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REVIEW ARTICLE

Pyridazin-3(2*H*)-ones: the versatile pharmacophore of medicinal significance

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Abstract Pyridazin-3(2*H*)-one derivatives have attracted the attention of medicinal chemists during the last decade due to their diverse pharmacological activities. Easy functionalization of various ring positions of pyridazinones makes them an attractive synthetic building block for designing and synthesis of new drugs. The incorporation of this versatile biologically accepted pharmacophore in established medicinally active molecules results in wide range of pharmacological effects. Pyridazinones constitute an interesting group of compounds, many of which possess wide spread pharmacological properties such as antihypertensive, platelet aggregation inhibitory, cardiotonic activities and some are also well known for their pronounced analgesic, anti-inflammatory, antinociceptive, and antiulcer activities. Recently pyridazinones have also been reported as antidiabetic, anticonvulsant, antiasthmatic, and antimicrobial agents. These encouraging reports suggest that this privileged skeleton should be extensively studied for the therapeutic benefits. In view of this, a detailed and updated account of the pharmacological properties of pyridazinones is described in this review. The wide range of synthesized pyridazinone analogs along with their medicinal significance is also presented.

Keywords Pyridazin-3(2*H*)-one · Pharmacological activity · Anti-inflammatory · Cardiovascular effects

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Introduction

Among pyridazine derivatives, 3(2*H*)-pyridazinones form an important class of compounds mainly due to their diverse pharmacological activities. This privileged structure attracts the interest of medicinal chemists as a nucleus of potential therapeutic utility. The easy functionalization at various ring positions makes them an attractive synthetic building block for designing and synthesis of new drugs. The pyridazin-3(2*H*)-one skeleton was first prepared by E. Fischer by cyclizing the phenylhydrazone of levulinic acid followed by oxidation in the presence of PCl_5. The most common synthesis consists of the reaction of hydrazine or aryl hydrazines either with mixtures of ketones and esters, or with 1,4-dicarbonyl compounds (Lee *et al.*, 2004; Matyus, 1998). Chemical and biological aspects of 4,5-disubstituted 3(2*H*)-pyridazinones derivatives have been detailed in a number of comprehensive reviews (Coates, 1996; Matyus and Czako, 1993; Dal Piaz *et al.*, 1994; Heinisch and Frank, 1990, 1992). In this review the varied pharmacological properties and related medicinal significance of various pyridazinone derivatives is presented.

Diverse pharmacological properties

Pyridazinones show a diverse range of agrochemical and pharmacological activities including cardiotonic, bronchodilatory, anti-inflammatory, antiulcer, antidiabetic, and antiplatelet activity. Specially, the introduction of alkyl and aryl substituents on the 4-, 5-, and 6-positions may lead to products with diversified activities such as analgesic, anti-inflammatory and antipyretic, antihypertensive, antiulcer, antithrombotic, and bronchospasmodic activities (Dal Piaz *et al.*, 1994).

Cardiovascular actions

There are numerous reports available in the literature, which indicate the potential cardiovascular effects of pyridazinones (Fig. 1). These compounds are particularly important due to their antihypertensive, vasodilatory, inotropic, platelet aggregation inhibitory and antithrombotic and cardiotonic actions (Demirayak *et al.*, 2004; Laguna *et al.*, 1996). Introduction of 6-substituted-phenyl group on 4,5-dihydro-3(2*H*)-pyridazinones skeleton has been shown to enhance cardiovascular effects of this ring system. A variety of 6-phenyl-4,5-dihydro-3(2*H*)-pyridazinones have been synthesized and examined for hypotensive activity in the normotensive rats (Curran and Ross, 1974). Considerable activity in this area has been observed for a variety of substituents on the phenyl moiety. The compounds containing acetamido and cyano groups combined with a methyl group at position 5 of pyridazinone exhibited potent and long lasting hypotensive activity. SK&F-93741 (**1**) and compound **2** were the most active ones of the series. The pyridazinone **1** also emerged as a potent inodilator in cats in both in vivo and in vitro studies with good phosphodiesterase inhibition profile (Curran and Ross, 1974). It was observed that phosphodiesterase 3 (PDE3) inhibitory potency is associated with overall planar topology of the phenyl pyridazinone moiety and the presence of two electronegative centers. In comparison with milrinone, RS-1893 (**3**), an orally active pyridazinone was found about 20 times more active venous and arterial vasodilator with cardiotonic activity (Miyake *et al.*, 1989).

The pyridazinone derivative zardaverine (**4**) is a potent bronchodilator both in vivo and in vitro and exerts a positive inotropic action on heart muscle in vitro. The actions of **4** are mediated via inhibition of PDE activity. Fluromethoxy derivative zardaverine (**4**) is a mixed inhibitor of PDE3 and PDE4 isoenzymes (Schudt *et al.*, 1991). In another study, imidazolyl substituted 6-phenyl-3(2*H*)-pyridazinones were synthesized and investigated for positive inotropic activity. Among the series, a compound imazodan (CI-914, **5**) produced substantial increase in myocardial contractility (Bristol *et al.*, 1984).

Levosimendan, (*R*)-{[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl]hydrazon}propanedinitrile (**6**), has been marketed by the name Simadex® as a potential drug for treatment of congestive heart failure (CHF). This is a pyridazinone-dinitrile derivative that is both a calcium sensitizer and a phosphodiesterase inhibitor (PDI) at high concentrations. Its calcium sensitizing effect is through stabilizing the calcium-induced conformational changes of

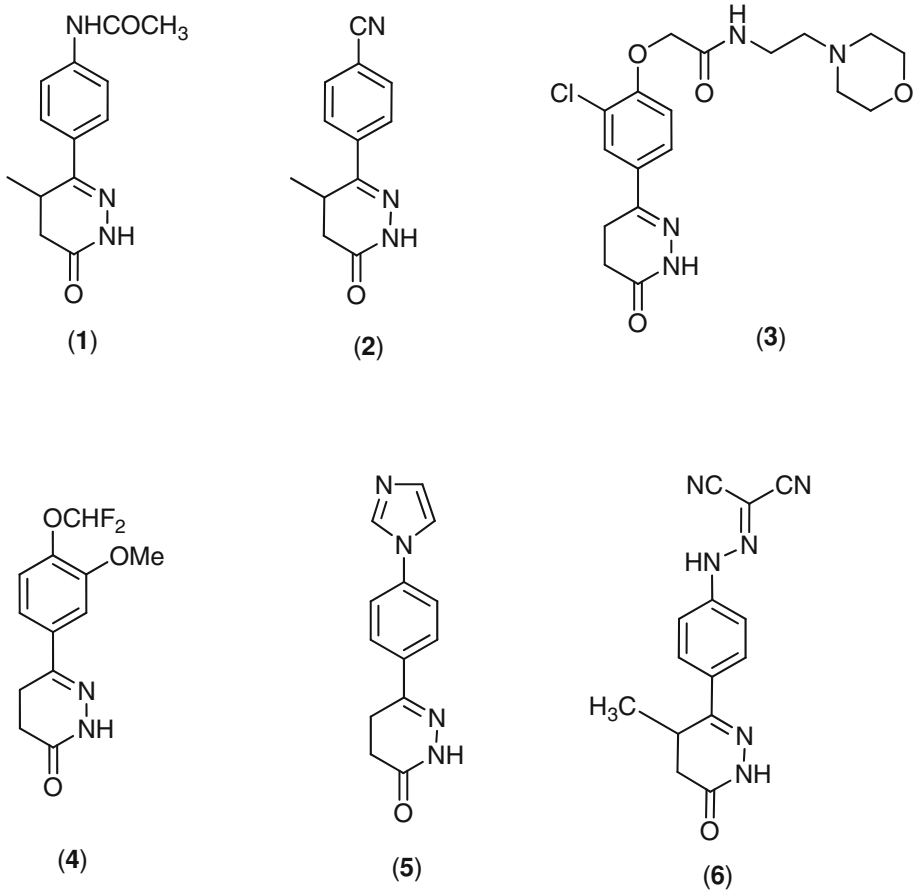


Fig. 1 Various pyridazinone derivatives exhibiting cardiovascular effects

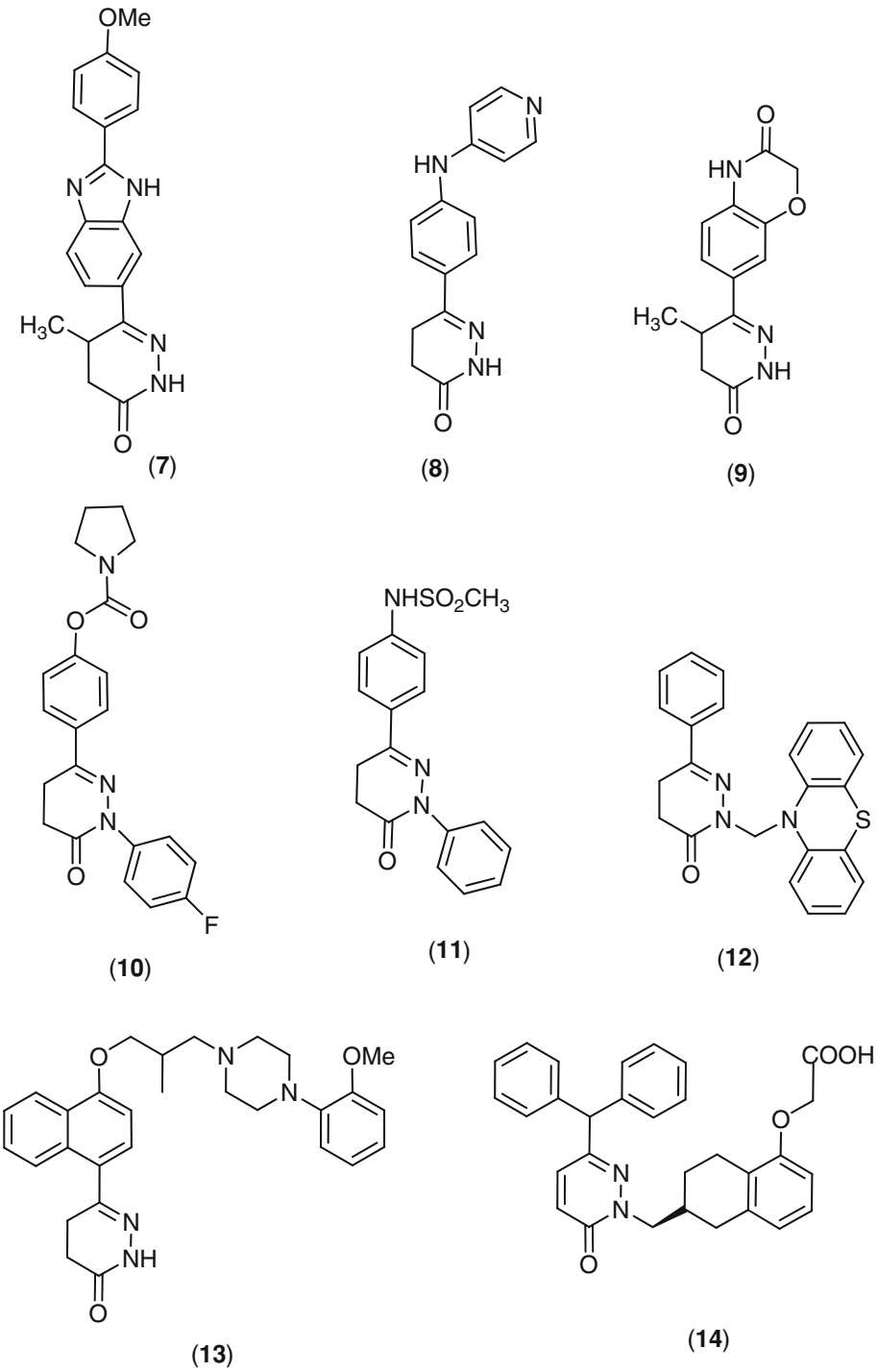


Fig. 1 continued

troponin C. Its hemodynamic profile is that of an inodilator. It also has a lusitropic effect, with reduction of the relaxation time in experimental studies of isolated failing human myocardium. Experimental studies have shown that at lower concentrations, levosimendan acts mainly as a calcium sensitizer, but at higher concentrations, it is mainly a PDI. The lusitropic effect persists through different dose levels (Bowman *et al.*, 1999; Innes and Wagstaff, 2003). Levosimendan is also a vasodilator both in vitro and in vivo, but its mechanism is not well understood. The evidence points to a novel mechanism that might involve its direct effect on the smooth muscle contractile or regulatory proteins (Ajiro *et al.*, 2002; Mathieu and Crai, 2011; Kasikcioglu and Cam, 2006).

A benzimidazole-pyridazinone hybrid, pimobendan (**7**), which is chemically, 4,5-dihydro-6-(2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl)-5-methyl-3(2*H*)-pyridazinone, was discovered with both vasodilating and inotropic properties and is marketed in the name of Acardi®. It is a new inotropic drug that augments Ca^{2+} sensitivity and inhibits phosphodiesterase in cardiomyocytes (Xu *et al.*, 1999; Fitton and Brogden, 1994). Pimobendan exerts its inotropy acting as both a PDI and a calcium sensitizer. Its calcium sensitizing effect is mediated by increasing the affinity of calcium binding sites on troponin C to calcium. A recent review of five controlled, randomized prospective trials of pimobendan demonstrated significant improvement in exercise capacity and quality of life in patients with heart failure. Two of these studies compared pimobendan with enalapril, and both demonstrated improved exercise capacity with pimobendan (Kubo, 1997).

A novel pyridazinone derivative 6-[4-(4′-pyridylaminophenyl]-4,5-dihydro-3(2*H*)-pyridazinone hydrochloride (MCI-154, **8**) exerted a unique effect in the chemically skinned papillary muscles of the guinea pig ventricle. Its cardiotonic activity was about 5.4 and 2.5 times more potent than those of amrinone and milrinone, respectively (Narimatsu *et al.*, 1987; Kawasumi *et al.*, 1999; Jiang *et al.*, 2002; Korvald *et al.*, 2002; Chen *et al.*, 2004a, b; Warren *et al.*, 1989; Kitada *et al.*, 1989; Sata *et al.*, 1995).

6-Benzoxazinylpyridazin-3-ones exemplified by bemoradan (**9**) were prepared and evaluated for inhibition of PDE3 in vitro and for positive inotropic activity in vivo. Bemoradan was an extremely potent and selective inhibitor of canine PDE3 and a long acting, potent, orally active inotropic vasodilator agent in various canine models (Combs *et al.*, 1990). Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone have been reported by Bansal et al. (2009). An effect of substitution at 2-position of pyridazinone ring on vasodilatory potential has also been explored. The most active compound 6-4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)phenyl-2-(4-fluorophenyl)-4,5-dihydropyridazin-3(2*H*)-one (**10**) exhibited vasodilating activity in nanomolar range (IC_{50} = 51 nM).

Recently Kumar et al. reported the synthesis and pharmacological evaluation of 2-substituted-6-(4-acylaminophenyl)-4,5-dihydropyridazin-3(2*H*)-ones as potent inodilating agents. In this series 6-(4-methanesulfonamidophenyl)-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one (**11**) exhibited significant inodilatory properties and showed vasorelaxant activity in a nanomolar range (IC_{50} = 0.08 μM) (Kumar *et al.*, 2008).

Some 6-(substituted-phenyl)-2-(substituted-methyl)-4,5-dihydropyridazin-3(2*H*)-one derivatives have been synthesized and evaluated for antihypertensive activities by Siddiqui *et al.* using Tail Cuff method. The compound **12** showed good antihypertensive activity (Siddiqui *et al.*, 2010). PC-09 (**13**) was a potent platelet inhibitor, the action of which may be mediated by inhibition of TXA_2 formation, intracellular calcium mobilization and platelet surface GPIIb/IIIa expression accompanied by increasing cyclic AMP level. PC-09 itself significantly increased the cyclic AMP level through inhibiting cyclic AMP phosphodiesterase activity (Cherng *et al.*, 2006). A novel optically pure pyridazinone derivative **14** has been reported as a nonprostanoid PGI_2 agonist. It inhibited ADP-induced aggregation of human platelets with an IC_{50} value of 0.081 μm and has high oral bioavailability (56 %) with a long half life (4.3 h) in rats (Tsubaki *et al.*, 2000).

α-Adrenoceptor (α_1-AR) antagonists

In recent years, the search for new and selective α_1-adrenoceptor antagonists has increased due to their therapeutic potential in the treatment of hypertension and prostatic hypertrophy (Cinone *et al.*, 1999). According to the reports available in the field of α_1-AR antagonists, the addition of arylpiperazinyl alkyl side chain into pyridazin-3(2*H*)-one moiety provides compounds that effectively lower blood pressure by antagonizing the α_1-adrenoceptors (Fig. 2) (Manetti *et al.*, 2002). Moreover, great attention has been paid to the compounds containing a pyridazin-3(2*H*)-one moiety, due to their potential biological activities as antihypertensive agents. The literature survey suggests that both the arylpiperazinyl and the pyridazinone moieties are key elements for α_1-AR affinity and it led to the discovery of a series of novel pyridazin-3(2*H*)-one derivatives **15** and **16** as potentially selective α_1-AR antagonists (Barbaro *et al.*, 2001).

Monocyclic or bicyclic substituted pyridazinones **17** and **18** bearing phenylpiperazinyl alkyl moieties showed remarkable potency and selectivity towards α_{1a} and α_{1d} with respect to α_{1b} subtype (Montesano *et al.*, 1998) Betti *et al.* reported the affinity and selectivity of cyclic substituents at the pyridazinone ring and alkoxy groups at the arylpiperazine moiety. Compound **19** showed α_1-AR affinity about fivefold higher than prazosin. Compound **20** showed an interestingly $5\text{-}HT_{1A}/\alpha_1$ affinity ratio of 119 (Betti *et al.,* 2003).

Analgesic, anti-inflammatory, and antinociceptive activities

Pain is a clinical status that human beings have been coping with for centuries. The majority of currently known non-steroidal anti-inflammatory and analgesic drugs (NSAIDs), i.e., aspirin and ibuprofen, mainly act peripherally by blocking the production of prostaglandins through inhibition of cyclooxygenase (COX) enzymes. These drugs tend to produce side effects such as gastrointestinal ulceration and suppression of renal functions. Therefore, the main trend now-a-days in pain therapy focuses on improved

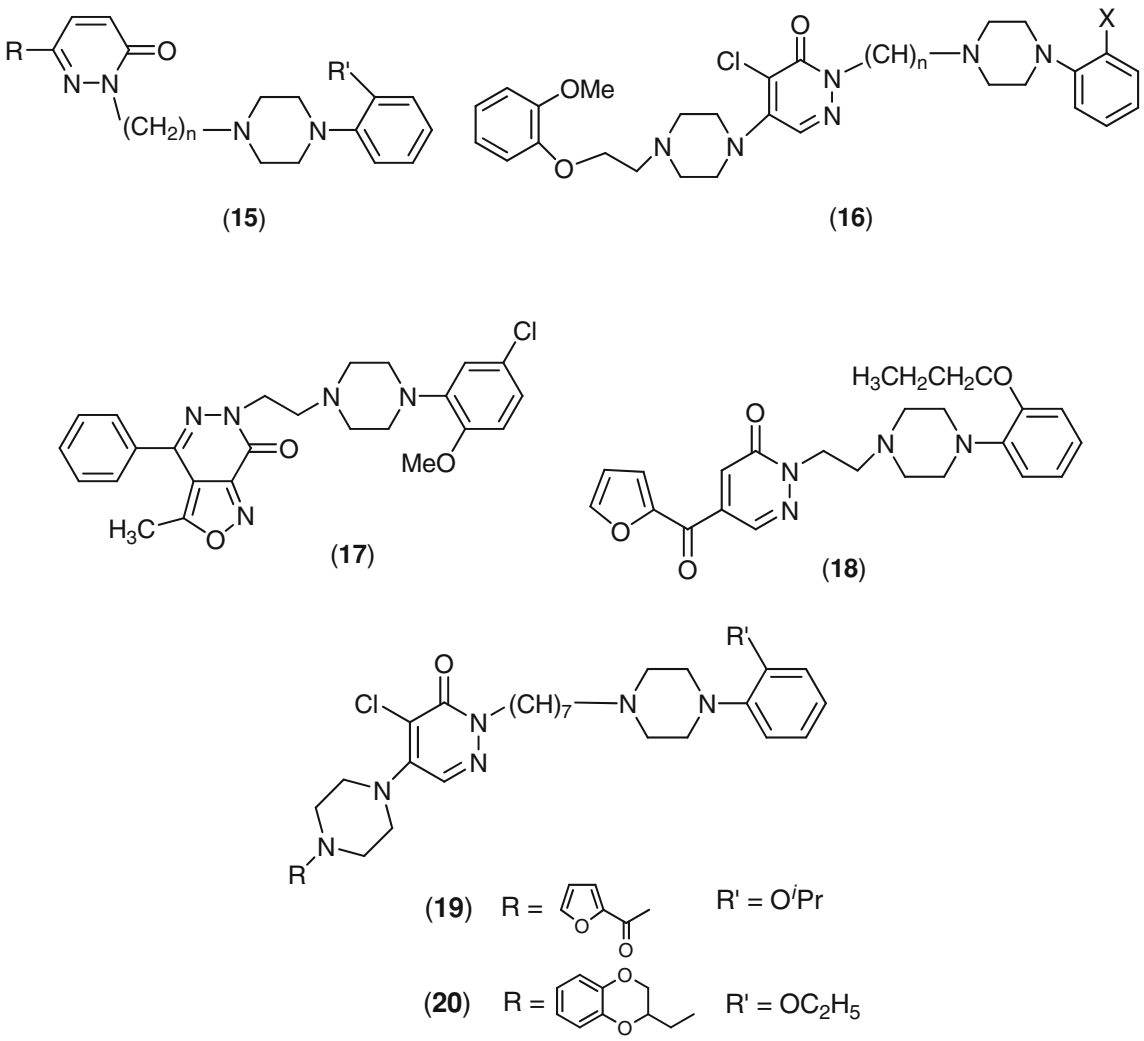
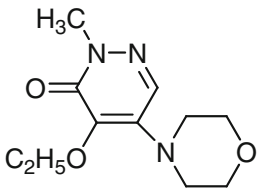


Fig. 2 Pyridazinones as α-adrenoceptor (α_1-AR) antagonists

nonsteroidal analgesics, which are effective pain relievers but devoid of the side effects inherent to traditional NSAIDs (Regina, 2006). In terms of this aspect, many studies have been focused on 3(2*H*)-pyridazinones (Malinka *et al*., 2011), which are characterized to possess good analgesic, anti-inflammatory, antinociceptive activity and also very low ulcerogenicity (Fig. 3). Among the various pyridazinone derivatives, 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**21**, emorfazone®) is currently being marketed in Japan as an analgesic, anti-inflammatory, and antinociceptive drug (Sukuroglu *et al*., 2005) Further studies in this direction reported highly potent 4-amino-2-methyl-6-phenyl-5-vinyl-3(2*H*)-pyridazinone in comparison to compound **21** in producing analgesic and anti-inflammatory response. Its action mechanism was distinct and was not mediated by interaction with prostaglandin synthesis or by affinity for opioid receptors, which was inherent to the currently used nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics, respectively (Dal Piaz *et al*., 1996).

Additionally, Santagati's group synthesized 2-substituted 4,5-dihalo-3(2*H*)-pyridazinone derivatives with high analgesic activity and no ulcerogenic side effects. Subsequently, more 2-substituted 4,5-functionalized 6-phenyl-3(2*H*)-pyridazinone derivatives have been reported to bear potent analgesic activity with negligible general side effects as those of currently used NSAIDs (Santagati *et al*., 1985). Rohet et al. (1996) reported the trazodone-like analgesic activity of 4,6-diaryl pyridazinones having arylpiperazinyl alkyl moiety linked to the 2-nitrogen of the pyridazinone ring, which was followed by various studies in the field introducing the 3(2*H*)-pyridazinone core as the new structure for analgesic drug development. Further, studies in this area have also reported many examples of potent analgesic and anti-inflammatory agents without ulcerogenic side effects bearing an arylpiperazine linked to



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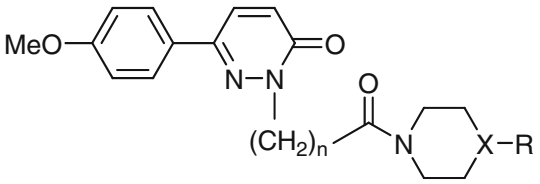

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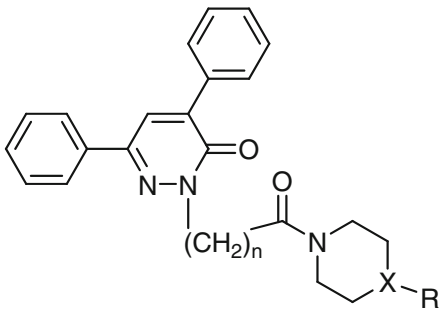

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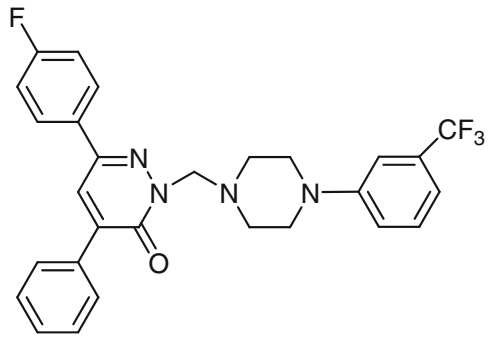

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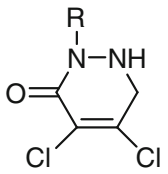

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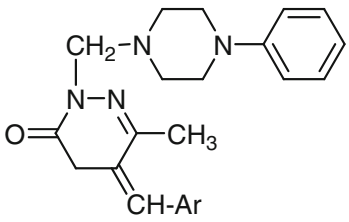

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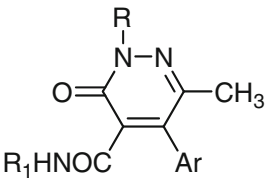

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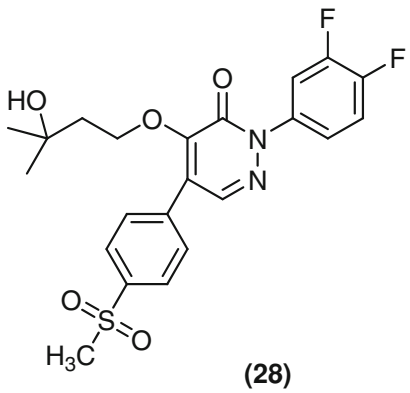

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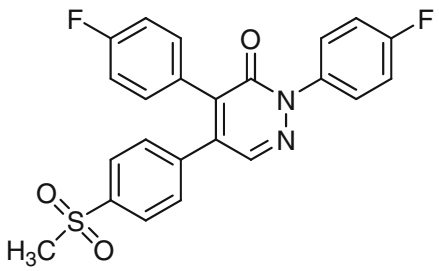
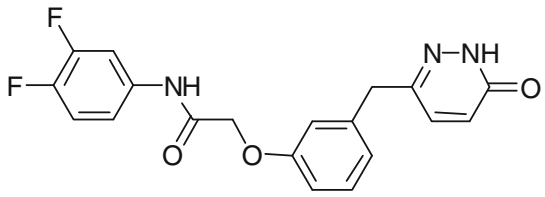


(29)

Fig. 3 Pyridazinones as analgesic, anti-inflammatory, and antinociceptives

the 2-nitrogen of the pyridazinone ring through an alkyl spacer such as **22** and **23** (Rubat *et al*., 1992). Introduction of an arylpiperazinomethyl moiety at position 2 of the pyridazinone ring resulted in increased analgesic activity in a series of *N*-substituted 4,6-diaryl-3-pyridazinones like compound **24** (Rubat *et al*., 1989).



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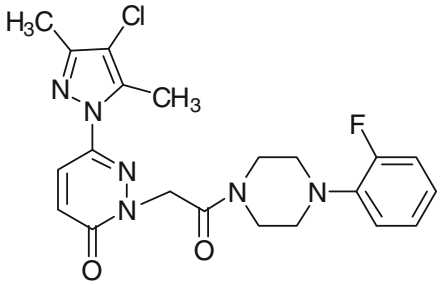

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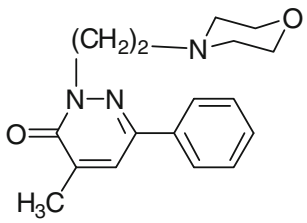

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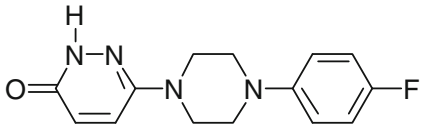

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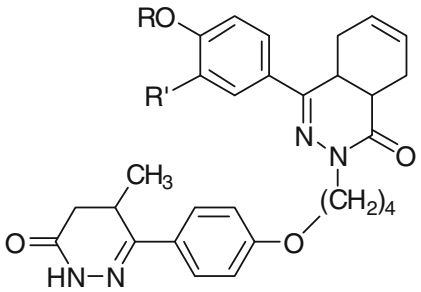

(34) R=C_2H_5, R'=OC_2H_5

(35) R=CH_3, R'=Cl

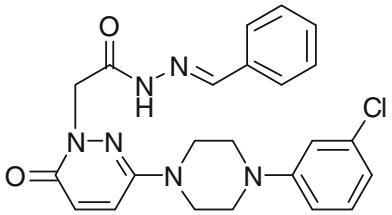

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Fig. 3 continued

In addition, 4,5-dihalopyridazinone, 5-arylidenepyridazinone, and 4-carbamoyl-pyridazinone derivatives represented by structures **25**–**27**, respectively, have been reported as new potent analgesic agents (Gokce *et al*., 2004). ABT-963 (**28**) has recently been shown to be a potent and highly selective COX-2 inhibitor that may have utility for the treatment of rheumatoid arthritis and osteoarthritis. The compound is efficacious in preclinical inflammation models and causes less gastric irritation than NSAIDs in animal models. ABT-963, chemically 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-(4-methane-sulfonylphenyl)-2*H*-pyridazin-3 one (**28**) is a highly potent and selective disubstituted pyridazinone cyclooxgenase-2 inhibitor. Similar-substituted pyridazinone derivative such as A-241611 (**29**) has also been reported to be new potent analgesic agent (Harris *et al*., 2004; Kerdesky *et al*., 2006).

In addition, 3-*O*-substituted benzylpyridazinone derivatives represented by compound **30** were recently shown to exhibit in vivo potent anti-inflammatory activity using the carrageenan-induced rat paw edema assay through the mechanism involving selective cyclooxygenase-2 (COX-2) inhibition (Chintakunta *et al*., 2002).

Additionally, structurally diverse amide derivatives of [6-(3,5-dimethyl-4-chloropyrazole-1-yl)-3(2*H*)-pyridazinone-2-yl]acetic acid were prepared and tested for their in vivo analgesic and anti-inflammatory activity by using

p-benzoquinone-induced writhing test and carrageenan-induced hind paw edema model, respectively. The analgesic and anti-inflammatory activities of **31** were found to be equipotent to aspirin as an analgesic and indomethacin as an anti-inflammatory drug, respectively. (Dogruer and Sahin, 2003)

Among the pyridazine derivatives endowed with antinociceptive effects, AG 246 (**32**) and emorfazone (**21**) had emerged as potent molecules, the latter had also been launched in Japan (Dal Piaz *et al*., 2003). The literature reports many examples of antinociceptive agents such as compound **26** bearing an arylpiperazinyl moiety linked to the 2-nitrogen of a pyridazinone ring either through an alkyl chain or a different lactamic system.

In a series of 3-pyridazinones with morpholino, arylpiperazino moiety at position C_6, 4-(4-flurophenyl)piperazine (**33**) was found to be the most active antinociceptive agent (Gokce *et al*., 2001).

PDE4 inhibitors have proven potential as anti-inflammatory drugs, especially in inflammatory pulmonary diseases such as asthma, COPD, and rhinitis. Some new pyridazinones have also displayed PDE4 inhibitory activity (Biagini *et al.,* 2010). Margaretha et al. synthesized a new series of phthalazinone/pyridazinone hybrids with both PDE3/PDE4 inhibitory activities. PDE4 inhibition is responsible for anti-inflammatory activity and PDE3 inhibition is for producing cardiovascular effects. These compounds combine the pharmacophores of recently discovered 4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one type inhibitors of PDE4 and the well-known 2*H*-pyridazin-3-one type PDE3 inhibitors such as the tetrahydrobenzimidazoles. Most of the synthesized compounds, pharmacologically spoken PDE3/PDE4 hybrids, show potent PDE4 inhibitory activity ($pIC_{50} = 7.0–8.7$), whereas the pIC_{50} values for inhibition of PDE3 vary from 5.4 to 7.5. In general, analogs with a 5-methyl-4,5-dihydropyridazinone moiety exhibit the highest PDE3 inhibitory activities. The highest in vivo anti-inflammatory activity is displayed by phthalazinones **34** and **35** showing, at a dose of 30 μmol/kg po, 46 % inhibition of arachidonic acid induced mouse ear edema (Margaretha *et al*., 2003).

Gokce et al. reported new 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(*p*-substituted benzal)hydrazone derivatives as analgesic and anti-inflammatory agents. Compound **36** exhibited more potent analgesic activity than aspirin. Also these derivatives demonstrated anti-inflammatory activity. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference nonsteroidal anti-inflammatory drugs (NSAIDs) (Gokce *et al*., 2009).

Aldose reductase inhibitory activity

ALR 2 is responsible for an enhanced reduction of glucose to sorbitol. In particular, ALR 2 is the first and rate-limiting enzyme of the polyol pathway converting glucose to sorbitol followed by the subsequent NADC-dependent oxidation of sorbitol to fructose by sorbitol dehydrogenase. As a consequence, enhanced flux of glucose through the polyol pathway leads to various imbalances altogether, the pathophysiological activity of aldose reductase plays a key role in the development of diabetic complications such as angiopathy, nephropathy, diabetic retinopathy, and cataract formation. In vitro and in vivo studies suggest a clear benefit of the administration of aldose reductase inhibitors (ARIs) in various model systems exposed to high levels of glucose as well as in the treatment of diabetic patients. Encouraged by these observations, extensive efforts have been made within the last two decades to develop appropriate drug candidates. A broad variety of agents inhibiting ALR2 have been synthesized or extracted from natural sources. However, for various reasons, most of these inhibitors failed in clinical trials. The first clinically investigated candidate, sorbinil, a hydantoin-type, led to the occurrence of hypersensitivity reactions independent of the ALR2 inhibition. The carboxylic acid-type inhibitors zopolrestat **37** show a remarkable in vitro affinity but lack sufficient in vivo efficiency due to poor bioavailability (Steuber *et al*., 2006) (Fig. 4).

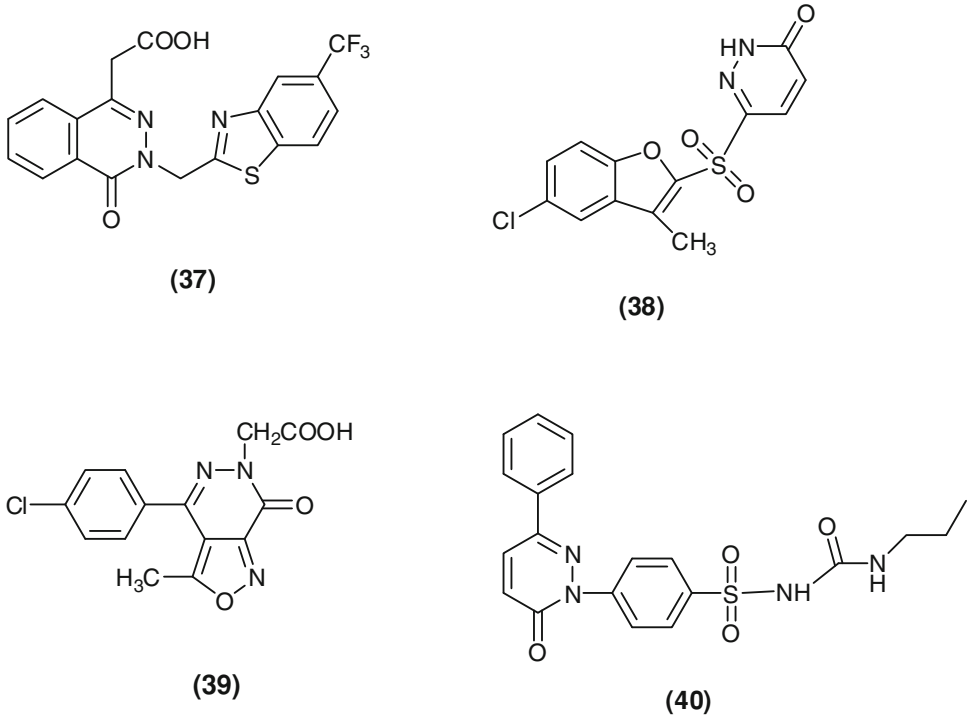
In 2003, Mylari et al. reported the development of a novel non-carboxylic acid, non-hydantoin inhibitor with excellent properties, the compound shows a sub-nanomolar IC_{50} value (840 pM), a more than 1,000-fold selectivity advantage for aldose reductase compared to aldehyde reductase, an almost perfect oral bioavailability as well as a pronounced in vivo efficiency. The ligand **38** consists of a benzofuran moiety, a pyridazinone scaffold, and a sulfonyl group linking these components together. The p*K*a of the titratable pyridazinone and the log *P* of the inhibitor were determined as 6.9 and 3.05, respectively, one prerequisite for good tissue penetration behavior (Mylari *et al*., 2003). Costantino et al. synthesized another series of new pyridazinone derivatives as aldose reductase inhibitors. The isoxazolo-[3,4-*d*]-pyridazin-7-(6*H*)-one and its corresponding open derivatives 5-acetyl-4-amino-(4-nitro)-6-substituted-*3*(2*H*)pyridazinones were used as simplified substrates for the synthesis of new aldose reductase inhibitors. The 3-methyl-4-(*p*-chlorophenyl)isoxazolo-[3,4-*d*]-pyridazin-7-(6*H*)-one acetic acid (**39**) has been reported to be new potent aldose reductase inhibitor (Costantino *et al*., 1999)

Blood glucose lowering effect of novel pyridazinone substituted benzenesulfonylurea derivatives have been reported by Rathish et al. From the results, compound **40** exhibited considerably potent blood glucose lowering activity (Rathish *et al.*, 2009).

Antiulcer activity

To develop new type of antiulcer agents without anticholinergic activity, a series of novel 3(2*H*)-pyridazinone

Fig. 4 Pyridazinones as aldose reductase inhibitors



derivatives bearing thioamide moiety was synthesized. Various substituents were introduced on the nitrogen of thioamide, on the carbon in the side chain, and also on the 3(2*H*)-pyridazinone ring system. It was observed that 3(2*H*)-pyridazinone derivatives **41** and **42** having a thioamide moiety possess marked gastric antisecretory activity in rats without histamine H_2 receptor antagonistic action. SAR studies indicate that 3(2*H*)-pyridazinones with a C-6 phenyl group and an N-2 alkyl side chain with a terminal thioamide group were the most potent among the compounds tested (Yamada *et al*., 1982). Further studies in the field of non-anticholinergic antisecretory drugs development reported a new series of pyridazinone methide thioamide **43** having marked gastric antisecretory activity (Fig. 5) (Yamada *et al.,* 1983a).

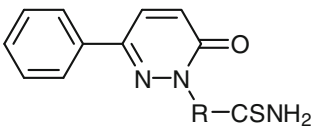
Another series of pyridazinone derivatives **44** (MUN-114) and **45** (MUN-118) having a thiourea or a 2-cyanoguanidine moiety exhibited marked gastric antisecretory activity in rats without histamine H_2 receptor antagonistic action. The molecular structural features essential for the activities are a thiourea group or a cyanoguanidine group, a phenyl grouping at the 6 position of the 3(2*H*)-pyridazinone ring, a four-carbon chain length between the 3(2*H*)-pyridazinone ring and the functional group, and a methyl group at the N-3 position of the functional group (Yamada *et al.,* 1983b).

Antimicrobial activity

Increasing occurrence of antibiotic-resistant human pathogenic microorganisms and infections caused by these microorganisms pose a serious challenge to the medical community and there is a need for an effective therapy, which has led to a search for novel antimicrobial agents. Recently some pyridazinone derivatives have been reported as potent antibacterial and antifungal agents (Ungureanu *et al*., 1997).

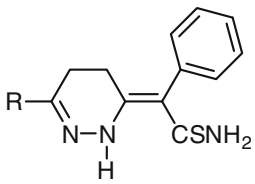
A series of 2-arylsulpho-6-substituted-3(2*H*)-pyridazinones on testing for the antimicrobial activity exhibited moderate to good antimicrobial activity against bacteria and fungi. Some of the compounds **46** and **47** displayed remarkable antibacterial activity against *Bacillus megaterium*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas fluorescens* and antifungal activity against *Aspergillus awamori* in comparison with those of standard drugs at the same concentration (Purohit and Shah, 1998). A new type of antibiotics and antimicrobial agents, synthesized by preparing metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-2*H*-pyridazin-3-one were evaluated for their antimicrobial activities, Cd(II) and Ni(II) complexes **48** exhibited selective and effective activities against gram-positive, gram-negative bacteria and also yeasts. The ligand showed weak activity, whereas the complex compounds had the highest antimicrobial activities against gram-positive, gram-negative bacteria, and fungi with minimum inhibitory concentrations in the range of 0.16–0.005 mg/ml (Sonmej *et al*., 2005). *Leishmania* are causative agents for a variety of diseases representing a major health problem known as Leishmaniasis. The available drugs such as stibogluconate, meglumine, antimonate, pentamidine, and allopurinol are of limited efficacy and display serious side effects. In the series of isoxazole[3,4-*d*] pyridazinones compounds **49** and **50** showed inhibitory activity against *Leishmania mexicana* phosphodiesterase (Fig. 6) (Dal Piaz *et al*., 2002). The

Fig. 5 Structures of various pyridazinones exhibiting antiulcer activity

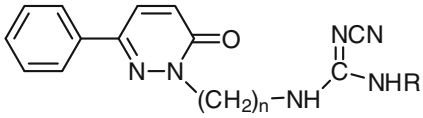


(41) R=$CH_2CH(CH_3)$

(42) R=$(CH_2)_3$



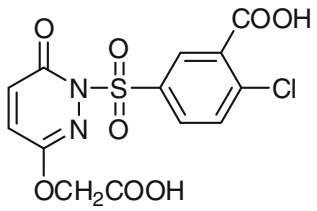
(43)



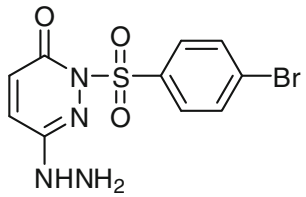
(44) n=4, R=CH_3

(45) n=5, R=C_2H_5

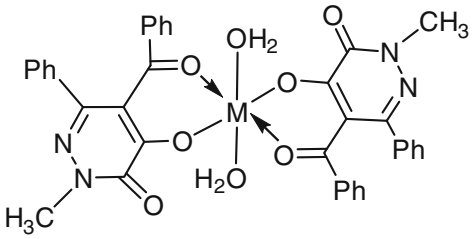
Fig. 6 Pyridazinones as antimicrobial agents



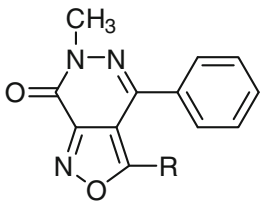
(46)



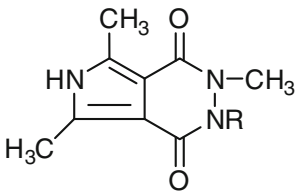
(47)



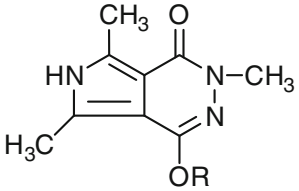
(48)



(49) R=CH_3, **(50)** R=C_2H_5

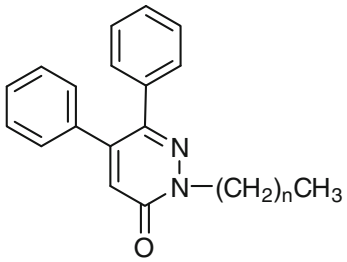


(51)

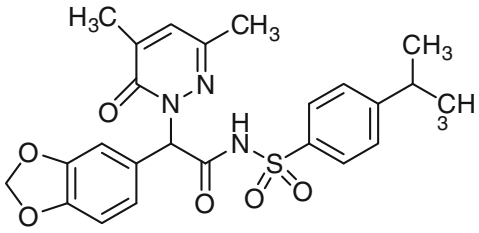


(52)

Fig. 7 Pyridazinones displaying miscellaneous activities



(53)



(54)

derivatives of pyrrolopyridazinones are type of compounds rarely mentioned in literature and there are few reports, indicating the various biological properties of members of this system. These are known for their antiproliferative and antiviral activity, antiulcer and antibacterial action against *Helicobacter pylori*, NMDA and ANDA receptor antagonistic action, antimicrobial and antifungal activity. Among these, compounds **51** and **52**, bearing different R substituents, were tested in a preliminary screening for antimycobacterial and anticancer action. Derivative **52**, possessing a fatty chain, reduced growth of *Mycobacterium tuberculosis*. The profile and potency of their biological activity was greatly influenced by the position of the R substituent. Compound **52**, with pyrimidinylpiperazinyl residue, exhibited moderate antitubercular action. However this derivative was particularly interesting as a cytostatic agent in cell experiments. Biological activity of compounds **51** and **52** was moderate and not selective (Malinka *et al*., 2004)

Miscellaneous activities

Exploratory studies in this area reported several pyridazinones as Acyl-coA cholesterol *O*-acyltransferase (ACAT) inhibitors. In a series of 2-substituted pyridazinones (**53**), activity was displayed by compounds bearing a long linear alkyl chain, the optimum being found for $n = 5$, ($IC_{50} = 57$ μM) (Fig. 7). Inhibition of ACAT enzyme could represent a good therapeutic approach to treat hypercholesterolemia (Giovannoni *et al*., 2001).

Highly active endothelin receptor antagonists such as compound **54** can be obtained by replacing the aryloxy group of L-749329 (one of the most potent ET antagonists) by diversely substituted pyridazinone residues. Pharmacological studies suggest the usefulness of such antagonists in the treatment of myocardial infarction, hypertension, heart failure, atherosclerosis, cerebral and coronary vasospasm, renal failure and asthma (Giovannoni *et al*., 2001).

Histamine H_3 receptor antagonists/inverse agonists can be therapeutically useful in the treatment of various CNS, metabolic syndrome, allergic disorders and comprise an attractive target in the search for new drugs (Lazewska and Kiec-Kononowicz, 2010). Novel 4,5-fused pyridazinones reported as histamine H_3 receptor antagonists. These compounds displayed high affinity at rat, human H_3 receptors and showed potent antagonistic and inverse agonistic activity (Tao *et al*., 2011).

Recently, pyridazin-3(2*H*)-one derivatives have also been reported to possess antiviral (Rossotti and Rusconi, 2009; Meade *et al*., 1993), anticonvulsant (Sivakumar *et al*., 2003; Xu *et al*., 1991), antifungal (Zhou *et al.,* 2011; Ungureanu *et al*., 1997), antifeedant (Cao *et al*., 2003), and antiasthma (Allen *et al*., 1985; Biagini *et al.,* 2010) activities.

Conclusions

The aforementioned literature reveals that pyridazinone is a versatile heterocyclic nucleus having high potential for the development of new chemical entities for the treatment of various disorders. The incorporation of pyridazinone nucleus, a biologically accepted pharmacophore in medicinal compounds results in wide spectrum of biological activities ranging from cardiovascular, anti-inflammatory to antidiabetic effects. The understanding and extensive structural exploration of this privileged structure is useful for the researchers for designing of the future drug molecules.

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