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MINI REVIEW

Various Biological Activities of Pyridazinone Ring Derivatives

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In the recent years there has been an increasing interest in the chemistry of pyridazinone derivatives because of their biological significance. Pyridazinones have been reported to possess variety of biological activities like antidiabetic, anticancer, anti-AIDS, cardiovascular activity, antiinflammatory activity, anticonvulsant activity and potentially usable cerebroprotective agent. This paper summarizes the previous work on the various biological activities such as cardiovascular properties, antiinflammatory properties, analgesic properties, nociceptive properties, antidepressant properties, anticonvulsant properties, antidiabetic properties, antiasthmatic properties, anti-HIV1 properties, antiproliferative properties, antimicrobial properties, insecticidal properties of the pyridazine ring and pyridazinone derivatives.

Key Words: Pyridazinone, Pyridazine, Pharmacological activity.

INTRODUCTION

Literature survey reveals that various pyridazin-3(2*H*)-ones have attracted considerable attention as they are endowed with a variety of pharmacological activities. These derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activity ranging from cardiovascular properties, antiinflammatory, antidiabetic, antidepressant, analgesic, anti-AIDS, anticancer, antimicrobial and anticonvulsant activities. As a result a number of pyridazinone derivatives have reached clinical trial level as cardiotonic and antihypertensive drug[1]. In present study, a review of different biological activities such as cardiovascular, antiinflammatory, analgesic, antinociceptive, antiasthmatic, antidiabetic, antidepressant, anticonvulsant, anti-HIV-1, antiproli-ferative, antimicrobial and insecticidal activities have been dealt in detail.

Biological activities

Cardiovascular activities: Although pyridazinone derivatives have been found to possess wide varieties of activities, most of the research work is focused on their cardiovascular activities. As a result, a number of pyridazinone derivatives have reached clinical trial as cardiotonic and antihypertensive drugs.

The extensive search to find a non-glycoside, non-catecholamine digitalis replacement led to the discovery of several new cardiotonic drugs[2] including amrinone, milrinone, enoximone, piroximone and imazodan and CI-930 (Fig. 1).

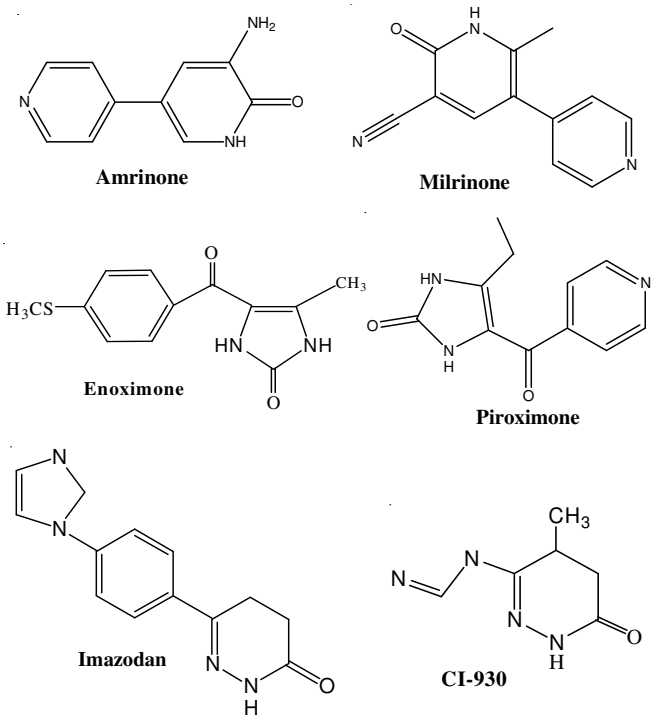


Fig. 1. Structure of new cardiotonic drugs

Sircar *et al.*[2] synthesized a novel series of analogues of (E)-4,5-dihydro-6-[2-[4-(1*H*-imidazol-1-yl)phenyl]ethenyl]-3(2*H*)-pyridazinone (Fig. 2) as a variation on the imazodan series. The insertion of the ethenyl moiety between the phenyl and dihydropyridazinone rings produced novel compounds that retained the potent inotropic/vasodilator activity of the parent imazodan series and enhanced the platelet aggregation inhibitory potency. This compound demonstrated most potent *in vivo* antithrombotic activity. The added feature of platelet antiaggregratory activity is considered to be beneficial for patients with congestive heart failure who are at risk of coronary thrombosis.

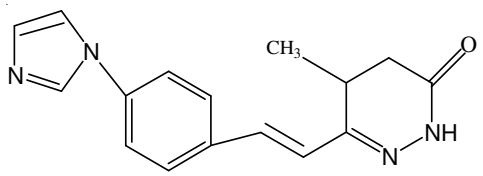


Fig. 2 (*E*)-4,5-Dihydro-6-[2-[4-(1*H*-imidazol-1-yl)phenyl]ethenyl]-5-methyl-3(2H)-pyridazinone

Combs *et al.*[3] developed 6-[3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methyl pyridaze-3-one (Fig. 3) which was an extremely potent and selective inhibitor of PDE fraction III and a long acting, potent, orally active inotropic vasodilator agent.

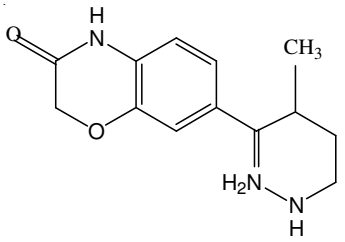
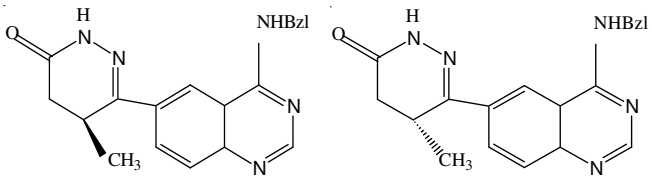


Fig. 3. 6-[3,4-Dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methyl pyridaze-3-one

Nomoto *et al.*[4] investigated novel pyridazinones as cardiotonic agents and reported the potent cardiotonic and myofibrillar Ca^{2+} sensitizing activity of (±)-6-(4-(benzyl amino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone (Fig. 4).



(+)1 (-)1

Fig. 4. (±)-6-(4-(Benzyl amino)-7-quinazolinyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone

Seki *et al.*[5] synthesized a series of pyridazinone derivatives having a phenoxypropanolamine moiety and developed 5-chloro-2-cyanophenoxy derivative (Fig. 5) showing promising dual activities of hypotensive and β-blocking activities.

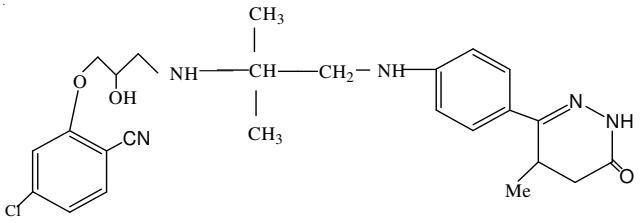


Fig. 5. 5-Chloro-2-cyanophenoxy derivative of pyridazinone

Laguna *et al.*[6] synthesized several 6-aryl-5-oxygenated substituted pyridazinones (Fig. 6), which were found to possess platelet aggregating action induced by adenosine 5-diphosphate (ADP), thrombin and collagen.

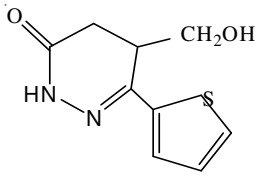
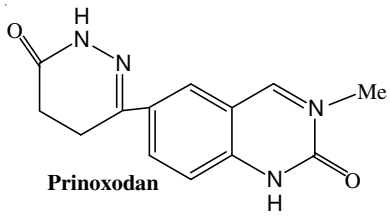


Fig. 6. 6-Aryl-5-oxygenated substituted pyridazinones

More recently, diverse series of piperazines linked at N 1-4,5 or 6 position of 3-(2*H*)-pyridazinone ring and at N-4, by a suitable alkyl spacer were found to posses a1 adrenoceptor antagonist activity[7].

Artigou *et al.*[8] developed prinoxodan (Fig. 7), a cardiotonic agent that is currently under clinical trials.



Prinoxodan

Fig. 7. Prinoxodan

A new group, including levosimenden, pimobendan, sulmazole and EMD 53998 that enhance the isotropic state by modulating the response of contractile elements to Ca^{2+} have recently been developed[9].

Siddiqui *et al.*[10] developed some 6-(aryl substituted)-4-methyl-2,3-dihydropyridazin-3-ones (Fig. 8), which showed significant hypotensive activity.

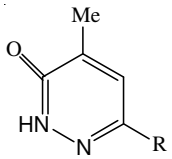
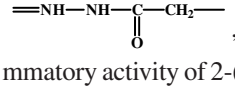
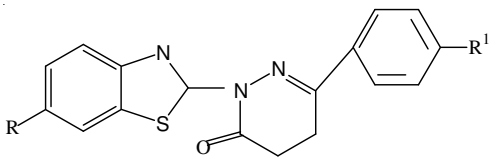


Fig. 8. [6-(Aryl substituted)-4-methyl-2,3-dihydropyridazin-3-ones]

Antiinflammatory activity: In order to explore the anti-inflammatory properties of a six-membered heterocyclic system incorporating the structural moiety such as,  , Sawhney *et al.*[11] the potential antiinflammatory activity of 2-(2-benzothiazolyl)- and 2-(2-benzimidazolyl) -6-aryl-4,5-dihydro-3(2*H*)-pyridazinones (Fig. 9).



R:H,Cl,OCH$_3$ **R^1:H,Cl,OCH$_3$**

Fig. 9. [2-(2-Benzothiazolyl)- and 2-(2-benzimidazolyl)-6-aryl-4,5-dihydro-3(2*H*)-pyridazinones]

Siddiqui *et al.*[10,12] have reported a number of pyridazinone derivatives and their antiinflammatory activity (Fig. 10).

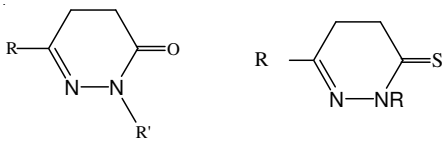


Fig. 10. Pyridazinone derivatives with antiinflammatory activity

Analgesic activity: Gregory and Wiggins[13] indicated that 4-amino-2-phenyl-6-methyl-3-pyridazone (Fig. 11) exhibited marked analgesic activity when compared with phenazone.

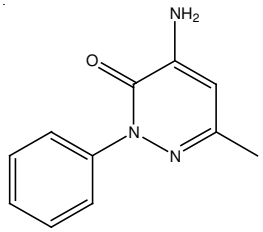
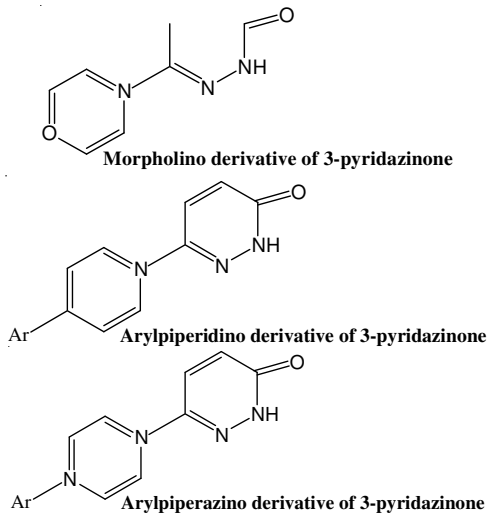


Fig. 11. 4-Amino-2-phenyl-6-methyl-3-pyridazone

It appears therefore that the presence of a basic group in the pyridazone nucleus exerts a powerful and important contribution towards the analgesic activity of this type of compound.

Antinociceptive activity: A series of 3-pyridazinone carrying morpholino, arylpiperidino and arylpiperazino moiety in the position 6 (Fig. 12) were synthesized and evaluated for antinociceptive activity. These compounds were more active than aspirin in the antinociceptive activity test[14].



Morpholino derivative of 3-pyridazinone

Arylpiperidino derivative of 3-pyridazinone

Arylpiperazino derivative of 3-pyridazinone

Fig. 12. Structures of 3-pyridazinone derivatives

Antiasthmatic agents: Hibi *et al.*[15] investigated the effect of a newly synthesized compound N2-107, 4-bromo-5-(3-ethoxy-4-methoxybenzylamino)-3(2*H*)-pyridazinone (Fig. 13) on bronchoconstriction induced by slow reacting substance of anaphylaxis (SRS-A) in the guinea pig. N2-107 is a selective inhibitor of the SRS-A response and may be useful in the therapy of bronchial asthma and other diseases in which the leucotrienes are thought to be involved.

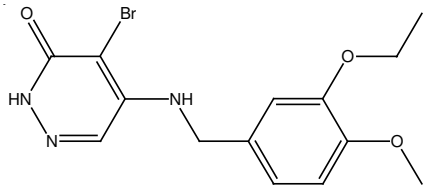


Fig. 13. 4-Bromo-5-(3-ethoxy-4-methoxybenzylamino)-3(2*H*)-pyridazinone

Antidiabetic activity: In year 1995, zopolrestat (Fig. 14) was developed as a potent aldose reductase inhibitor, with IC_{50} of 3.1 nM against human placenta enzyme. It was manufactured by Pfizer[16].

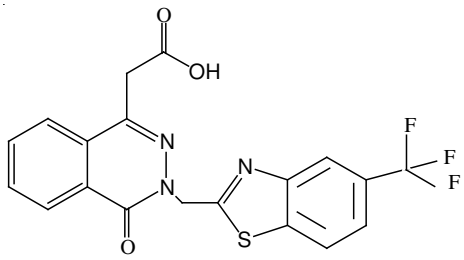


Fig. 14. Zopolrestat

Costantino *et al.*[17], synthesized three new series of tricyclic pyridazinones (Fig. 15), which showed ability to inhibit aldose reductase enzyme (ALR2). The compounds also had inhibitory effects on ALR1, sorbitol dehydrogenase and glutathione reductase.

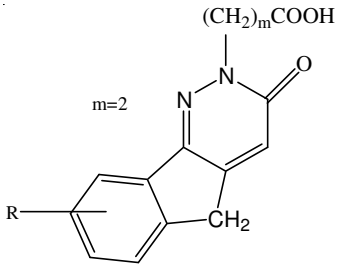
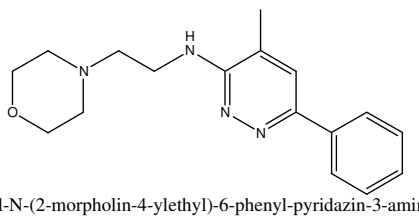


Fig. 15. Tricyclic pyridazinones

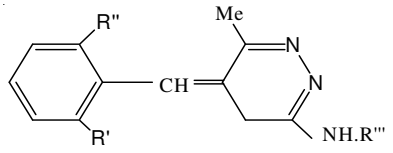
Antidepressant activity: Minaprine (Fig. 16) proved to be effective in the treatment of various depressive disorders. This 3-amino-6-phenylpyridazine derivative is known to represent a new class of psychotropic drugs.



4-methyl-N-(2-morpholin-4-ylethyl)-6-phenyl-pyridazin-3-amine

Fig. 16. Minaprine

Rubat and Coudert[18] synthesized analogues containing a 5-disubstituted benzylidene pyridazine moiety (Fig. 17), which proved to be effective antidepressants.



In the most effective compound;

R'=H,H

R"=Cl,H

R'"=$CH_2CH_2N(CH_3)_2$

Fig. 17. Antidepressant 5-disubstituted benzylidene pyridazine moiety

Anticonvulsant activity: Coudert *et al.*[19] synthesized and reported the anticonvulsant activity of 4,6-diaryl-3-pyridazinones or N-ethoxycarbonyl alkyl pyridazinones (Fig. 18).

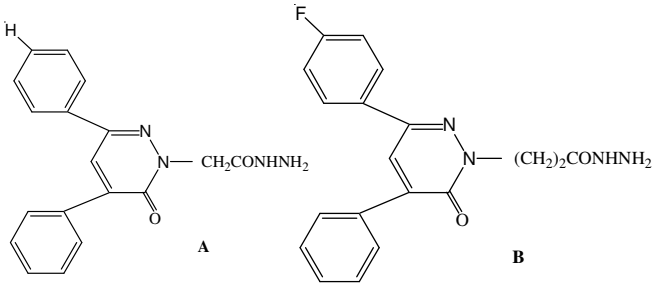
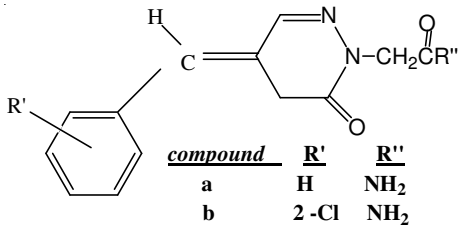


Fig. 18. Structure of 4,6-diaryl-3-pyridazinones or N-ethoxycarbonyl alkyl pyridazinones

Rubat *et al.*[20] synthesized a series of 3-oxo-5-substituted benzylidene-6-methyl-(4*H*)-2-pyridazinylacetamides and 2-pyridazinylacetylhydrazides and showed that most of the derivatives showed an anticonvulsant effect better than that of sodium valproate, a commonly used anticonvulsant agent. The most active compounds in this series are given in Fig. 19.



compound	R'	R''
a	H	NH_2
b	2 -Cl	NH_2
c	4-F	NH_2
d	4-Me	NH_2

Fig. 19. A series of 3-oxo-5-substituted benzylidene-6-methyl-(4*H*)-2-pyridazinylacetamides

Anti-HIV-1 activity: Livermore *et al.*[21] identified the imidazo[1,5-b]pyridazine as an inhibitor of HIV-1 RT (RT1) with a 50 % inhibitory concentration (IC_{50}) of 1.34 μM. Exceptional activity against the reverse transcriptase of HIV-1 (IC_{50} = 0.65 nM) was obtained with a 2-imidazolyl-substituted derivative, 7-[2-(1*H*-imidazol-1-yl)-5-methylimidazo-[1,5-b]pyridazine-7-yl]-1-heptanone which is attributed to additional binding of the imidazole sp^2 nitrogen atom. A number of compounds in this series also inhibit the replication of HIV-1 *in vitro* in MT-4 and C8166 cells at levels observed with the nucleoside AZT. The active pyridazinone derivative in the series is given in Fig. 20.

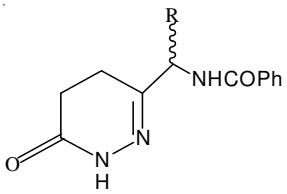
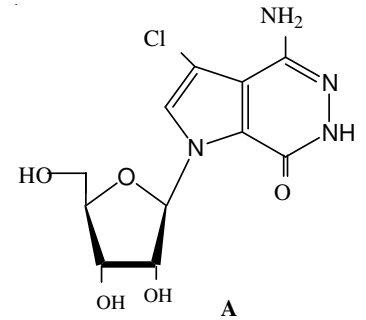
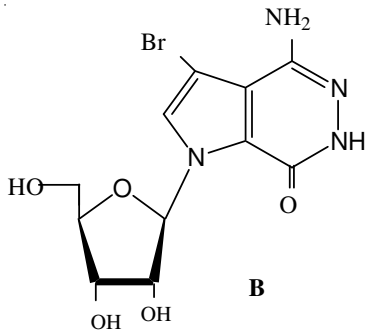


Fig. 20. Active pyridazinone derivative exhibiting anti-HIV-1 activity

Antiproliferative activity: Meade *et al.*[22] synthesized 4-amino-1-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyridazin-7(6*H*)-one and related derivatives and furnished their antiproliferative activity in L1210, H.Ep.2 and several additional human tumor cell lines. In L1210 cells, the 3-halo-substituted compounds A, B, C exhibited significant cytotoxicity (Fig. 21), in contrast to the 3-unsubstituted compound, which had only slight activity. The antiviral evaluation of these compounds revealed that compounds A, B, C were active against human cytomegalovirus in both plaque and yield reduction assays.





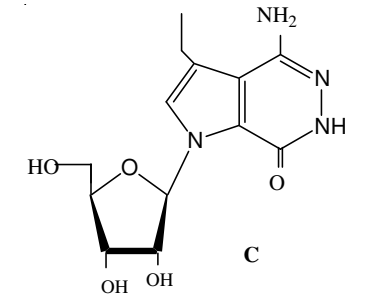


Fig. 21. Structure of 4-amino-1-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyridazin-7(6*H*)-one and related derivatives showing antiproliferative activity

Antimicrobial activity: Peesapsti and Venkata[23] reported the synthesis of fused triazolo, tetrazolo and pyridazinone derivatives, which showed good inhibitory activity against gram-positive bacterium *Staphylococcus aureus* and gram-negative bacterium *Escherichia coli*.

Mogilaiah and Kankaiah[24] reported the synthesis of 6-aryl-2-(2-phenyl-1,8-naphthyridine-3-carbonyl)-4,5-dihydropyridazin-3(2*H*)-ones (Fig. 22) that showed inhibitory activity against *E. coli* and *Bacillus subtilis*.

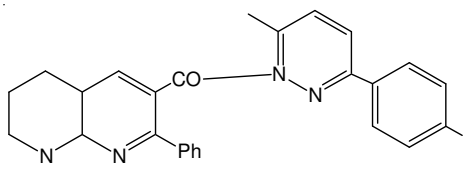


Fig. 22. 6-Aryl-2-(2-phenyl-1,8-naphthyridine-3-carbonyl)-4,5-dihydropyridazin-3(2*H*)-ones

Velezheva *et al.*[25] designed and synthesized new series of synthetic 3-amino-4-arylpyridazino[4,3-b]indoles(pyridazinoindoles) (Fig. 23) and identified them as inhibitors of *Mycobacterium tuberculosis*. Most of the pyridazinoindoles with appreciable antituberculosis activity also inhibit monoamine oxidase, suggestive of a novel inhibitory effect on mycobacterial redox reactions.

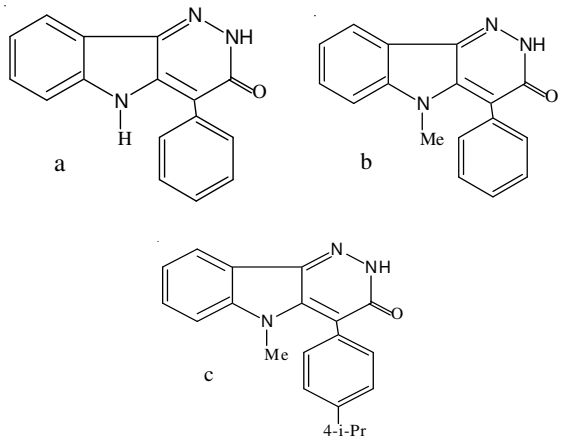
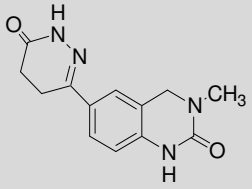
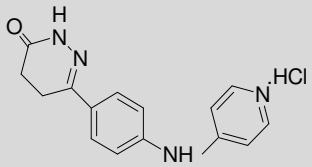
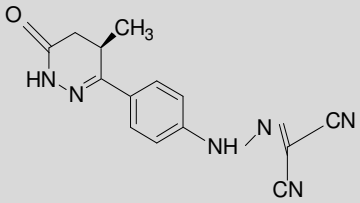
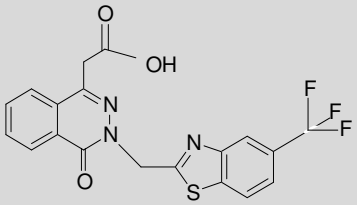
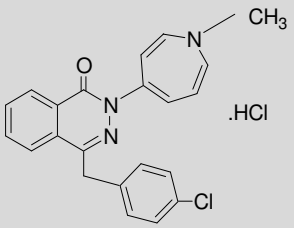


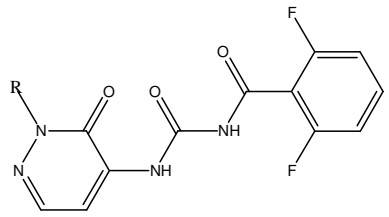
Fig. 23. Series of synthetic 3-amino-4-arylpyridazino[4,3-b]indoles(pyridazinoindoles)

Dichloro and dithione derivatives of 4,5-dihydro-3(2*H*)-pyridazinone have been reported to possess antibacterial activity when screened *in vitro* against bacteria[26].

Insecticidal activity: A series of novel chitin synthesis inhibitors, benzoylphenylureas containing the 3(2*H*)-pyridazinone (Fig. 24), were synthesized and evaluated whereupon they were found to possess significant activity[27].

TABLE-1
PYRIDAZINONE DERIVATIVES PROJECTED AS DRUGS OF FUTURE

Name	Effect	Structure	Clinical trial	Manufacturer
Prinoxodan RGW-2938	Cardio tonic		Animal study	Rhone Poulenc
MCI-154	Cardio tonic, Phosphodiesterase III inhibitor		Phase II Trials	Mitsubishi Chemical
Levosimendan	Treatment of heart failure, calcium sensitizer, K_{ATP} channel activator		Phase II Trials	Orion Pharma
Zopolrestat	Symptomatic antidiabetic, Aldose reductase inhibitor		Phase III Clinical trials	Pfizer, Inc., U.S.
Azelastin hydrochloride	Antihistaminic		Animal study	Asta, Carter-Wallace



1-(2,6-Difluorobenzoyl)-3-(2-alkyl-3-oxopyridazin-4-yl)urea

Fig. 24. Benzoylphenylureas containing the 3(2*H*)-pyridazinone

Conclusion

A large number of pyridazinone derivatives have shown diverse biological activities. Most of the research work on pyridazinone ring derivatives is focused on cardiovascular properties and as a result of this a large number of pyridazinone derivatives have reached various phases of clinical trials as cardiotonic and antihypertensive agents. A few pyridazinone derivatives in various phases of clinical trials are given in Table-1.

From the plethora of pharmacological activities exhibited, pyridazinone ring derivatives serve as potential targets for further drug development.

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