

Review Article

6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone - An important chemical moiety for development of cardioactive agents: A review

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Abstract

6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone moiety is a vital structural part of many cardio-active pyridazinone derivatives which are either in clinical use or have been tested in clinical trials. These include imazodan, CI-930, pimobendan, indolidan, levosimendan, SK&F-93741, Y-590, meribendan, NSP-804, NSP-805, bemoradan, senazodan, amipizone, prinoxodan, SKF 95654, siguzodan and KF 15232. This article briefly reviews relevant literature on various reports on the synthesis and use of this moiety for development of cardio-active agents.

Keywords: 6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone, Cardio-active agents, Imazodan, Pimobendan, Indolidan, Levosimendan

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INTRODUCTION

Cardiovascular disease is a major public health problem worldwide, even in the United States of America, and it accounts for approximately 30 % of all deaths [1]. Cardiovascular disease has also been considered to be the major cause of death in the Kingdom of Saudi Arabia [2]. Due to increasing prevalence of cardiovascular disease in children, researchers have recommended the establishment of well-equipped hospitals to for the care of children with cardiovascular disease in developing countries as well as in Kingdom of Saudi Arabia [3]. Studies have also revealed that there is a need for more research in the field of cardiovascular disease in developing countries because of the likelihood of prevalence of cardiovascular disease in all age groups in these countries [4,5].

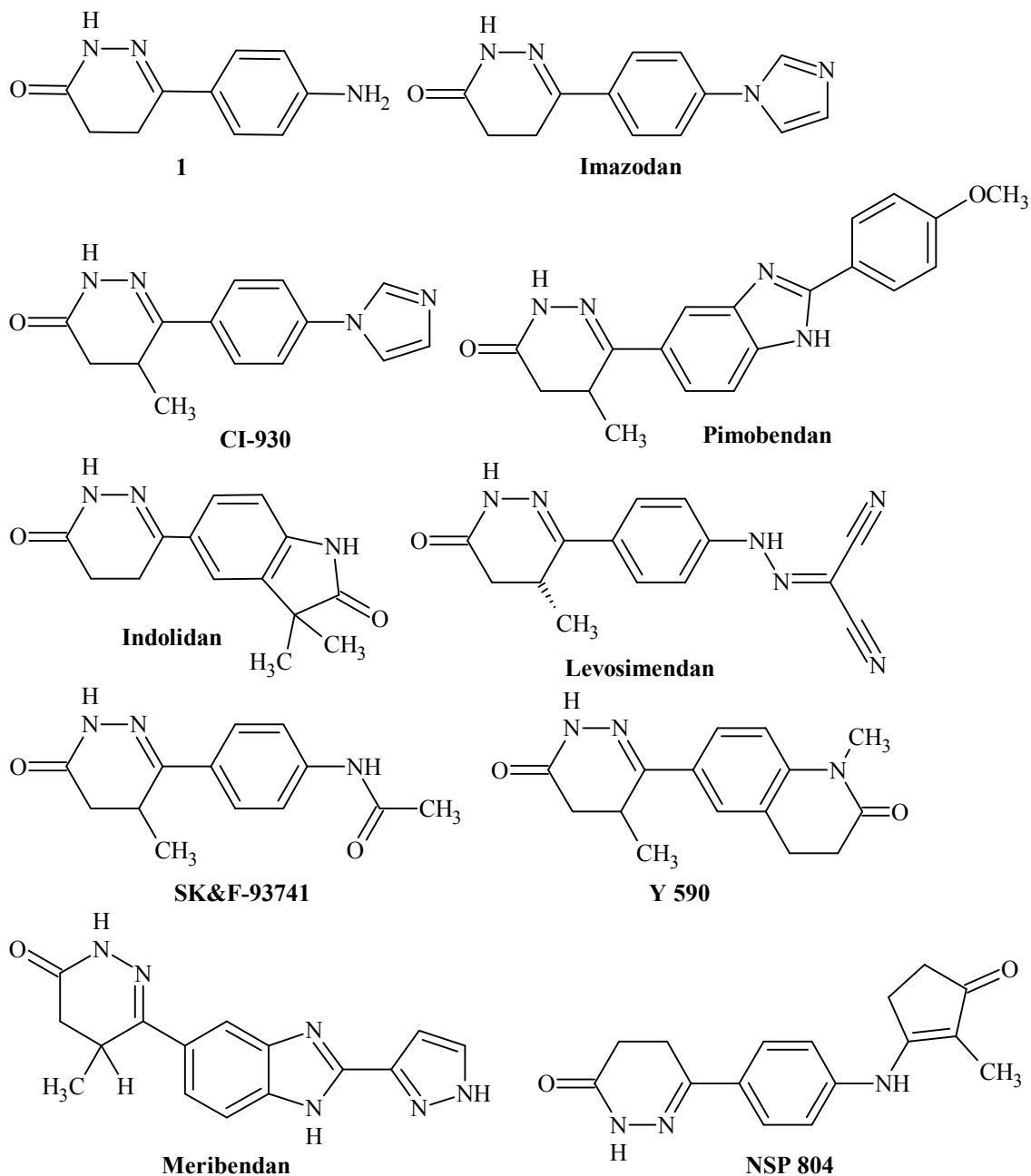
There are many cardio-active derivatives of 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone containing 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone moiety (1) as their vital structural component. These derivatives are either in clinical use or have been tested in clinical trials. They include imazodan [6,7]; CI-930 [7,8]; pimobendan [7,9]; indolidan [7,10]; levosimendan [7,11]; SK&F-93741 [7,12]; Y-590 [7,13]; meribendan [14]; NSP-804 [15]; NSP-805 [15]; bemoradan [16,17]; senazodan [18]; amipizone [7,17]; prinoxodan [19]; SKF 95654 [20]; siguzodan [21] and KF 15232 [21].

Some reviews on pyridazinone derivatives have been published [22-25]. However, these reviews are directed towards the general chemistry and general biological activities of diverse pyridazine

derivatives. None of these articles focused on the use of any specific chemical moiety for the development of cardio-active agents.

The current review gives an insight on the potential of 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone moiety for the development of cardio-active agents, and briefly discusses relevant literature related to the synthesis and

use of this chemical for the preparation of cardio-active agents. Accordingly, literature references wherein 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone moiety was not synthesized and/or not used for the preparation of cardio-active agents were excluded.



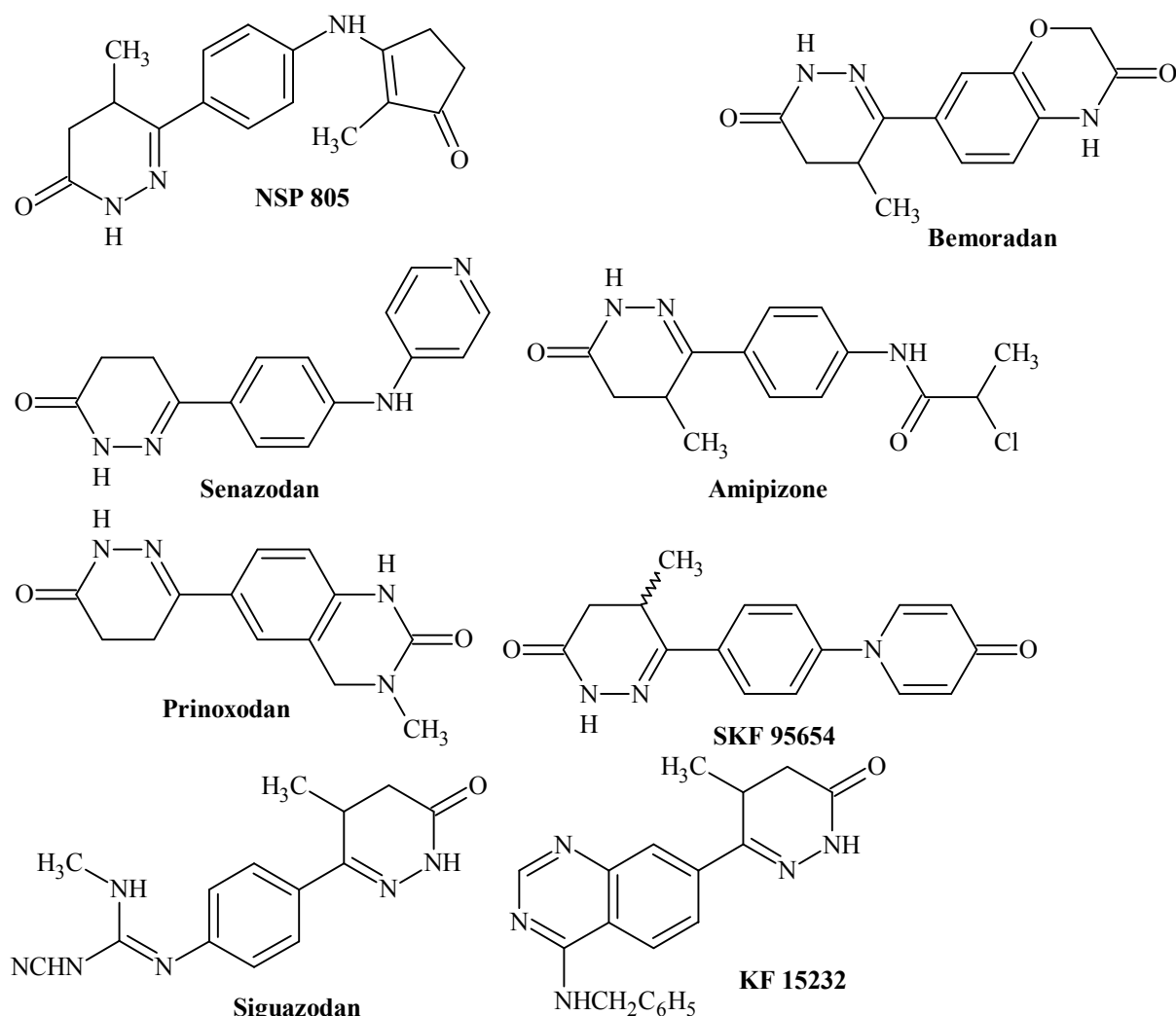
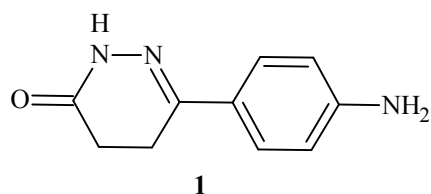


Figure 1: Some pyridazinone derivatives

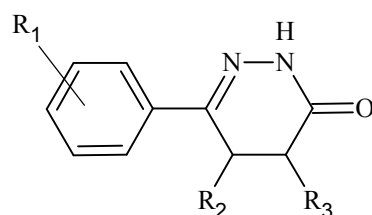
6-(4-AMINOPHENYL)-4,5-DIHYDRO-3(2H)-PYRIDAZINONE DERIVATIVES AS CARDIOACTIVE AGENTS

6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone (1) was first reported in 1967 by Gerhard and August [26]. Gerhard and August also reported that this compound is associated with anti-inflammatory and sustained blood pressure reducing activities [27].



Curran and Ross [28] prepared and tested a series of 6-phenyl-4,5-dihydro-3(2H)-pyridazinones. They concluded that the potent and most active hypotensive agents (2) in normotensive rats were derivatives with

acetamido and cyano groups in the para or meta position of the benzene ring, combined with 5-methyl substituent in the hetero ring.

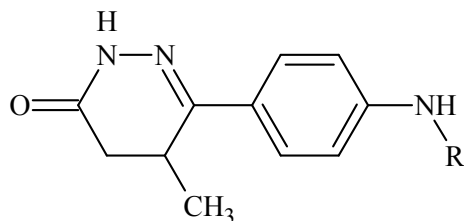


$R_1 = \text{NHCOCH}_3$ or CN ; $R_2 = \text{CH}_3$ $R_3 = \text{H}$

2

Thyes *et al* [29] prepared 6-Aryl-4,5-dihydro-3(2H)-pyridazinones which exhibited aggregation-inhibiting activity on human platelets *in vitro* and on rat platelets *ex vivo*, as well as a hypotensive action on rats. The strongest pharmacological effects were found with dihydropyridazinones that have $R =$ chloroalkanyl substituent, together with a methyl group in the 5-position (3). The hypotensive

actions of these compounds were 40 times higher than that of dihydralazine.

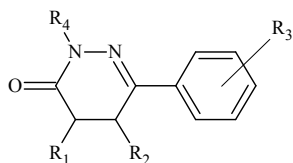


R = chloroalkanoyl substituent

3

These authors further demonstrated that the para-substituted compounds had a strong inhibiting effect on collagen-induced and ADP-induced aggregation of human platelets. It is known that platelet aggregation plays an important role in the pathogenesis of cardiovascular disease [30].

The *in vitro* human platelet aggregation and the *ex vivo* rat platelet aggregation-inhibiting activities of 6-aryl-4,5-dihydropyridazinones (4) with $R_1 = R_2 = R_4 = \text{Me}$ or H ; and $R_3 =$ amine containing groups were correlated with the van der Waals volume (Vw) of R_3 by Gupta *et al* [31]. Their results suggested that the size of the substituent on the aryl group plays an important role in the inhibition of platelet aggregation in this series of compounds. Based on the correlating equations obtained, it was further suggested that the inhibition of platelet aggregation most likely involved hydrophobic interaction. A moderate correlation existed between the hypotensive activity of these drugs in rats and Vw, indicating that hypotensive activity also was partly affected by the size of the substituent on the aryl group. Although it was assumed that hydrophobic interactions also played some role in the hypotensive action, it was argued, based on the results, that platelet aggregation inhibition and hypotensive activity involved two different receptor sites.

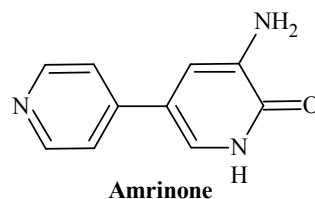


$R_1 = R_2 = R_4 = \text{Me}$ or H ; $R_3 =$ amine containing groups

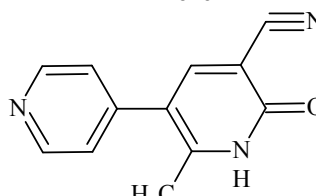
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A series of 4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones and related compounds were synthesized and evaluated for positive inotropic activity by Sircar *et al* [32]. Most members of this series produced dose-related increases in myocardial contractility that were

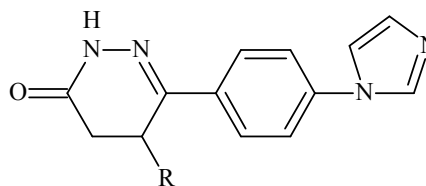
associated with relative minor increase in heart rate and decrease in systemic arterial blood pressure. Among the synthesized compounds (5), the one with $R = \text{H}$ (CI-914) and $R = \text{Methyl}$ (CI-930) were more potent than amrinone and milrinone, respectively. It was also postulated that the positive inotropic effect of these compounds was due to the inhibition of cardiac phosphodiesterase fraction III, rather than the stimulation of β -adrenergic receptors.



Amrinone



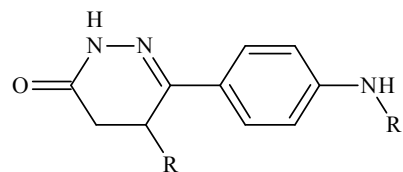
Milrinone



R = H (CI-914); Methyl (CI-930)

5

Okushima *et al* [33] reported pyridazinone derivatives with cardiac activity. These pyridazinones, with $R = \text{H}$ and Me ; $R_1 = 4\text{-pyridyl}$, 2-pyridyl , 2-pyrimidyl and 4-quinolyl , were evaluated for inotropic activities *in vitro* and for cardio-hemodynamic effects *in vivo*. The hydrochloride salts of compound (6) with $R = \text{H}$ (MCI-154) or Me and $R_1 = 4\text{-pyridyl}$ showed extremely potent positive inotropic and vasodilating activities, and good ED_{50} relative to amrinone.

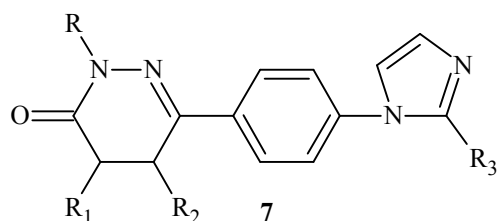


R = H (MCI-154) or Me; $R_1 = 4\text{-pyridyl}$

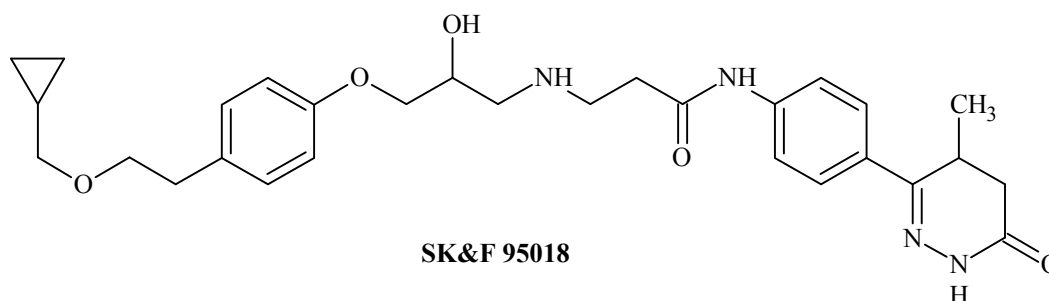
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Sircar *et al* investigated the structure-activity relationships of a series of 4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones (7) with $R = \text{H}$, Me , CH_2Ph , $\text{CH}_2\text{CH}_2\text{OH}$,

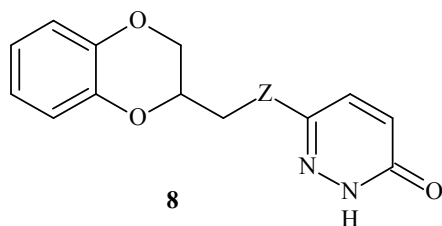
$\text{CH}_2\text{CH}_2\text{OAc}$; $\text{R}_1 = \text{H, Me, NH}_2, \text{CONH}_2$; and $\text{R}_2 = \text{H, Me, Et}$; $\text{R}_3 = \text{H, Me, SH, SMe, SOMe, Et}$, for their *in vivo* inhibition of different forms of cyclic nucleotide phosphodiesterase (PDE) isolated from guinea pig ventricular muscle [34]. With few exceptions, these 4,5-dihydropyridazinones were potent inhibitors of cardiac type III phosphodiesterase. The most selective PDE III inhibitor was CI-930 ($\text{R} = \text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{Me}$) with an ED_{50} of 0.6 μM .



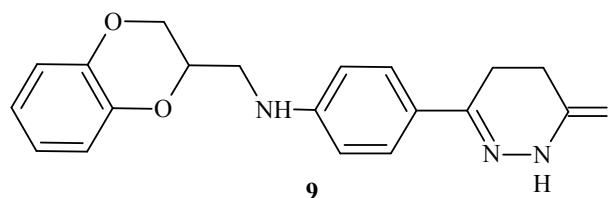
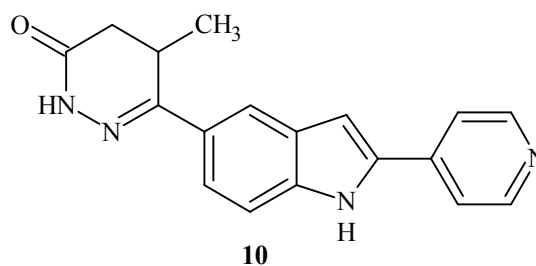
Slater *et al* [35] reported the design and synthesis of a series of combined vasodilator- β -adrenoceptor antagonists based on 6-arylpyridazinones, and evaluated them as vasodilator- β -adrenoceptor antagonists and potential antihypertensive agents. Many of the synthesized compounds showed high level of intrinsic sympathomimetic activities (ISA) and relatively short durations of action. Di-substitution in the 2,3-positions or in the 4-position of the aryloxy ring produced compounds with low ISA levels and, in some cases, improved duration of action. The 5-methylpyridazinone derivatives displayed more antihypertensive activity than their 5-H homologs. The compound, SK&F 95018, was selected for further development.



Benzodioxane pyridazinones (8) and benzodioxane dihydropyridazinone (9) have been reported as antihypertensive agents by Stefano *et al* [36]. Derivatives with $\text{Z} = 1,4$ -disubstituted piperazine showed good hypotensive activities, which were related to anti-adrenergic effects.



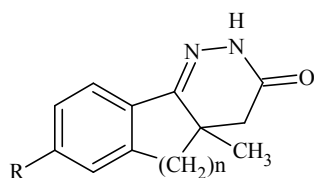
It has been suggested that, for optimal cardiotoxic activity within this class of indole derivatives, a heterocyclic aromatic ring in position 2, a hydrogen or a Me group in position 3 and a dihydropyridazinone ring system in position 5 of the indole are necessary.



Alfred *et al* [37] have reported 4,5-dihydro-6-(1H-indol-5-yl)-pyridazin-3(2H)-ones and related compounds with positive inotropic activities. Most of these compounds produced increases in myocardial contractility with little effects on heart rate and blood pressure. The cardiotoxic effect of compound (10) was at least 2-fold higher than that of pimobendan following oral administration.

7-substituted-4,4a-dihydro-4a-methyl-5H-indeno[1,2-c]pyridazin-3[2H]-ones and 8-substituted-4a-methylbenzo[h]cinnolin-3[2H]-ones have been synthesized and their PDE III inhibitory, inotropic and vasodilator potencies compared with those of their normethyl and their bicyclic 4,5-dihydro-6-phenylpyridazinone analogues by Bakewell *et al* [38]. The study revealed that the structure-activity relationships of the tricyclic pyridazinones differ from those of bicyclic pyridazinones mainly in respect of the effect produced by introducing a methyl group in the pyridazinone ring. Introduction of a 5-methyl group has been widely reported to lead to compounds of significantly greater potencies in

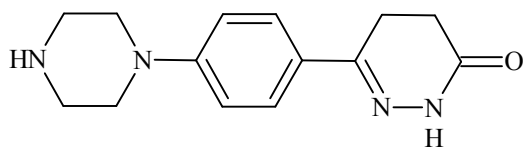
the 4,5-dihydro-6-phenylpyridazin-3(2H)-ones. On the other hand, the tricyclic 4a-methylpyridazinones showed similar levels of inotropic, vasodilator and PDE III inhibitory potencies to their normethyl analogues. In this series of compounds, the tricyclic 4a-methylpyridazinones (11) with R = cyano, CONH₂, NH₂, NHAc, or OMe, and n = 1,2, ..., showed good inotropic, vasodilator and PDE III inhibitory potencies.



R = cyano, CONH₂, NH₂, NHAc, OMe, n = 1,2,

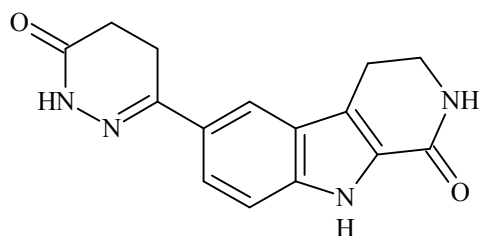
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Jiang and Sun [39] synthesized 6-(4-substituted phenyl)-4,5-dihydro-3(2H)-pyridazinones and demonstrated that compound (12) was a good inhibitor of platelet aggregation in rats. Preliminary pharmacological tests of the other compounds revealed that they inhibited ADP-induced platelet aggregation.



12

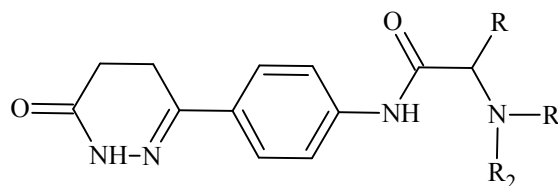
Lee *et al* [40] have reported potential antihypertensive properties of 8-methyl derivatives of 6-(1,4,5,6-tetrahydro-6-oxopyridazin-3-yl)-1,2,3,4-tetrahydro-1-oxo-β-carboline. *In vitro* studies revealed that compound (13) exhibited particularly potent and long lasting hypotensive activity. Molecular modeling also revealed that this compound (13) met all the stipulations of 5-point model required for inhibition of cAMP phosphodiesterase activity.



13

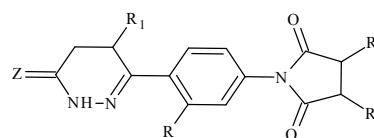
A series of 6-[4-(amino)phenyl]-4,5-dihydropyridazin-3(2H)-ones (14) derivatives with R = H, Me; R₁ = R₂ = alkyl; R₁R₂ = piperazinyl, piperidinyl, and related compounds have been evaluated as inhibitors of cardiac cAMP

phosphodiesterase (cAMP PDE) by Abou-Zeid *et al* [41]. However, none of the tested compounds exhibited considerable inhibitory activity on cAMP PDE.



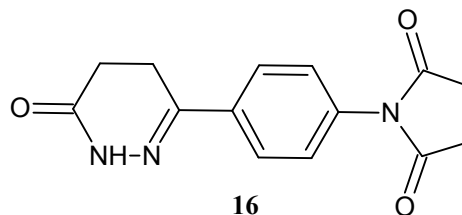
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Abou-Zeid *et al* [42] have also reported synthesis of positive inotropic 6-substituted 4,5-dihydropyridazin-3(2H)-ones, for example compound (15) with Z = O, S; R = H, OH, Me; R₁ = H, Me; R₂ = R₃ = H, and alkyl; and a ring between R₂ and R₃. An example of these compounds is compound (16).



Z = O, S; R = H, OH, Me; R₁ = H, Me; R₂, R₃ = H, alkyl; R₂R₃ form a ring

15



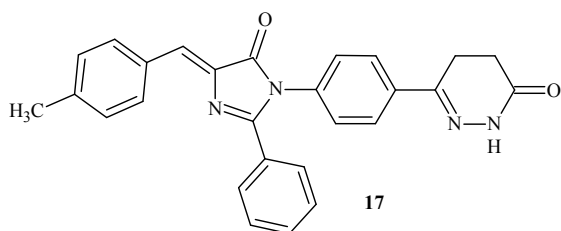
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The synthesis and platelet aggregation-inhibitory activities of 6-(4-substituted acylamido)phenyl-4,5-dihydro-3(2H)-pyridazinones and 6-(4-substituted acylaminophenyl)-4,5-dihydro-3(2H)-pyridazinones have been described by Liu *et al* [43,44]. Preliminary pharmacological tests revealed that all the synthesized compounds inhibited appreciable ADP-induced platelet aggregation activities in rabbits. Liu *et al* [45] have further reported synthesis of 6-(4-substituted acylaminophenyl)-4,5-dihydro-3(2H)-pyridazinones and their inhibitory actions on platelet aggregation. These compounds were synthesized based on structure-activity relationships of anti-platelet aggregation of dihydropyridazinones. The synthesized compounds showed different levels of inhibitory activities on ADP induced-platelet aggregation. Synthesis of 6-(4-(substituted amino) phenyl)-4,5-dihydropyridazin-3(2H)-ones as potential positive inotropic agents has been described by Abou-Zeid *et al* [46]. Some of the synthesized compounds exhibited good positive inotropic effects.

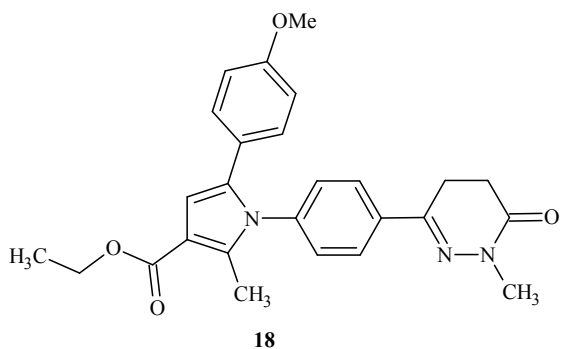
The synthesis and anti-platelet aggregation activities of 6-(4-substituted acylaminophenyl)-4,5-dihydro-3(2*H*)-pyridazinones have been reported by Liu *et al* [47]. These compounds appreciably inhibited ADP-induced platelet aggregation, with some having more potencies than the standard compound, CI-930. Zhao *et al* [48] have reported synthesis of analogues of pyridazinones and their inhibition of platelet aggregation, with evidence of their ADP-induced platelet-inhibitory activities.

Zhao and Liu [49] have reported synthesis of 6-substituted acylpiperazinyl phenyl dihydro pyridazinones and their inhibition of platelet aggregation. Preliminary *in vitro* tests showed that all the compounds were effective against platelet aggregation induced by ADP.

Synthesis and vasodilator activities of some [(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl) phenyl]-4,5-dihydro-3(2*H*)-pyridazinones and 4-[(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-1(2*H*)-phthalazinones have been reported by Demirayak *et al* [50]. The most significant decrease in blood pressure *in vivo* occurred with compound (17).



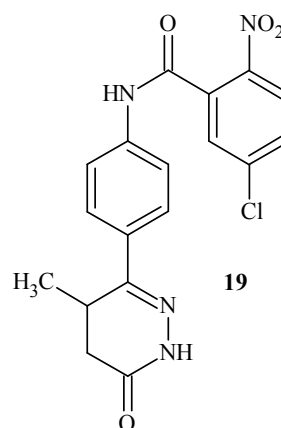
Demirayak *et al* [51] have also reported some pyrrole-substituted aryl pyridazinones, for example compound (18), and demonstrated that some of them had antihypertensive activities.



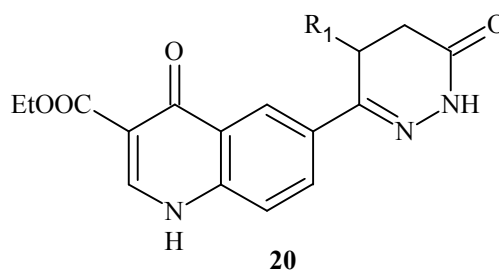
6-(4-substituted phenyl)-4,5-dihydro-3(2*H*)-pyridazinones have been synthesized prepared as anti-thrombotic agents by Ren *et al* [52]. Preliminary *in vitro* tests revealed that all the synthesized compounds were active against platelet aggregation induced by ADP.

Synthesis and cardiovascular activities of 6-(4-

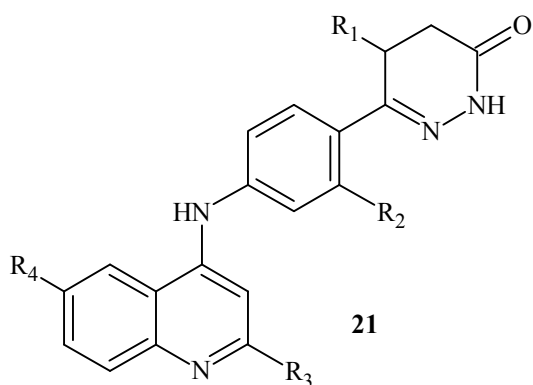
aminophenyl)-2,3,4,5-tetrahydropyridazine-3-one derivatives have been studied by Dong *et al* [53]. Although these compounds possessed strong inotropic activities, they had little effect on the right atria of the rat *in vitro*. Wang *et al*. [54] synthesized series of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones and studied their cardiotoxic activities on isolated perfused toad heart, relative to levosimendan. From the series, compound (19) exhibited very potent cardiotoxic activity.



Three series of pyridazinones were designed as vasorelaxant agents using three dimensional pharmacophore developed with catalyst software by Khaled *et al* [55]. Several compounds with higher fit scores to the developed pharmacophore were synthesized, for example, 6-(3-ethoxycarbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-5-substituted-4,5-dihydro-3(2*H*)-pyridazinones (20) and 6-[4-(2,6-disubstituted quinolin-4-ylamino)-2-substituted phenyl]-5-substituted-4,5-dihydropyridazin-3(2*H*)-ones (21). The vasodilator activities of the newly synthesized compounds were examined on isolated main pulmonary rabbit arteries. Some of the tested compounds showed moderate vasorelaxant activities relative to the standard drug, Milrinone.



The anti-platelet aggregation activities of 6-(4-substituted acetamido phenyl)-4,5-dihydro-3(2*H*)-pyridazinones derived from different piperazine groups have been studied by Xu *et al* [56]. All the synthesized compounds had potent anti-platelet aggregation activities. It was also found that anti-aggregation activity was influenced by the carbon chain length of the 4-substituted piperazine



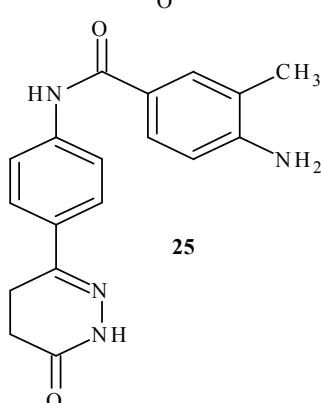
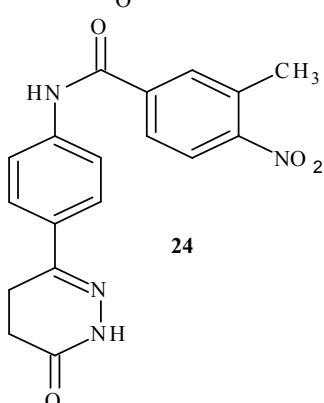
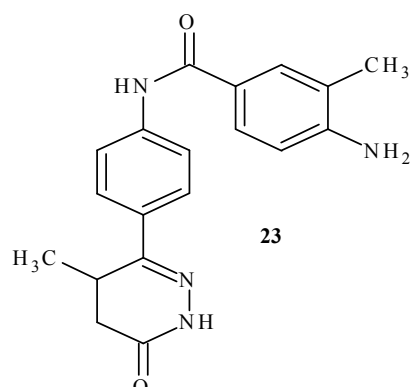
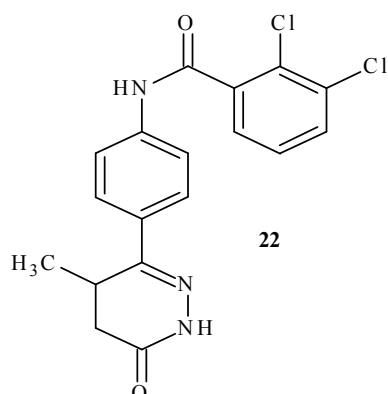
group. Sun *et al* [57] synthesized and demonstrated anti-platelet aggregative activities of 6-(4-substituted acetamidophenyl)-4,5-dihydro-3(2H)-pyridazinones bearing different heterocyclic groups. However stereospecific blockage and hydrophilicity of different heterocyclic groups had impacts on the anti-platelet aggregative activities of these compounds.

Wang *et al* [21] has designed, synthesized and studied the structure-activity relationships of 6-phenyl-4,5-dihydro-3(2H)-pyridazinone derivatives with respect to their cardiotoxic properties. Among these compounds, 2,3-dichloro-N-(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide (22), 4-amino-3-methyl-N-

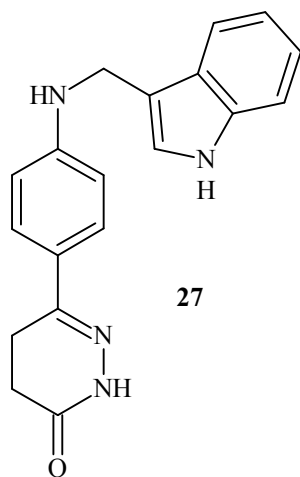
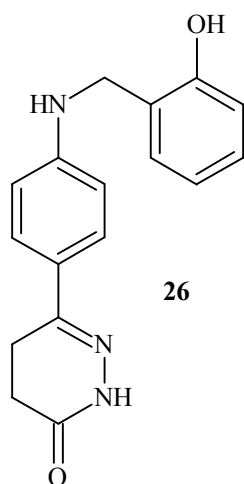
(4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide (23), 3-methyl-4-nitro-N-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl) benzamide (24) and 4-amino-3-methyl-N-(4-(6-oxo-1,4,5,6-tetrahydropyridazin-3-yl) phenyl) benzamide (25) exhibited cardiotoxic activities which were comparable to that of levosimendan.

Cai *et al* [58] reported anti-platelet aggregation activities of N-[4-(1, 4, 5, 6-tetrahydro-6-oxo-3-pyridazinyl) phenyl] acetamides. The *in vitro* activities of several of the derivatives were higher than that of MCI-154 [4,5-dihydro-6-[4-(4-pyridinylamino) phenyl]-3(2H)-pyridazinone hydrochloride]. It was also found that stereospecific blocking and hydrophilicity of different secondary amino groups in the target compounds affected their anti-platelet aggregation activities.

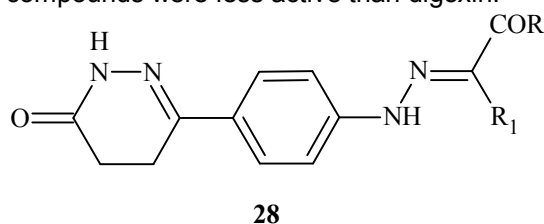
Chai *et al* [59] have reported synthesis and potent anti-platelet aggregation activities of 6-[4-(substituted aminoacetamidophenyl)]-4,5-dihydro-3(2H)-pyridazinones. It was also observed that the anti-platelet aggregation activities of the compounds were enhanced by introduction of different substituted amino groups enhanced. Thota *et al* [60] synthesized and reported significant anti-platelet aggregation



activities of a series of 6-(4-(substituted amino)phenyl)-4,5-dihydro-3(2H)-pyridazinones. The compounds (26) and (27) displayed two times more platelet aggregation-inhibitory effects than the standard drug aspirin.



Amin *et al* [61] successfully synthesized new 4,5-3(2H)-pyridazinone derivatives with the general formula (28), where R = alkyl, alkylamine, alkanoylamine or alkoxy group; R₁ = alkyl, acetyl, COOEt, CN; and RR₁ = five membered heterocycle. The cardiotoxic, hypotensive, and platelet-aggregation inhibition activities were also investigated. Results from *in vitro* studies of their positive inotropic effects on isolated rabbit heart revealed that twelve of the compounds exhibited higher effective responses than digoxin, while nine compounds were comparable to digoxin in their responses. However eight of the compounds were less active than digoxin.



CONCLUSION

Cardiovascular disease has become the leading cause of death worldwide and remains the foremost cause of preventable death globally. The need for more research in the field of cardiovascular disease in developing countries is underscored by the prevalence of cardiovascular disease in all age group of patients in these countries. 6-(4-Aminophenyl)-4,5-dihydro-3(2H)-pyridazinone is an important chemical moiety that is useful for the development of cardio-active agents. The potential of its derivatives as cardioactive agents is evident from the literature as reviewed in this article. It is our belief that the exploitation of 6-(4-aminophenyl)-4,5-dihydro-3(2H)-pyridazinone derivatives can produce more potent cardio-active agents for clinical use in the treatment of cardiovascular disease.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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