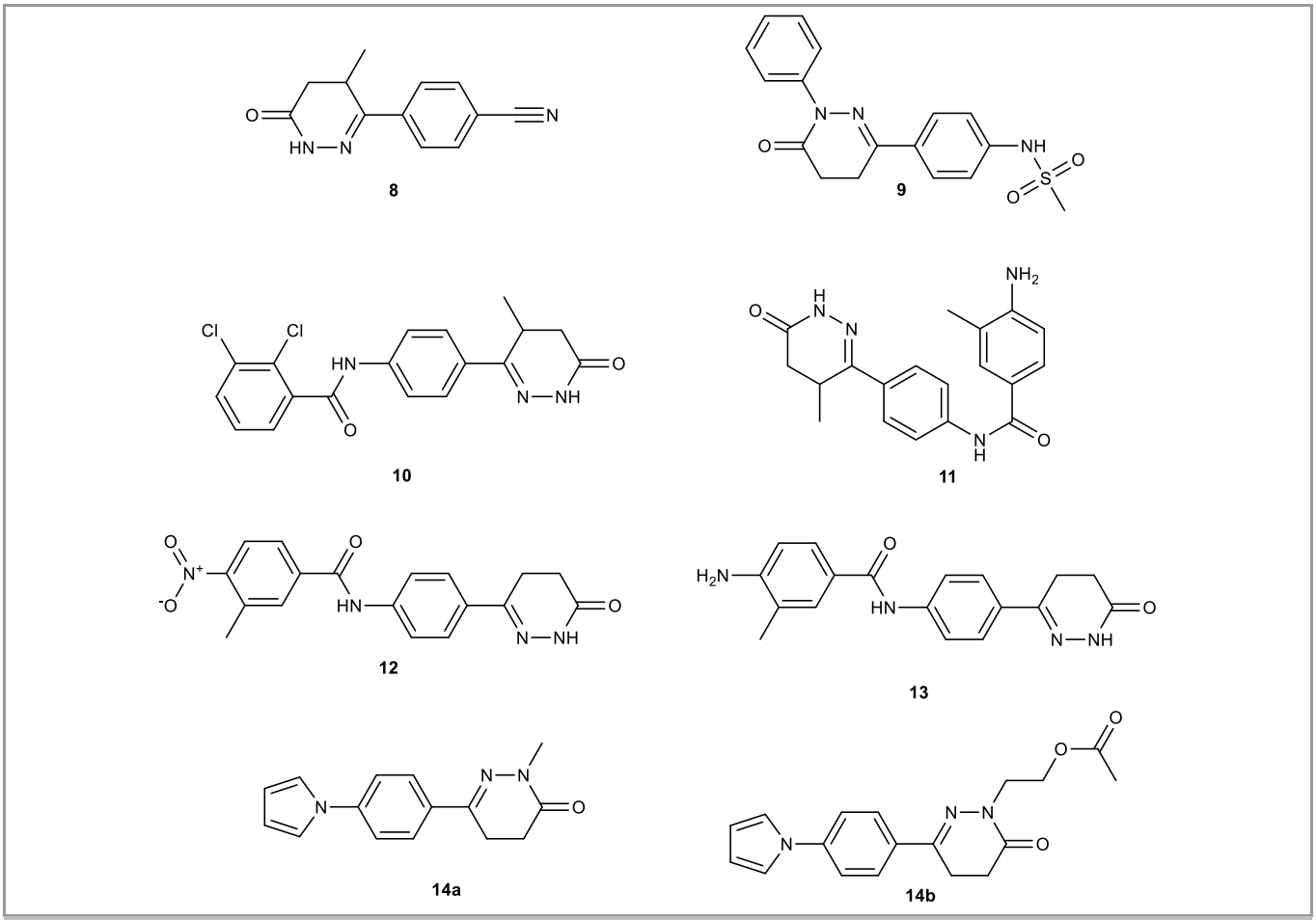
levosimendan regularly with opening of K^+ channels and a relaxation that is independent of $[Ca^{2+}]i$. The mechanism of action might involve the direct effect of levosimendan on the smooth muscle contractile or regulatory proteins themselves [53]. Positive inotropic activity and PDE-III inhibitory activity were reported by 4,5-dihydro-3(2H)-pyridazinone compounds [54].

The positive-inotropic and vasodilatating drug Pimobendan (racemate) and its enantiomers were explored to their cardiotoxicity in female Beagle dogs. Reduction of the BP take placed 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 females receiving the racemate. Racemate is equivalent to the eutomer, results gave evidence that cardiotoxicity by Pimobendan in dogs resulted from the overstated pharmacodynamic effect [55,56]. The UD-CG 115), is a cardiotonic vasodilator that increases myocardial contractility through Ca^{2+} sensitizer and vascular smooth muscle relaxant, possibly 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 N-glucuronide [57]. Pimobendan increases myocardial contractile force without increasing $[Ca^{2+}]i$. The pimobendan significantly improve in exercise capacity and quality of life in patients with CHF. The benefits of pimobendan found distinct with the adverse incident noted with milrinone and enoximone. This may be associated to the different mechanism of action of pimobendan. The pimobendan may have a useful adjunctive role in CHF [58]. The hemodynamic and cardiac electrophysiologic properties of pimobendan were studied in urethane-anesthetized dogs. The cumulative i.v. administration of pimobendan caused a dose-dependent decrease in mean arterial pressure (MAP) and an increase in sinus heart rate. The cardiac electrophysiologic changes linked with pimobendan administration included decreases in the atrial, ventricular, and atrio-ventricular nodal functional and effective refractory periods. Atrioventricular conduction velocity was enhanced after pimobendan. Pretreatment with propranolol attenuated the pimobendan-induced decrease in the ventricular refractory period and the increase in heart rate, whereas the decrease in arterial pressure was enhanced. This indicated that the i.v. administration of pimobendan to anesthetized dogs produces a dose-related positive inotropic effect, coronary and peripheral vasodilation, and cardiac electrophysiologic effects that include decreases in atrial, atrioventricular, ventricular refractoriness and facilitation of atrioventricular conduction. The electrophysiologic changes may be mediated, by a baroreceptor-mediated increase in sympathetic nervous system activity [59]. Pimobendan (UD-CG 115 BS), is a positive inotropic as well as coronary and peripheral vasodilator activities. Pimobendan has been reported to prolong the duration of the cardiac action potential of ventricular myocardial tissue, increasing the myocardial refractoriness and possibly exert antiarrhythmic activity. The effects of pimobendan cause the induction of ventricular tachycardia by planned ventricular stimulation, and upon the improvement of ischemic ventricular fibrillation were assessed after experimental anterior MI. The i.v. administration of 0.3 mg/kg pimobendan to post infarction dogs cause significantly reduced the rate-corrected QTc and paced QT intervals. It reduced the relative and effective refractory periods in normal ventricular myocardium. Electrophysiologic parameters in infarcted ventricular myocardium were not changed by pimobendan. Ventricular tachycardia stayed inducible early after anterior MI in pimobendan-treated post infarction dogs test. Six of the eight pimobendan-treated animals that had non sustained tachyarrhythmias brought out as initial responses to baseline planned stimulation testing had sustained tachycardias induced at post drug testing, with a reduction in the extra stimuli required to induce the post pimobendan tachyarrhythmias occurring in three animals [60-62]. Cardiovascular effects of the pimobendan and its O-demethylmetabolite UD-CG 212 in conscious pigs, utilizing consecutive i.v. 10 min infusions of 10, 25, 50 and 100 µg/kg/min and 2, 4 and 8 µg/kg/min respectively. Pimobendan caused dose-dependent increases in LVdP/dt max (up to 115%) and heart rate (up to 30%), while cardiac output (CO) was slightly elevated (up to 15%) and stroke volume decreased by 12%. Left ventricular end-diastolic pressure decreased in a dose-related manner. Mean arterial BP was not appreciably affected because systemic vascular resistance

decreased dose-related up to 15%. After β-adrenoceptor blockade, the pimobendan-induced increases in heart rate and CO were attenuated. The responses of left ventricular end-diastolic and mean arterial BP, systemic vascular resistance and stroke volume were not changed. UD-CG 212 caused dose-related increases in LVdP/dtmax (up to 100%) and heart rate (up to 25%). The CO was minimally raised (up to 8%) as stroke volume decreased dose-related up to 15%. As systemic vascular resistance decreased up to 12%, mean arterial BP was slightly reduced (5%). Left ventricular end-diastolic BP decreased dose-related. After β-adrenoceptor blockade, the UD-CG 212-induced increases in heart rate and almost abolished up to 15% and 20%, respectively. The other responses of the other systemic haemodynamic parameter were not changed. Pimobendan and UD-CG 212 Cl are marked inotropic and venodilator properties in the pigs. The attenuation of the inotropic effects by pretreatment with propranolol suggests that, in the pig, the β-adrenergic system is extensively involved in the inotropic actions. The lack of effect of β-adrenoceptor blockade on the vasodilator responses to both drugs suggested a mechanism not related to β-adrenergic activity [63, 64]. The inotropic drug, pimobendan (UD-CG 115 BS) enhances Ca^{+2} induced contraction of cardiac muscle possibly by increasing the Ca^{+2} sensitivity of troponin [65].

The 5-methyl-6-p.cyanophenyl-4,5-dihydro-3(2H)-pyridazinone (**8**) act as antihyper-tensive agent. The benzimidazolo-pyridazinones were showed inotropic effect with 'calcium sensitizing' effects. 5-methyl-6-[2-(3-pyrazolyl)-5-benzimidazolyl]-2,3,4,5-tetraahydro-pyridazinone.HCl (meribendan) is a compound for development of positive inotrope [66]. The 2-substituted-6-(4-acylaminophenyl)-4,5-dihydropyridazin-3(2*H*)-ones and 6-(4-Methane sulfonamido phenyl)-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one (**9**) showed important inodilatory properties in rats [67]. Comparative cardiotonic effects of a variety of 6-phenyl-4,5-dihydro-3(2H)-pyridazinones, 2,3-dichloro-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl) phenyl) benzamide (**10**), 4-amino-3-methyl-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydro pyridazin-3-yl) phenyl)benzamide (**11**), 3-methyl-4-nitro-N-(4-(6-oxo-1,4,5,6-tetrahydro-pyridazin-3-yl) phenyl)benzamide (**12**) and 4-amino-3-methyl-N-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide (**13**) when compared to levosimendan (CAS 141505-33-1) [46]. Some 2-nonsubstituted/2-methyl-/2-(2-acetyloxyethyl)-6-[4-(substitutedpyrrol-1-yl)phenyl]-4,5-dihydro-3(2H)-pyridazinone (**14a** & **14b**) derivatives were exhibited antihypertensive effects. Some compounds showed appreciable cardiotonic activity [68].

The Ca^{2+} sensitizers have been shown to exert 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. MCI-154, 6-[4-(4'-pyridylamino)phenyl]-4,5-dihydro-3(2*H*)-pyridazinone. HCl trihydrate is a Ca^{2+} sensitizer is a more potent positive inotropic effect than pimobendan, adibendan and sulmazole. MCI-154 improved not only cardiac systolic function but also diastolic relaxation in CHF [69]. However, the MCI-154, also a Ca^{2+} sensitizer, has no impairment to cardiomyocyte relaxation. The effects of MCI-154 on Ca^{2+} transient and cell contraction using ion imaging system, and its influence on L-type Ca^{2+} current and $Na+/Ca^{2+}$ exchange current with patch clamp technique in rat ventricular myocytes as well. The MCI-154 (1~100 μmol/L) had no effect on L-type Ca^{2+} current; MCI-154 concentration-related increased cell shortening, with a slight increase in Ca^{2+} transient amplitude. MCI-154 dose dependently increased the electrogenic Na^{+}/Ca^{2+} exchange current both in inward and outward directions in rat ventricular myocytes. The MCI-154 exerted a positive inotropic action without impairing myocyte relaxation. The stimulation of inward Na^{+}/Ca^{2+} exchange current may accelerate the Ca^{2+} efflux. The progress by MCI-154 of myocyte relaxation is credited to the forward mode of Na^{+}/Ca^{2+} exchange [70]. The interaction effects of MCI-154 and isoflurane on myocardial contractility and hemodynamics. MCI-154 increased heart rate and left ventricular function with no change in rate pressure product and coronary blood flow, with a decrease in coronary vascular resistance (CVR).



Scheme 2. Structure some pyridazine compounds with calcium sensitizing and phosphodiesterase-III inhibitory activity.

However, the MCI-154, also a Ca^{2+} sensitizer, has no impairment to cardiomyocyte relaxation. The effects of MCI-154 on Ca^{2+} transient and cell contraction using ion imaging system, and its influence on L-type Ca^{2+} current and $Na+/Ca^{2+}$ exchange current with patch clamp technique in rat ventricular myocytes as well. The MCI-154 (1~100 μmol/L) had no effect on L-type Ca^{2+} current; MCI-154 concentration-related increased cell shortening, with a slight increase in Ca^{2+} transient amplitude. MCI-154 dose dependently increased the electrogenic Na^{+}/Ca^{2+} exchange current both in inward and outward directions in rat ventricular myocytes. The MCI-154 exerted a positive inotropic action without impairing myocyte relaxation. The stimulation of inward Na^{+}/Ca^{2+} exchange current may accelerate the Ca^{2+} efflux. The progress by MCI-154 of myocyte relaxation is credited to the forward mode of Na^{+}/Ca^{2+} exchange [70]. The interaction effects of MCI-154 and isoflurane on myocardial contractility and hemodynamics. MCI-154 increased heart rate and left ventricular function with no change in rate pressure product and coronary blood flow, with a decrease in coronary vascular resistance (CVR). Isoflurane decreased heart rate and LV function, with a decrease in rate pressure product. Isoflurane also decreased CVR, but not coronary blood flow. The MCI-154 during isoflurane anesthesia were qualitatively similar to those observed in the conscious state. The conscious state, MCI-154 reversed the decrease in CO and preload recruitable stroke work caused by isoflurane, but these are not considerably different from the effects of isoflurane alone. The MCI-154 increases cardiac contractility (CC) and decreases CVR without changing calculated myocardial oxygen consumption (MOC) during both the conscious state and isoflurane anesthesia. MCI-154 restores the CC depressed by isoflurane and enhances the coronary vasodilating effect of isoflurane in chronically instrumented dogs [71]. The MCI-154 exhibited hemodynamic, inotropic, mechano-energetic and oxidative metabolic effects. MCI-154 induced a progressive dose-dependent decrease in systemic vascular resistance (SVR), with a connected increase in heart rate and cardiac output (CO). Contractility increased only in the high-dose range, and mechano-energetic efficiency was significantly reduced. The MCI-154 has minimal inotropic action, induces a significant "oxygen waste", and decreases SVR [72]. As in cardiac muscle, MCI-154 potentiated isometric tension and improved isometric tension cost at full Ca^{2+} activation and

showed little Ca^{2+}-sensitizing effect. In contrast to its effect on cardiac muscle, MCI-154 decreased all the kinetic parameters such as shortening velocity, the rate of rise of tension, and actomyosin ATPase activity. MCI-154 acts directly on skeletal actomyosin and inhibits a reaction step(s) of the ATPase cycle later than the force-generating event [73]. MCI-154, had deleterious effects on ventricular arrhythmias, since several PDE-III inhibitors have been shown to aggravate arrhythmias. Continuous infusion of MCI-154 (1 µg/kg/min for 15 min) did not suppress or aggravate the arrhythmias generated in the two-stage coronary ligation-, digitalis- and adrenaline-induced canine arrhythmia models. In case of a bolus injection of 30 µg/kg, MCI-154 did not aggravate the adrenaline-induced arrhythmias. MCI-154 (10-100 µM) did not increase the inward Ca^{2+} current under the condition where these currents were increased by isoprenaline. The results indicated that MCI-154 does not aggravate ventricular arrhythmias and does not act on membrane currents associated with arrhythmogenesis. Thus, MCI-154 may be useful positive inotropic agent with little arrhythmogenic effect [74]. MCI-154, has more potent positive inotropic effect than pimobendan, adibendan and sulmazole. Ca^{2+} sensitizers 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+}. However, most of the Ca^{2+} sensitizers may impair cardiac diastolic function as a result of increased Ca^{2+} sensitivity of the myofilaments. MCI-154 improve not only cardiac systolic function but also diastolic relaxation in CHF. However, the mechanisms of inotropic effects of MCI-154 are poorly understood. The possible mechanisms are Ca^{2+} transient and cell shortening in ventricular myocytes of rats and also L-type Ca^{2+} current and Na^{+}/Ca^{2+} exchange current [75]. The MCI-154 increased ATPase activities of canine myofibrils and reconstituted actomyosin. In myofibrils and reconstituted actomyosin, MCI-154 caused a parallel shift of the Ca^{2+}-ATPase activity relation curve to the left without affecting the maximum activity causes an increase in Ca^{2+} sensitivity. MCI-154 had little effect on actin-activated, Mg^{2+}, Ca^{2+} and (K^{+}, EDTA)-ATPase activities of myosin. Ca^{2+} binding to cardiac myofibrils or purified cardiac troponin were increased by MCI-154. The MCI-154 enhances Ca^{2+} binding to cardiac troponin C to elevate the Ca^{2+} sensitivity of myofilaments and may cause a positive inotropic action in cardiac muscle [76]. A series of [4-(substituted-amino)phenyl] pyridazinones and [4-(substituted-methyl) amino] phenyl] pyridazinones was exhibited inotropic and cardio hemodynamic effects. 6-[4-(4-pyridylamino)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone hydrochloride showed extremely potent inotropic activity along with vasodilating activity [77].

The cardiovascular effects of 6-[4-[2-[3-(5-chloro-2-cyanophenoxy)-2-hydroxy propyl amino]-2-methylpropylamino]phenyl]-4,5-dihydro-5-methyl-3(2H)pyridazinone mono ethyl maleate (TZC-5665**)** and its metabolite in human, M-2, in isolated atrial and ventricular muscles of guinea pigs and dogs and 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 the M-2 was not modified by phentolamine, propranolol and cimetidine, but fully depressed by carbachol. In blood-perfused dog heart, M-2 increased the contractile force and coronary blood flow of paced papillary muscles and sinus rate. Although TZC-5665 hardly affected the contractile force and sinus rate, it increased coronary blood flow. TZC-5665 hardly affected atrio-ventricular (AV) conduction time, whereas M-2 somewhat shortened AV conduction time. The rate of ventricular automaticity was slightly increased by M-2, howeversuppressed by TZC-5665 at higher doses. 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 [78, 79].

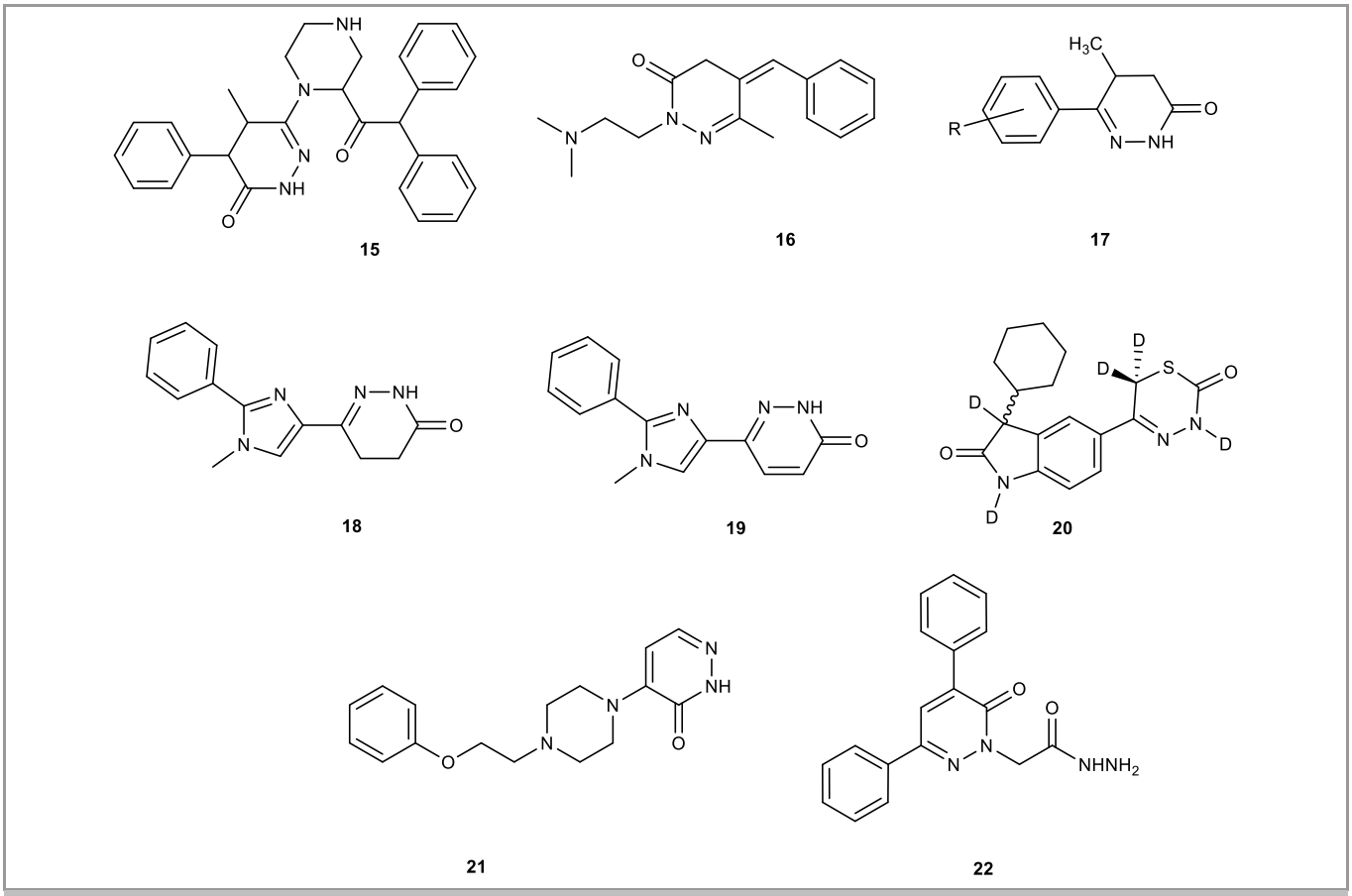
The pyridazinone compound zardaverine is a selective inhibitor of PDE-isozymes as a potent bronchodilator. It exerts a positive inotropic action on heart muscle. Zardaverine inhibited the cGMP-inhibitable PDE-III from human platelets and the rolipram-inhibitable PDE-IV from canine trachea and human polymorphonuclear (PMN) cells, respectively. The zardaverine compound affected the calmodulin-stimulated PDE-I, the cGMP-stimulated PDE-II and the cGMP-specific PDE-V only slightly at concentrations. Zardaverine inhibits the ADP-induced aggregation of human platelets; this inhibition was synergistically increased by activators of adenylate cyclase such as PGE1 and forskolin. In human PMN cells, zardaverine inhibited the zymosan-induced superoxide anion generation. This effect was increased by activators of adenylate cyclase. Zardaverine is a selective inhibitor of PDE- III and PDE-IV isozymes [80]. Several 4,5-dihydropyridazinone ring open analogues of imazodan (Cl-914) were exhibited inotropic effect in anesthetized dogs. The cardiovascular profile of the acyl hydrazones was similar to the corresponding cyclic analogues, the inotropic effect was considerably reduced. The guanyl hydrazone series enhanced inotropic potency that was comparable to 4,5-dihydropyridazinones. The

inotropic mechanism of the guanylhydrazones seems to be different from the corresponding acyl hydrazones and cyclic 4,5-dihydropyridazinones [40].

The PC-09 is a pyridazinone derivative. It has antiplatelet activity and ATP release induced by arachidonic acid (AA), collagen or thrombin. The TX formation caused by collagen or thrombin was clearly inhibited by PC-09, but there was no alteration in that caused by AA. The PC-09 considerably increased the cAMP level through inhibiting cAMP-PDE activity. The PC-09 is an inhibitor of platelet aggregation and $[Ca^{+2}]i$ mobilization [3]. The 6-(α,α-diphenyl acetyl piperazinyl)phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (**15**) inhibited AA, adenosine di-phosphate (ADP) and platelet activating factor-induced rabbit platelet aggregation. This compound depressed thromboxane-B2 (TXB2) and to increase cAMP levels in rabbit platelets [81]. The 2-(2-dimethylaminoethyl)-5-benzylidene-6-methyl (2H,4H)-3-pyridazinones (**16**) reduced the TXA_2 synthesize activity of heart tissue [82]. It was thought that the tetrahydro pyridazinones (**17**) might be able to provide suitable compound because few drugs belonging to this class were designed as PDE inhibitor [66]. Adrenolytic effect of 6-piperazinyl-3(2H)-pyridazinones to blocking activity of the pre- and postsynaptic a-adrenoreceptors of isolated rat vas deferens. The benzodioxane, 2-methoxyphenoxyethyl and phenoxyethyl group is indispensable for β-blocking activity [83]. Several 6-(substituted 1H-imidazol-4(5)-yl)-3(2H)-pyridazinones were exhibited positive inotropic activity. The 1H-imidazol-4-yl regioisomers 4,5-dihydro-6-(1-methyl-2-phenyl-1H-imidazol-4-yl)-3(2H)-pyridazinone (**18**) and 6-(1-methyl-2-phenyl-1H-imidazol-4-yl)-3(2H)-pyridazinone (**19**) were potent inotropic and also potent inhibitosrs of cardiac PDE-III [39]. The positive inotropic Ca^{2+}-sensitizing agent claimed to be totally devoid of PDE inhibitory activity or any other inotropic agents 5-methyl-6-phenyl-1,3,5,6-tetrahydro-3,6-methano-1,5-benzodiazocine-2,4-dione (BA 41899) and its (+)-isomer, CGP 48506, for this type of activity. Different activity ratios (PDE inhibition vs Ca^{2+} sensitization) for the enantiomers of sulmazole, pimobendan, meribendan, EMD 53 998, KF 15232 or ORG 20494 and different PDE inhibitory potencies for the enantiomers of siguazodan and simendan and stereospecificity for PDE inhibition versus Ca^{2+} sensitization remains when the chiral centre is introduced elsewhere on the molecule. Biological evaluation of the isomeric pairs of each compound was undertaken, the pimobendan, EMD 53998, simendan, meribendan, siguazodan and KF 15232. The diazinone series that the strongest PDE inhibition is supported by the (-)-isomer. In pyridazinone series, the (R) configuration seems to be necessary for the inhibition of PDE. The Ca^{2+} sensitizing effect in the pyridazinone compounds like meribendan and simendan. In the thiadiazinone series, the (R)-configuration may be essential for the Ca^{2+}-sensitizing effect. The stereoselectivity between these isomers is less marked and a single isomer, (-), was found to be the more potent on both enzymatic activities. The pyridazinone/thiadiazinone cycle is fully compatible with the topographical model of the cardiac cAMP-PDE receptor and optimized the difference between the (+) and the (-) isomers (**20**) [84]. The 4-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinones (**21**) and alkane-bridged dimers of 4-,S- and 6-[4-(phenoxyethyl)-1-piperazinyl]-3(2H)-pyridazinones were blocking activity on the pre- and postsynaptic α-adrenoreceptors on rat vas deferens. The adrenoreceptor antagonists have increased the development of postsynaptically selective α-adrenoreceptor antagonists due to their significance in the cure of hypertension and prostatic hypertrophy. The 3(2H)-pyridazinone derivatives is a potential antagonists of the α-adrenoreceptor [85]. The activity of pyridazin-3(2H)-one derivatives for affinity at adenosine receptors in bovine brain cortical membranes, and bovine brain striatal membranes, respectively. Compounds in which the 6-chloro-pyridazin-3(2H)-one or 6-phenyl-pyridazin-3(2H)-one (**22**) group is linked through a chain of two carbon atoms in the 6 position of the adenosine showed good affinity towards, adenosine receptor, particularly compound in which a phenyl-pyridazinone group shows highest affinity.

Adenosine is a neuromodulator which regulates several physiological effects, including vasodilatation, antilipolytic, inhibition of platelet aggregation, inhibition of lymphocyte effects and depression of CNS activity. The adenosine has inhibitory effects on neurotransmission and on spontaneous activity of central neurons. The 3(2H)-pyridazinone derivatives showed many activities, reduction of BP [86]. The cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2H-indol-2-one (LY195115) is a potent, competitive inhibitor of SR derived PDE and have potent inotropic agent.

The geminal methyl substituents in the indol-2-one ring and the C5' methylene unit of the dihydro pyridazinone ring. The 4-methyl analogue of LY195115, was 2-fold more potent activity than LY195115, and the methyl substituent maybe caused minor perturbations in general molecular topology [87].

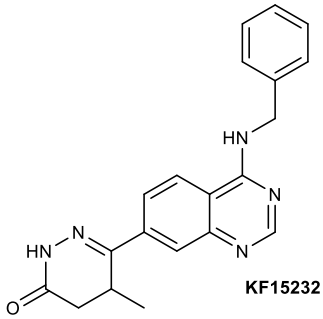


Scheme 3. Structure some pyridazine compounds with calcium sensitizing and phosphodiesterase-III inhibitory activity.

Pharmacological effects of the 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (M73101) is a non-steroidal anti-inflammatory drug (NSAID), i.v. administration of M73101 produced a small transient fall in BP, increase in heart rate and respiratory stimulation. The contraction induced by epinephrine in the isolated ear vessels of rabbits relaxed by use of M73101 and in isolated trachea of guinea pigs, M73101 relaxed the contraction that induced by histamine. Moreover, M73101 inhibited the broncho-constriction by histamine but not by bradykinin in guinea pigs. These properties of M73101 on the tracheal smooth muscle were similar to aminopyrine but different from aspirin which inhibited only the contraction by bradykinin. M73101, unlike the aminopyrine and phenylbutazone, somewhat increased urine volume and electrolytes excretion in rats, indicating that this compound does not produced edema. M73101 showed no significant activities on the blood sugar level, platelet aggregation, blood coagulation, methemoglobin formation and local irritation [88].

Several different chemical classes of cardiotonic drugs, were correlated with effects on contractility, cAMP-dependent protein kinase activation ratios, and cAMP content in the intact tissue [89]. Cardiotonic drugs of the bipyridine, benzimidazole, imidazole and pyridazinone classes combine positive inotropism with vasodilating properties. The mechanism of action of these drugs have shown that many are relatively selective inhibitors of a cytosolic form of cardiac cyclic nucleotide PDE activity [90, 91]. A high-affinity cytosolic PDE activity has been observed in bovine heart with high affinity for cAMP and a lack of stimulation by calmodulin or cGMP [92]. This enhance contractile function by increasing cAMP levels and subsequent activation of cAMP-dependent protein kinase [93]. This activity, isolated by immune-precipitation, has kinetic properties similar to the SR-PDE and is also inhibited by certain cardiotonic agents like milrinone, enoximone, and amrinone by cGMP [94].

Theophylline as the first PDE-inhibitor used in the treatment of asthma. Derivatives of theophylline (6-(7-theophylline)-3(2H)-pyridazinone) and other purine analogs were tested as PDE-inhibitors and cardiac stimulants, some of them were several times more active than theophylline. 4,5-dihydro-6-phenyl-3(2H)-pyridazinone derivatives are PDE-inhibitors like CI-



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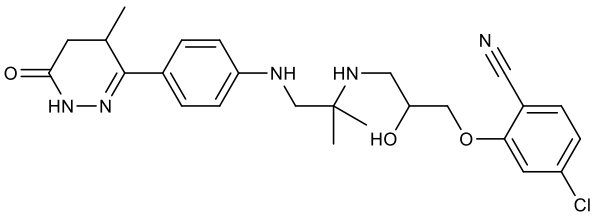
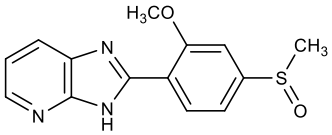
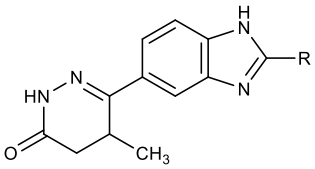


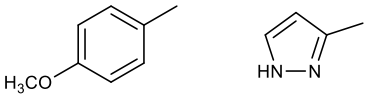
TZC-5665



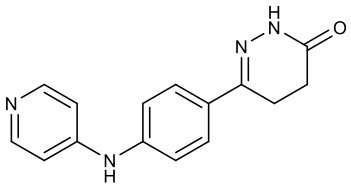
Sulmazole



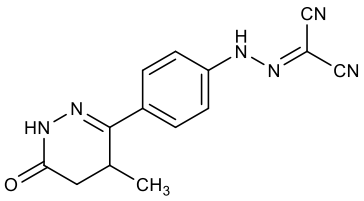
R= Pimobendan (UD-CG 115 BS)



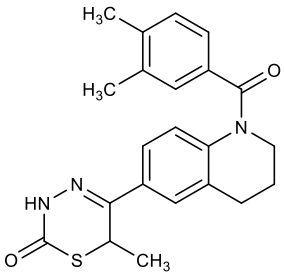
R=Meribendan



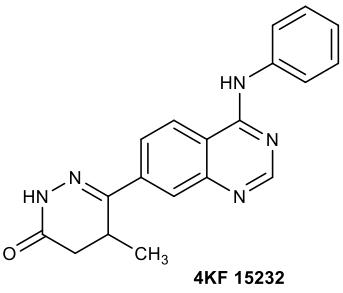
MCI-154



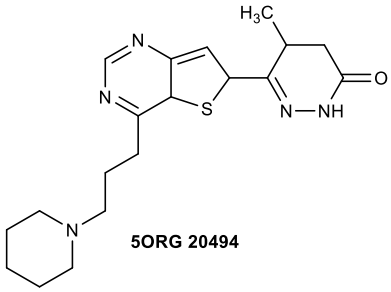
Simendan



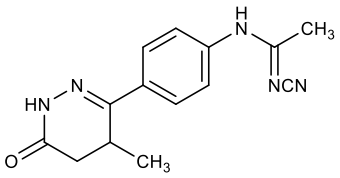
EMD 53998



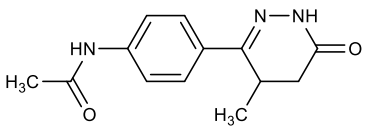
4KF 15232



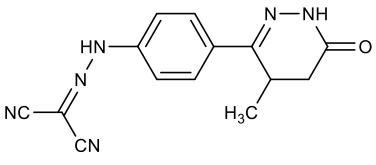
5ORG 20494



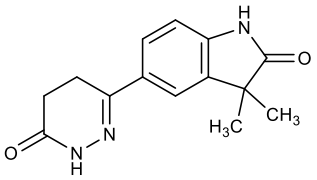
Siguazodan



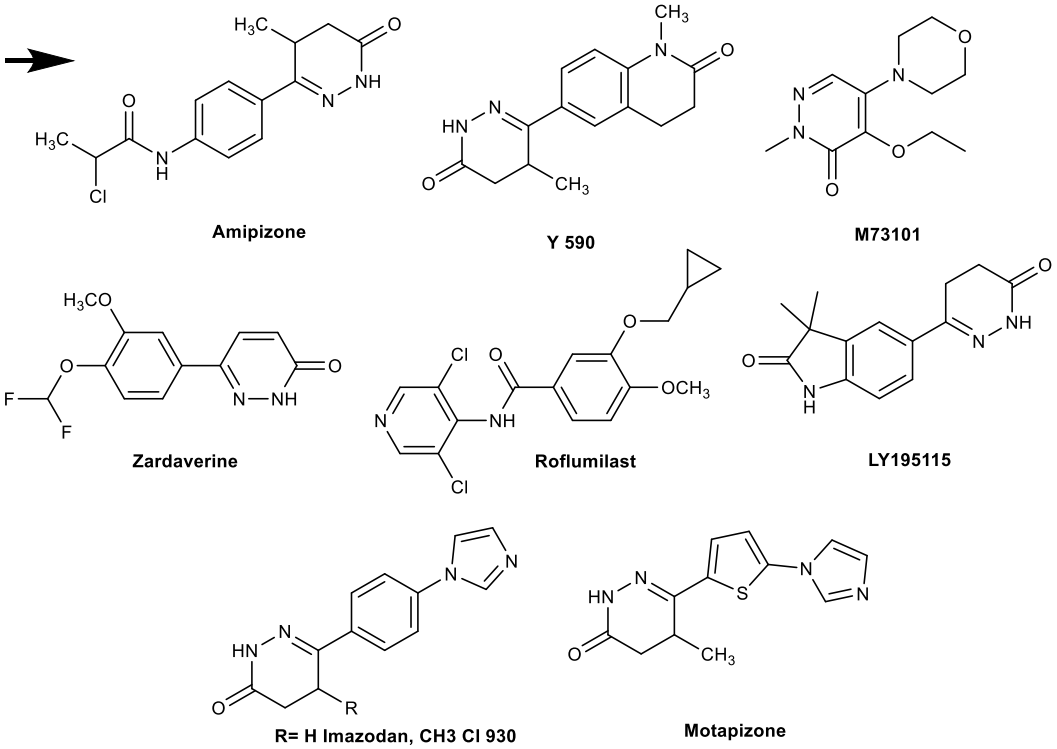
SK&F-93741



Levosimendan



Indolidan

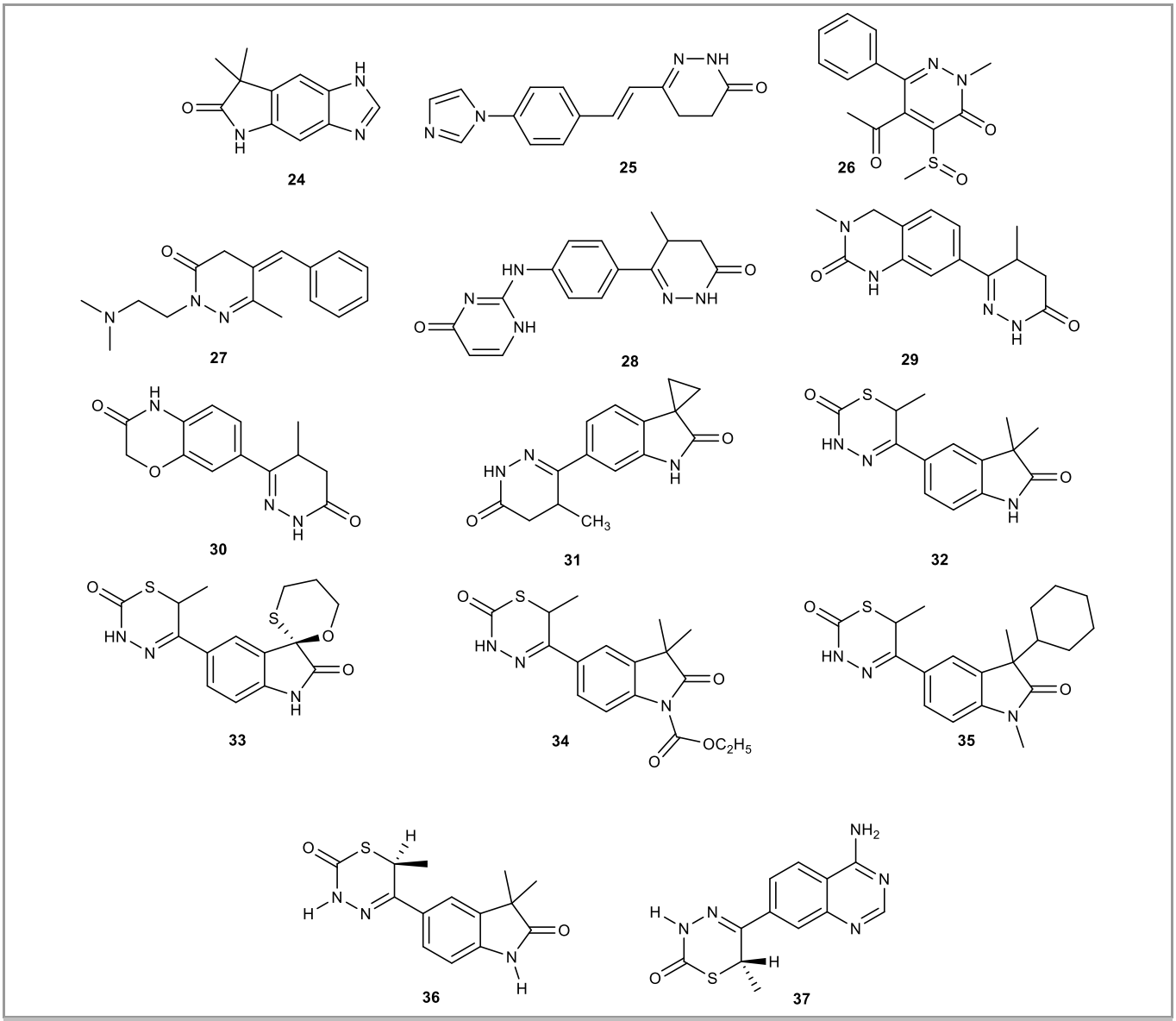


Scheme 4. Structure some pyridazine compounds with calcium sensitizing and phosphodiesterase-III inhibitory activity.

914 which produced a cardiotonic effect accompanied by only slight decreases in BP and moderate increases in heart rate (HR). Some 6-phenyl-3(2H)-pyridazinones showed broncho-spasmolytic effect more than that of xanthenes [95]. The cardiovascular effects of RG W-2938, 6-[6-(3,4-dihydro-3-methyl-2(1H)-2-oxoquinazolinyl)]-4,5-dihydro-3-(2H)-pyridazinone, a non glycoside, noncatecholamine cardiotonic or vasodilator agent were examined in vivo in dogs and in vitro in the isolated guinea pig hearts; RG W-2938 5 nmol-5 mumol increased contractility in a dose-related manner. RG W-2938 30-300 µg/kg administered i.v. to anesthetized dogs increased contractile force while decreasing arterial pressure and total peripheral resistance in a dose-related manner. Heart rate was only slightly increased, and aortic flow was not appreciably altered. A single oral dose of RG W-2938 0.3 mg/kg administered to conscious dogs produced a marked and sustained increase in contractility 15-240 min after treatment while only slightly increasing HR. RG W-2938 is an orally effective positive inotropic/vasodilator agent. The effects of 30-300 µg/kg, i.v. were studied in a mecamylamine-propranolol-induced model of heart failure. RG W-2938 effectively reversed the drug-induced heart failure (HF) by increasing the myocardial contractility and decreasing the arterial pressure while only slightly affecting HR. [96].

Cardiac PDE-III inhibitors derived from pyridinone, imidazolone, pyridazinone and related structures form a new class of positive inotropic vasodilator agents (e.g. milrinone) that are useful in the treatment of CHF. These agents inhibit the intracellular hydrolysis of cAMP, thereby encouraging cAMP-catalysed phosphorylation of sarcolemmal Ca^{2+} channels and activating the Ca^{2+} pump. Drugs like milrinone have a wider therapeutic index than the cardiac glycosides. They also have vasodilator and lusitropic actions and are devoid of the central stimulant actions that narrow the therapeutic index of theophylline and other methyl xanthines. Receptor down-regulation, which curtails the inotropic efficacy of β-adrenoceptor agonists, does not compromise the efficacy of PDE inhibitors. The effectiveness of these new drugs is, however, dependent upon some degree of basal adenylate cyclase activity. Individual PDE inhibitors differ in terms of both chronotropic and extracardiac properties [97]. The adibendan is a potent and long-acting cardio-tonic drug and increase in contractility was not mediated via stimulation of β-adrenergic receptors. The intrinsic positive inotropic activity of the compound of this series is 5,7-dihydro-7,7-dimethylpyrrolo[2,3-f]benzimidazol-6(1H)-one (**24**). The most compounds effect on left ventricular dP/dt was compared with that of pimobendan and indolidan. After administration of pimobendan, and indolidan were equipotent, but only with pimobendan, and indolidan, durations of action exceeded 6 h [98]. A series of analogues of (E)-4,5-dihydro-6-[2-[4-(1H-imidazol-1-yl) phenyl]ethenyl]-3(2H)-pyridazinone (**25**) was produced as a variation on the imazodan series. These 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 moiety produced compounds that retained the potent inotropic/vasodilator activity of the imazodan series and enhanced the platelet aggregation inhibitory activity [39, 40]. A series of 6-phenyl-3(2*H*)-pyridazinones having different substituents in the 5-position of the pyridazinone ring [99] and 5-acetyl-2-methyl-4-methylsulfinyl-6-phenyl-3(2H)-pyridazinone5-acetyl-2-methyl-methylsulfinyl-6-phenyl-3(2H)-pyridazinone (**26**) exhibited platelet aggregation inhibitory activity [100]. The effects of 2-(2 dimethylaminoethyl) 5-benzylidene 6-methyl (2H,4H)-3-pyridazinone (**27**) 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 arachionic acid (AA) as a substrate and horse platelet and aorta microsomes as sources of TXA_2 and PGI_2 synthetases respectively. Compound **26** behaves as a specific inhibitor of the TXA_2 synthetase activity of heart tissue and could have a beneficial use in therapeutics [82]. The Y-590 (pyridazinone derivative) is a potent anti-thrombotic agent by inhibition of platelet PDE [101]. Various other pyridazinone compounds have cardiovascular activities (**28-37**). Three major classes of inotropic drugs have been clinically evaluated in patients with left ventricular dysfunction, agents that increase the concentration of [cAMP]i by stimulating the β-adrenergic receptor or inhibiting PDE; drugs that increase the $[Na^+]i$ concentration; c) the Ca^{2+} sensitizing drugs [27, 102].



Scheme 5 . Structure some pyridazine compounds with calcium sensitizing and phosphodiesterase-III inhibitory activity.

5. Conclusions

Positive inotropic agents are efficacious and unique tool in the short-term treatment of patients with severe left ventricular dysfunction. The positive inotropy by Ca^{2+} sensitization and phasphodiestrase-III should be measured as a developing approach for the treatment of CHF and MI. The pyridazine derivatives have diverse biological potential and taken attention of the pharmacologists and researchers to explore this nucleus to its multiple potential particularly against cardio-vascular disorders and its cardio tonic activity is one of the most encouraging activities. By the present scenario, it can be concluded that, the pyridazinone nucleus have a great potential which remain to be disclosed till date. Also, the biological profile of the pyridazine represented much progress.

6. References

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