A Review on Pyridazinone Ring Containing Various Cardioactive Agents

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Abstract: In this work, some pyridazinones were studied for their cardioactive activity. These compounds showed significant cardio-active action with respect to the regular used drugs. However, it was found that the existence of the pyridazine ring is a crucial necessity in the structure of these pyridazinone compounds to show the improved cardioactive activities. It was also understood that the substitution of the different group on the pyridazinone ring with other related bioisosteres or isosteres along with the existence of pyridazine ring may provide better cardioactive compounds. Pyridazinone is, a component of various cardio-active agents, which are in uses clinically or in clinical trials. These contain pimobendan, indolidan, levosimendan, imazodan, CI-930, meribendan, bemoradan, senazodan, siguazodan, amipizone, prinoxodan, Y-590, SK&F-93741, SKF 95654, NSP-805, NSP-804 and KF 15232. This study briefly reviews the pyridazinone ring for the progress of new cardio-active drugs.

Key words: Pyridazinone; Cardio-active drugs; Biological activities.

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1. introduction

The pyridazinone derivatives have been tested for their chemical and biological actions and achieved extra magnitude in current years. The pyridazinones are known as “wonder nucleus” as it gives out diverse derivatives with all types of pharmacological activities. The 3(2H)-pyridazinones are vital scaffolds in drug discovery and development. Various pyridazinone analogs are being used in the treatment of various human pathological conditions. They were explained as anti-inflammatory drugs including, Emorfazone and related compounds, for therapeutic intervention of renal-urologic (FK838), cardiovascular (EMD57283), respiratory (NIP502), dermatologic diseases (FR-181877) [1-5]. Pyridazines and pyridazinones demonstrate a wide spectrum of biological activities in the literature as potent inodilators [6], vasorelaxants, antihypertensive and potent cardiotonic agents [7-8]. They also showed anticonvulsant [9-11], vasodilatory

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[12], and antihypertensive [13] activities. They possess antimicrobial [14], anti-inflammatory [15, 16], anti-feedant [17], herbicidal [18], and anti-nociceptiv [19] activities, as well. Some pyridazinones are well known as potent analgesics, antiplatelet [20, 21] and anticoagulant agents [22] antidepressant, antithrombotic, diuretic, anti-HIV makes curious interest towards the construction of new pyridazinone compounds as well as other anticipated biological and pharmacological properties [23-25]. Cardiovascular disease (CVDs) is the main health problem worldwide and is responsible for about 30 % of total deaths [26]. There is a necessity for extra investigation in the field of cardiovascular disease (CVDs) do the prevalence of CVDs in all age groups [27, 28]. There are many cardio-active drugs containing pyridazinone moiety in their crucial structural. These drugs are either in use clinically or under the clinical trials. They contain imazodan [27, 28], Cl-930 [29]; indolidan; pimobendan, levosimendan [30-32], SK&F-93741, Y-590, meribendan [33-35], NSP- 805; NSP-804 [35, 36, 37], bemoradan [38], amipizone [39], senazodan [40], prinoxodan [41], SKF 95654 [42], siguazodan and KF 15232 [43]. The review focused on the pyridazinone compounds for the development of the cardio-active agents and discussed the approach on the prospective of pyridazinone moiety for the development of cardio-active drugs.

2. Pyridazinone Derivatives as Cardioactive Agents

Although pyridazinone analogs have been possessing wide varieties of biological activities, most of the research studies in this field focused on their cardiovascular activities. Various pyridazinone derivatives have reached a clinical trial as cardiotonic and antihypertensive drugs. To discover a non-glycoside, noncatecholamine digitalis substitute resulting in developing various new cardiotonic drugs. The 6-(4-aminophenyl)-4,5-dihydro-pyridazinone (1) has anti-inflammatory and antihypertensive activities was first reported by Gerhard and August in 1967 [44, 45]. Various 6-phenyl-4,5-dihydro-3(2H)-pyridazinone compounds (2) have the potent antihypertensive activity in normotensive rats, these compounds were analogs with acetamido and cyano groups in the meta or para-position of the aryl ring, united with a 5-methyl substituent in the hetero ring [46]. The 6-Aryl-4,5-dihydro-3(2H)-pyridazinones were showed anti-platelets action as well as antihypertensive actions. The highest actions initiated with dihydro-pyridazinone analogs that contain R= chloro-alkanoyl substituent, together with a methyl group in position 5 (3). The hypotensive effects of these compounds were found 40 times more potent than dihydralazine [47]. The para-substituted derivatives have a powerful inhibiting action on collagen-induced and ADP induced anti-platelet activities. Platelet aggregation act a vital role in the pathogenesis of CVDs [48]. The platelet aggregation-inhibiting activities of 6-aryl-4,5-dihydro-pyridazinones (4) with R1= R2= R3=Me or H; and R3= amine containing groups [49]. The magnitude of the substituent on the aryl ring act a vital role in the anti-platelet aggregation effects. Various 4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones and were tested for positive inotropic action. Most of the compounds were created an increase myocardial contractility in a dose-dependent manner and that was linked with relative minor raise in heart rate and reduce in systemic arterial blood pressure (B.P.). Compounds (5), with R=H (CI-914) and R=Methyl (CI-930) were more effective than amrinone and milrinone. The positive inotropic action of these compounds was due to the cardiac phosphodiesterase (PDE) III inhibition, rather than the stimulation of β-adrenergic receptors [50].

Pyridazinone derivatives with cardiac effects, pyridazinones, with R=H and CH3; R1=4-pyridyl, 2-pyridyl, 2-pyrimidyl and 4-quinoxy, were tested for inotropic actions and for cardio-hemodynamic effects. The hydrochloride salts of compound (6) with R=H (MCI-154) or CH3 and R1=4-pyridyl was showed highly potent positive inotropic and vasodilator actions [51]. The 4,5-dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3-(2H)-pyridazinones (7) with R=H, CH3, CH2CH3, CH2CH2OH, CH2CH2OAc; R1=H, CH3, NH2, CONH2 and R2=H, CH3, C2H5, R3=H, CH3, SH, SCH3, SO CH3, C3H5, for their inhibition of different forms of cyclic nucleotide PDE in ventricular muscle. With few exceptions, these dihydropyridazines were effective inhibitors of PDE-III. The most selective PDE-III inhibitor was CI-930 (R= R1=R2= H, R3=CH3) with an ESD0 of 0.6 μM [52]. Combined vasodilator β-adrenoceptor blockers based on 6-arylpypyridazines were tested as vasodilator β-adrenoceptor blockers and antihypertensive agents. Some compounds demonstrated a high level of intrinsic sympathomimetic effects and short duration of action. Di-substitution in the 2,3-positions or in the 4-position of the arylxy ring formed-compounds with low intrinsic sympathomimetic levels, in some cases, enhanced duration of action. The 5-methylpyridazinones were exhibited more antihypertensive activity than their 5-H homologs. The compound, SK&F 95018 was selected for further development [53].
Benzodioxanepyridazinones (8) and benzodioxanedihydropyridazinone (9) were exhibited vasodialator action and their derivatives with Z=1,4-disubstituted piperazine were showed good hypotensive activities, which were related to anti-adrenergic actions [54]. The 4,5-dihydro-6-(1H-indol-5-yl)-pyridazin-3(2H)-ones and other similar compounds with positive inotropic actions. Most of the compounds increase the myocardial contractility with low effects on heart rate and BP. The cardiotonic effect of compound (10) was at least 2-fold more than that of pimobendan. For optimal cardiotonic action of indole derivatives, a heterocyclic aromatic ring in 2 positions, a H or a CH$_3$ group in 3 position and a pyridazinone ring in 5 position of the indole is crucial [55]. The 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 PDE-III inhibitory, inotropic and vasodilator effects compared with their normethyl and their bicyclic dihydro-6-phenyl-pyridazinonedervatives. The tricyclic pyridazinones differ from those of bicyclic
pyridazinones in respect of the effect produced by introducing a CH3 group in the pyridazinone ring. The inclusion of a 5-methyl group to lead to compounds have significantly higher activities in the 6-phenylpyridazin-3(2H)-ones.

The tricyclic 4-methylpyridazinones were showed similar inotropic, vasodilator and PDE-III inhibitory effects to their normethyl analogs. The tricyclic 4-methyl-pyridazinones (11) with R=CN, CONH2, NH2, NHaC, or OCH3 and n=1, 2, 3,..., were showed highinotropic, vasodilator and PDE-III inhibitory effects [56]. The 6-(4-substituted phenyl)-3(2H)-pyridazinones (12) werea goodinhibitor of antplatelet effects in rats. Other compounds also showed that they inhibited ADP-induced platelet aggregation [57].

The potential antihypertensive actions of 8-methyl analogues of 6-(1, 4, 5, 6-tetrahydro-6-oxy-pyridazin-3-yl)-1, 2, 3, 4-tetrahydro-1-oxo-β-carboline. Compound (13) was exhibited powerful and long-acting antihypertensive activity. This compound met all the conditions of 5-point representation required for cAMP PDE inhibition activity [58]. The 6-[4-(amino)phenyl]-pyridazin-3(2H)-ones (14) with R=H, CH3; R1=R2=alkyl; R1,R2=piperazinyl, piperidinyl and related compounds were tested as inhibitors of cardiac cAMP PDE [59]. The positive inotropic 6-substituted-pyridazin-3(2H)-ones, compound (15) with Z= O, S; R=H, OH, Me; R1=H, CH3; R2,R3=H and alky; and a ring between R2 and R3. An example of these analogues is compound (16) [60].

The antplatelet activities of 6-(4-substituted acylaminophenyl)-3(2H)-pyridazinones and 6-(4-substituted acylaminophenyl)-3(2H)-pyrazononeswere inhibited appreciable ADP-induced antplatelet activities in rabbits [61, 62]. The 6-(4-substituted acylaminophenyl)-3(2H)-pyrazinonesshowed antplatelet activities. These compounds were showed different levels of inhibitory action on ADP induced-platelet aggregation [63]. The 6-(4-(substituted amino) phenyl)-pyridazin-3(2H)-ones as potential positive inotropic drugs, some of the compounds were exhibited good positive inotropic effects [64]. The anti-platelet activities of 6-(4-substituted acylaminophenyl)-3(2H)-pyrazinones, appreciably inhibited ADP-induced platelet aggregation, with some having more activities than CI-930 [65]. Pyridazinone derivatives were exhibited antplatelet effects, with evidence of their ADP-induced antplatelet activities [66]. The 6-substituted acylpiperazinephenyl pyrazidinones exhibited antplatelet action. All these compounds were effective against the platelet aggregation induced by ADP [67]. Vasodilator activities of some [(4-arylidene-2-phenyl-5-oxoimidazolin-1-yl)phenyl]-4,5-dihydro-3(2H)-pyrazidinones (17) [68]. Some pyrrole-substituted aryl pyridazinones, compound (18) exhibited inantihypertensive activities [69].
The 6-(4-substituted phenyl)-4, 5-dihydro-3(2H)-pyridazinones were exhibited anti-thrombotic activity. All these compounds were active as antiplatelet action induced by ADP [70]. The cardiovascular effects of 6-(4-aminophenyl)-2, 3, 4, 5-tetrahydropyridazine-3-one derivatives were possessed powerful inotropic action, they had smallaction on the right atria of the rat [71]. A series of 6-phenyl-4, 5-dihydro-3(2H)-pyridazinones were exhibited cardiotonic actions on isolated perfused toad heart, and compare to levosimendan. Compound (19) was exhibited very powerful cardiotonic action [72]. Some pyridazinones exhibited vasorelaxant agents, several compounds, 6-(3-ethoxy carbonyl-4-oxo-1,4-dihydroquinolin-6-yl)-5-substituted-4, 5-dihydro-3(2H)-pyridazinones (20) and 6-[4-(2, 6-disubstituted quinolin-4-ylamino)-2-substituted phenyl]-5-substituted-4, 5-dihydropyridazin-3(2H)-ones (21) were exhibited significant vasorelaxant activity [73] relative to the reference drug, Milrinone. The anti-platelet actions of 6-(4-substituted acetamidophenyl)-3(2H)-Pyridazinones were exhibited potent anti-platelet activities. Antiplateletactivity was influenced by the carbon chain length of the 4-substituted piperazine group [74].

The anti-platelet activities of 6-(4-substituted acetamidophenyl)-3(2H)-pyridazinones were bearing different heterocyclic groups. However stereospecific blockage and hydrophilicity of different heterocyclic groups were impacts on the antiplatelet activities of these compounds [75]. The 6-phenyl-3(2H)-pyridazinone derivatives with respect to their cardiotonic properties, compounds, 2, 3-dichloro-N-(4-(methyl-6-oxo-tetrahydro-pyridazin-3-yl)phenyl) benzamide (22), 4-amino-3-methyl-N-(4-(4-methyl-6-oxo-tetrahydro-pyridazin-3-yl)phenyl) benzamide (23), 3-methyl-4-nitro-N-(4-(6-oxtetrahydro-pyridazin-3-yl)phenyl) benzamide (24) and 4-aminomin-3-methyl-N-(4-(6-oxo--tetrahydro-pyridazin-3-yl)phenyl) benzamide (25) were exhibited cardiotonic effects which were comparable to that of levosimendan. Anti-platelet action activities of N-[4-(tetrahydro-6-oxo-3-pyridazinyl)phenyl]acetamides. The in vitro activities of some of the derivatives were higher than that of MCI-154 (dihydro-6-[4-(4-pyridinylamino) phenyl]-3(2H)-pyridazinone, HCl). The stereospecific blocking and hydrophilicity of secondary amino groups in the target compounds affected and their anti-platelet activities. The anti-platelet activities of 6-[4-(substituted amino acetamidophenyl)]-3(2H)-pyridazinones. The anti-platelet activities of the compounds were enhanced by the introduction of different substituted amino groups improved [76]. The anti-platelet activities of a series of 6-(4-(substituted amino) phenyl)-3(2H)-pyridazinones, compounds (26) and (27) were displayed two times more antiplatelet effects than aspirin [77]. A 3(2H)-pyridazinone derivatives with the formula (28), where R=alkyl, alkylamine, alkanoylamino or an alkoxy group; R1=alkyl, acetyl, COOC2H5, CN; and R2=five membered heterocycle. The cardiotonic, anti hypertensive, and antiplatelet actions were also tested. The positive inotropic actions were exhibited that twelve of the compounds were exhibited higher effective responses than digoxin while eight of the compounds were less active than digoxin [78, 79].

Scheme 6. Some pyridazinone derivatives with cardiotonic activity.

The 6-(substituted phenyl)-2-(4-(substituted phenyl)-5-thioxo-4, 5-dihydro-1H1,2,4-triazol-3-yl)-dihydropyridazinones, compounds 6-(4-methylphenyl)-2-(4-(4-chlorophenyl)-5-thioxo-4, 5-dihydro-1H1,2,4-triazol-3-yl)-dihydropyridazinone (29), 6-(4-methoxyphenyl)-2[4-(4-methyl phenyl)-5-thioxo-dihydro-1H1,2,4-triazol-3-yl]-dihydropyridazinone (30) and 6-(4-ethylphenyl)-2-[4-(4-chlorophenyl)-5-thioxo-dihydro1H-1,2,4-triazol-3-yl]-dihydropyridazinone (31) were showed significant anti hypertensive activity.
The triazole included 4, 5-dihydro-pyridazinones can be further modified to exhibit improved activity than the references drugs. The 4, 5-dihydro-pyridazinones (32) may provide valuable anti-hypertension activity [80]. The 2-substituted-6-(4acylaminoaryl)-4, 5-dihydropyridazinones acts as potent inodilating compounds. The 6-(4- Methane sulfonamidophenyl )-2-phenyl-dihydropyridazinones (33) exhibited superior inodilatory properties and showed vasorelaxant activity in a nanomolar range (IC50= 0.08±0.01 mmol/L) [81].

![Scheme 8. Some pyridazinone derivatives with cardio active activity.](image)

The 6-substituted and 2, 6-disubstituted pyridazinones (34) were showed antiplatelet activity similar to aspirin. The pyridazinone analogs have been exhibited vasodialator and antiplatelet agents [82] and have identified as potential vasodilatory and cardiotonic agents. The 6-(3ethoxy carbonyl -4-oxo-1, 4-dihydropyrimidin-6-yl)-pyridazinones (35), 6-[4-(2, 6disubstituted -quinolin-4-ylmethyl)-phenyl]-dihydropyridazinones (36), and 6-[3-(5-cyano-6-oxo-4-aryl-1,6-dihydro-2-pyridyl)phenylamino] pyridazinone (37) were showed goodvasorelaxant activity as compared with Milrinine [83].

The 6-(4-(substituted-amino)phenyl)-dihydropyridazinones were exhibited significant antiplatelet activity, compounds 6-(4-(2-hydroxybenzylamino)phenyl)-dihydropyridazinone (38) and 6-(4-(1H-indol-3-ylmethylamino)phenyl)-dihydropyridazinone (39) were more than two times potent as aspirin. The 4-substituted-amino phenylpyridazinones and arylamino substituent at the para position of 6-phenylpyridazinone were also possessed antiplatelet activity [84].

The 6-phenyl-pyridazinones with different substituents at the 5 positions has antiplatelet activities. The

![Scheme 9. Some pyridazinone derivatives with cardio active activity.](image)

alteration of the substituent groups at position 5 of the 6-phenylpyridazinonesaffect variations in the antiplatelet activity. The compound (40) was showed the highest antiplatelet activity with IC50 value in the micromolar range (15 mM) [85]. The 6-[3, 4-dihydro-3-oxo-1,4(2H)-benzoxazin-7-yl]-2, 3, 4, 5-tetrahydro-5-methylpyridazone (41) was a potent and selective inhibitor of PDE fraction III and act as orally active potent inotropic and vasodilator agent [85].

![Scheme 10. Some pyridazinone derivatives with cardio active activity.](image)

A pyridazinones as cardiotonic agents and have potent ionotropic and myofibrillar Ca2+ sensitizing activity of (±)-6-(4-(benzyl amino)-7-quinazolinyl)-4, 5-dihydro-5-methy1pyridazinone (42) [86]. A series of pyridazinones having a phenoxypropanolamine moiety and developed 5-chloro-2- cyanophenoxy derivative (43) were showing promising dual actions of hypotensive and β-blocking activities [87]. Several 6-aryl-5-oxygenated substituted pyridazinones (44) possessed antplatelet action persuaded by adenosine diphosphate (ADP), thrombin and collagen [88]. Some 6-(aryl substituted)-4-methyl-2, 3-dihydropyridazin-3-ones (45), which showed significant hypotensive activity [89].
3. Discussion

Pharmacological importance of pyridazinones has indulged us to synthesize a novel pyridazinone. Pyridazinone derivatives have gained substantial attention within the field of medicinal chemistry. Pyridazine moiety has been tested extensively for its diverse biological activities including antiinflammatory, analgesic, anticancer, antiviral, antimicrobial, cardiovascular, antitubercular, antiobesity, antidiabetic, neuroprotective, and various other activities [90-96]. Cardiovascular diseases (CVDs) are the leading reason for death worldwide and remain the leading reason for avoidable death worldwide. The necessity for more investigation in the field of CVDs in developing countries is emphasized by the prevalence of CVDs. Pyridazinone is a vital moiety in heterocyclic chemistry that is useful for the progress of newer cardio-active drugs. The exploitation of pyridazine derivatives can create more potent cardio-active drugs for medicinal use in the treatment of CVDs. Some reviews of the biological importance of pyridazinone derivatives have also been published [97-101] wherein pyridazinone compounds are reported to possess very good cardio-active activity.

4. Conclusion

Various pyridazinone derivatives have shown diverse biological activities. Most of the research work on pyridazinone ring derivatives focused on the cardiovascular properties, so a large number of pyridazinone derivatives have reached on various clinical trial phases as cardiotonic and antihypertensive agents and few pyridazinone derivatives in various clinical trial phases. From the plethora of pharmacological activities exhibited, pyridazinone ring derivatives serve as potential targets for further drug development. This research study reported various successful cardioactive agents bearing pyridazine moiety. Some pyridazinone derivatives have significant cardioactive activities. Accordingly, this study may be extended to acquire more information about the activities of this series of compounds.

5. References


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