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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Pyridazinone: an important element of pharmacophore possessing broad spectrum of activity

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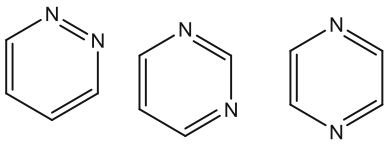
Abstract In the last few years, the pyridazine derivatives have been found to exhibit a wide range of pharmacological activities. A large number of research articles and patents described them, and several drugs based on its nucleus have come into light. Pyridazinone, a derivative of pyridazine, was initially exploited in search of cardiovascular drugs and for its use in agrochemicals, but later on this nucleus was found to be associated with plethora of activities. In this article, we have reviewed the influence of structural changes on the pharmacodynamic profile of the pyridazinone moiety.

Keywords Pyridazinone · Anti-inflammatory · Antiplatelet · Analgesic · Cytotoxic · Antihypertensive

Introduction

Pyridazines are the organic compounds derived by replacing the two carbons in the benzene ring by nitrogen atoms. This kind of replacement can have three isomeric forms depending on the position of nitrogen with respect to each other in the ring, which can be 1–2, 1–3, or 1–4 relationship, giving rise to the pyridazines (**1**), pyrimidine (**2**), and pyrazine (**3**), respectively. Out of these pyridazinone are those category of pyridazine which contain nitrogen atoms at positions 1 and 2 in the ring along with a keto functionality (Asif, 2010). In the past, a lot of research work has been done on pyridazinones. This nucleus is also known as "wonder nucleus" as it has given many compounds with a varied range of pharmacodynamic profile (Abubshait, 2007; Coudert *et al.*, 1991; Heinisch and Frank, 1990; Pahernik *et al.*, 1995; Sotelo *et al.*, 2000; Wang *et al.*, 2007). A variety of approaches to use pyridazinone system in drug design have been well described in number of recent articles (Asif, 2012, 2013a, b; Bansal and Thota, 2013; Lee *et al.*, 2004).



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A substantial number of pyridazinones in the recent past have been reported to possess antimicrobial (Kassab, 2002; Mojahidul *et al.*, 2008; Sayed *et al.*, 2002), antitubercular (Sayed *et al.*, 2002), analgesic (Piaz *et al.*, 1996; Giovannoni *et al.*, 2003; Gokce *et al.*, 2001; Dogruer *et al.*, 2000; Biancalani *et al.*, 2009a, b; Pieretti *et al.*, 1999; Rubat *et al.*, 1992), anti-inflammatory (Hallas, 1995; Takaya *et al.*, 1979; Dogruer *et al.*, 2003; Flouzat *et al.*, 1993; Gökce *et al.*, 2009; Santagati *et al.*, 1985a, b; Sato *et al.*, 1981; Raskin, 1999; Cignarella *et al.*, 1978; Deniz and Fethi, 2003; Banoglu *et al.*, 2004; Ayla *et al.*, 2003), cyclooxygenase inhibitor (Okcelik *et al.*, 2003; Chintakunta *et al.*, 2002), antidiabetic (Rathish *et al.*, 2009), antihypertensive (Barbaro *et al.*, 2001; Seki *et al.*, 1996; Siddiqui and Wani, 2004; Bansal *et al.*, 2009; Verdouw *et al.*, 1986; Korvald *et al.*, 2002; Rüegg *et al.*, 1984; Schneider *et al.*, 1979; Schudt *et al.*, 1991; Ranju *et al.*, 2008; Kubo, 1997; Kumar *et al.*, 2008; Wang *et al.*, 2008; Uhlmann *et al.*, 1995; Bowman *et al.*, 1999; Ishimori *et al.*, 1994; Iwamoto, 1998), antiplatelet (Cherng *et al.*, 2006; Coelho *et al.*, 2004; Sotelo

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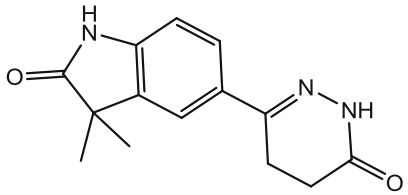
et al., 2002; Zeng *et al.*, 1993; Mikashima *et al.*, 1984; Pham *et al.*, 1988), anticancer (Miguel *et al.*, 2005; Malinka *et al.*, 2004), antifungal (Sayed *et al.*, 2002; Siddiqui *et al.*, 2008; Anwair *et al.*, 2003), antidepressant–anxiolytic (Griebel *et al.*, 1999), anticonvulsant (Xu *et al.*, 1991), bronchodilatory (for asthma) and anti-allergic (Nagai *et al.*, 1992; Yamamoto *et al.*, 1995; Hibi *et al.*, 1989), antifeedant (Cao *et al.*, 2003), inhibition of linolenic acid (Willemot, 1997), activity for neurological disorders (Sato, 1979; Laura *et al.*, 2006), and many other properties.

Some of the major pyridazinone derivatives which have appeared in market are indolidan (**4**) (Abouzid and Bekhit, 2008), bemoradan (Combs *et al.*, 1990), pimobendan (**5**) (Robertson *et al.*, 1987a, b), levosimendan (**6**) as antihypertensive (Archan and Toller, 2008), minaprine as antidepressant (Sotelo *et al.*, 2003), emorfazone (**7**) as anti-inflammatory (Bowman *et al.*, 1999), and azanrinone as a cardiotonic (Siddiqui and Wani, 2004).



Indolidan

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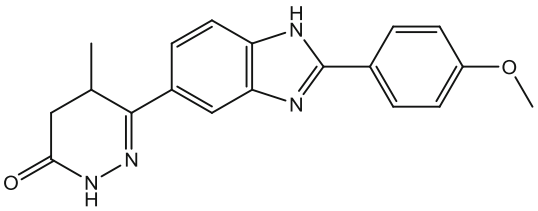

Primobendan

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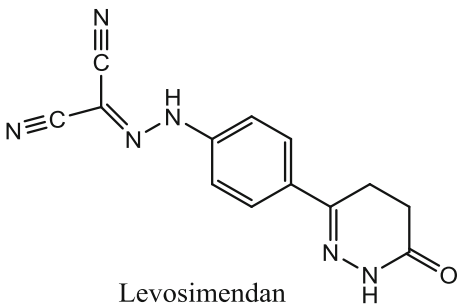

Levosimendan

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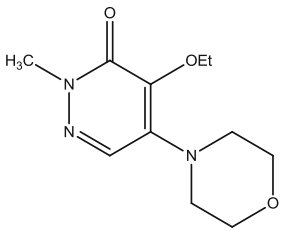


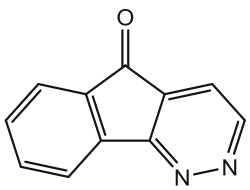
EMORFAZONE

7

In this review, we explore the various substitutions and modifications in the derivatives possessing pyridazinone moiety and exhibiting various pharmacological activities.

Antihypertensive

It was observed from the literature that among the oldest activity of pyridazinone nucleus is its antihypertensive activity. The pyridazinone derivatives exhibit antihypertensive activity by virtue of their vasorelaxant property. In 1980s, 6-arylpyridazinones were synthesized, and the compounds such as 7-fluoro and 5-keto-5*H*-indeno(1,2-c)pyridazines (**8**) (Cignarella *et al.*, 1982) were found to be antihypertensive. Around the same time, many other pyridazinone derivatives were synthesized and evaluated for various pharmacodynamic properties. Few of those compounds were found to posses antiplatelet aggregating activity along with antihypertensive activity, e.g., 7-amino or 7-acetyl-aminosubstituted-4,4a-dihydro-5*H*-indeno(1,2-c)pyridazin-3-ones (**9**, **10**) (Cignarella *et al.*, 1986, 1998) and 6-[*p*-[(chloroalkanoyl)amino]phenyl]-4,5-dihydo-3(2*H*)-pyridazinones (**11**) (Thyes *et al.*, 1983). Some 2-non-substituted/2-methyl-/2-(2-acetyloxyethyl)-6-[4-(substitutedpyrrol-1-yl)phenyl]-4,5-dihydro-3(2*H*) pyridazinone derivatives (**12**) were also synthesized and evaluated for their vasorelaxant effect. Some of these compounds have shown good activity on isolated rat aorta (Demirayak *et al.*, 2004a, b).



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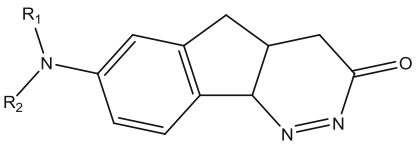

R1 = CH_3CO, R2= H
R1 = CH_3CO, R2= alkyl groups

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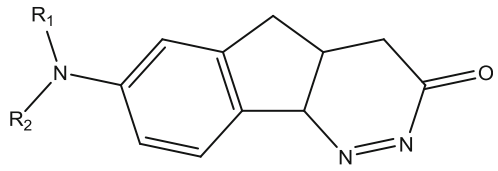

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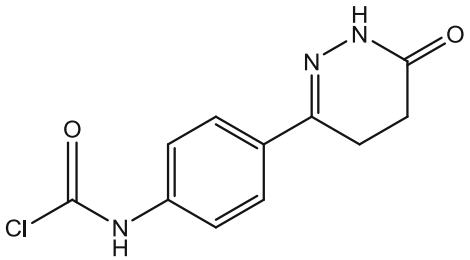

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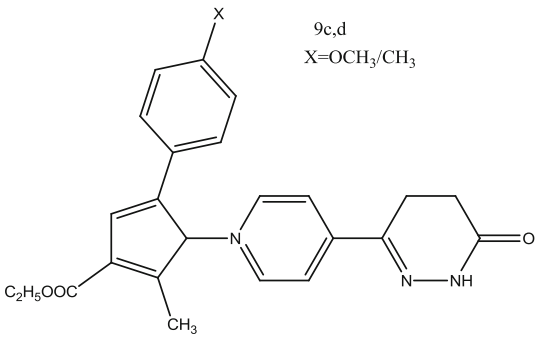

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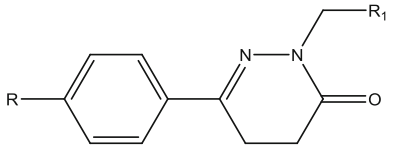
Siddiqui *et al.* (2010) synthesized various 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydropyridazin-3(*2H*)-ones (**13**). These compounds were compared for their antihypertensive property against hydralazine, as standard drug using tail cuff method. Compounds containing piperazine or its derivatives attached through nitrogen and bearing phenyl ring substituted with CH_3, C_2H_5, or OCH_3 were found to exhibit highly significant reduction in mean arterial BP. But the doses responsible for this effect were higher in comparison with hydralazine. Based on these results, it was inferred that groups such as *p*-CH_3 and *p*-C_2H_5 in phenyl ring at position 6 increase the activity, whereas the various cyclic secondary amines at position 2 in a methylene group have no influence on the activity. The influence on nitrogen-containing group at position 2 was also observed, and it was found out that *N*-piperazine, *N*-phenothiazine, *N*-(1,2,4-triazole), *N*-morpholine, *N*-(4-*N*-methylpiperazine), and *N*-pyrrolidine moieties when present in the structure showed good antihypertensive activity.



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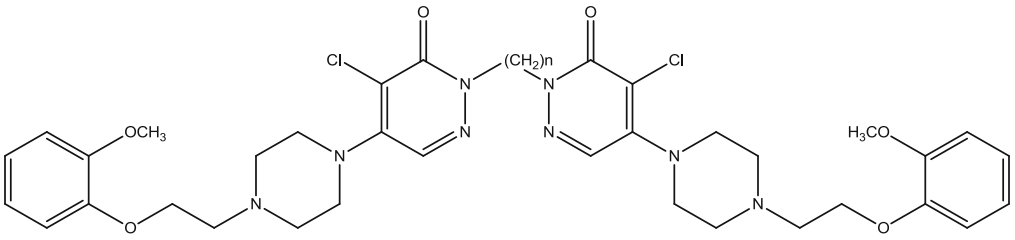
Adrenoceptor antagonists

The adrenoceptors (AR) which belong to superfamily of G-protein-coupled receptors are categorized into two types α1 and α2. They have many common structural features which could relate to the similarity in their mechanism of action (Strader *et al.*, 1989a, b). α1 AR are postsynaptically located, whereas α2 AR are located in presynaptic neuronal junction. Due to their importance in the treatment for hypertension (Curran and Ross, 1974) and benign prostatic hypertrophy (BPH; Hieble *et al.*, 1986), the search for new selective α1-adrenoceptor antagonists has increased. The antihypertensive activity of compounds depends on postjunctional α1-adrenoceptor blockage which causes peripheral vasodilatation.

4-Chloro-5-{4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl}-3(*2H*)-pyridazinone derivatives (**14**) were synthesized by Strappaghetti et al. which were good α1 antagonists. These compounds had four or five carbon linkers in them, which have made them good toward activity and selectivity for α-AR (Strappaghetti *et al.*, 2000).



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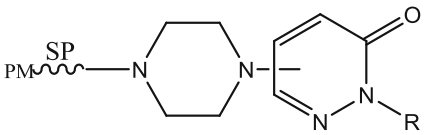
Synthesis of a series of 3(*2H*)-pyridazinone derivatives (**15**) was taken up, and the compounds were evaluated in vitro using radioligand receptor binding assays for their affinity toward adrenoceptors (α1 and α2) (Corsano *et al.*, 1999). The target compounds have shown good affinity toward α1 AR having Ki values in sub-nanomolar range. An increase in affinity was observed with increase in the polymethylene chain length in the series with maximum activity up to six and seven carbon chain lengths, and 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl moiety was linked at position 5 of the 3(*2H*)-pyridazinone ring. A further increase in the chain length in the homologous series led to decrease in the activity. When 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl group was linked at position 6, a different effect was observed. In this case, the highest affinity was observed when the polymethylene chain length was of four carbon atoms. It was also observed that this polymethylene chain length which acts as spacer between the two major constituents of the molecule can influence the affinity as well as the selectivity of the compounds.

(comparative molecular field analysis). The SAR and COMFA results of the study had put forward certain characteristic features required for good α1-adrenoceptor antagonist activity; these are: the presence of the benzodioxanyl nucleus or its 2-methoxyphenoxyethyl analog, the phenyl ring of the adrenoceptor pharmacophore moieties must be at a specific distance from the protonated piperazine nitrogen atom, the oxygen atom in the 2-methoxy-phenoxyethyl or benzoxanyl groups enhances the activity due to formation of hydrogen bond with the receptor. The modifications of 4- and 5-(1-piperazinyl)pyridazinone isomers did not have much effect on the activity, while a decrease in activity was observed in 6-substituted isomer. The substitution of N-2 acidic proton in 5-(1-piperazinyl) isomers lowered the activity, whereas it increased the activity in case of 4-(1-piperazinyl) isomers (Cinone *et al.*, 1999).



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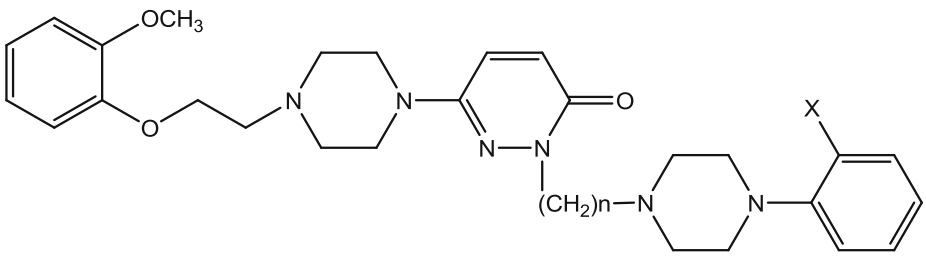


15

In another study, piperazine was linked from N-1 nitrogen to positions 4, 5, or 6 of pyridazinone ring, and the N-4 nitrogen was linked to a suitable adrenoceptor pharmacophore (1,4-benzodioxanyl, 2- methoxy-phenoxyethyl or phenoxyethyl groups) by a suitable spacer (sp). The acidic hydrogen N-2 of pyridazinone was also substituted by phenyl or methyl groups. The α1-adrenoceptor antagonist activity was obtained in terms of pk_b. The general structure of this class **16** was build by COMFA

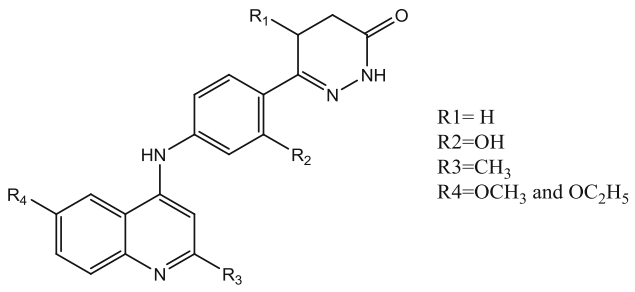
Cardiotonic

Congestive heart failure is a common, costly, disabling, and potentially deadly condition. Digoxin is widely used in the treatment for various heart conditions, namely atrial fibrillation, atrial flutter, and sometimes heart failure that cannot be controlled by other medication. Digitalis/digoxin has recently fallen out of favor because it did not demonstrate a

mortality benefit in patients with congestive heart failure, and due to its toxic side effects, the scientists have been encouraged to develop an alternative therapy (Braunwald, 1981; Packer, 1988).

Inhibition of the phosphodiesterase (PDE) isoenzyme III leads to an increase in intracellular concentrations of the second messenger cAMP, which mediates the phosphorylation of protein kinases, which in turn activates cardiac calcium channels. An increased calcium influx from the sarcoplasmic reticulum (SR) during phase 2 (the plateau phase) of the cardiac action potential leads to a positive inotropic effect of PDE III inhibitors: they increase the force of cardiac contraction. This increased reflux of calcium into the SR is also responsible for myocardial relaxation. In addition to that, PDE III inhibitors also act as vasodilators (Osadchii, 2007). Amirinone a pyridine PDE III inhibitor was the first drug in this category (Farah and Alousi, 1978). A further research in this field in search of safer and more potent compounds led to the discovery of milrinone and its analogs (Bekhit and Baraka, 2005; Abadi *et al.*, 1999). To develop SAR in the series, several pyridazinone derivatives of amrinone were also synthesized (Combs *et al.*, 1992; Bakewell *et al.*, 1990; McCall *et al.*, 1986; Pastelin *et al.*, 1983). Their mechanism of action was established, and a five-point model and pharmacophore were identified (Leclerc *et al.*, 1986; Erhardt *et al.*, 1988; Bristol *et al.*, 1984). It was found out from the study that most of the compounds acting as c-AMP PDE III inhibitors contained pyridazinone ring attached to an aromatic nucleus. In the sub category of these compounds were indolidan (**4**) (van Meel, 1985), bemoradan (Combs *et al.*, 1990), and pimobendan (**5**) (Robertson *et al.*, 1987a, b), in which the pyridazinone ring was attached to a benzo-fused heterocycle. This benzo-fused heterocyclic system governs the pharmacokinetics of the molecule (Abouzid *et al.*, 1999; Demirayak *et al.*, 2004a, b).

A series of compounds designed by Abouzid et al. (2008) had pyridazinone attached directly to the quinolone nucleus. In next series, an aminophenyl spacer was inserted between the pyridazinone and quinoline molecules (**17**). In the third series, they had engaged pyridazinone and pyridone ring systems via the same spacer moiety. All the compounds were evaluated for their vasorelaxant activity in vitro on isolated main pulmonary artery of the rabbit. The highest vasorelaxant activity was observed by two compounds in the 4-amino quinoline series when compared with milrinone. Both these compounds had higher values of pharmacophoric fit in the molecular mapping study as they possessed phenolic OH group and alkoxy group at position 6 on the quinoline ring.



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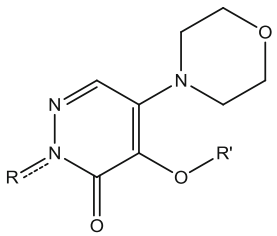
In another study, arylidene substituted meldrum's acid and 5-amino-6-phenyl-3(*2H*)-pyridazinone were used to synthesize 4-aryl-2,5-dioxo-8-phenylpyrido[2,3-d]pyridazines (Coelho *et al.*, 2004). In these compounds, it was revealed that the pyridine system is in skew boat conformation, the phenyl ring is in pseudo-axial position, and the pyridazinone ring is planar. Thus, these compounds possessed all the requirements for cardio tonic activity from structural point of view (Pita *et al.*, 2000).

Anti-inflammatory/analgesic/antipyretic

The literature reference of pyridazinones as analgesic, anti-inflammatory, and antipyretic is almost around four decades old. Various 2-alkyl or 2-alkenyl-4-alkoxy-5-(substituted amino)-3(*2H*)-pyridazinones (**18**) were synthesized and evaluated for analgesic and anti-inflammatory activities. The compound 4-ethoxy-2-methyl-5-morpholino-3(*2H*)-pyridazinone (emorfazone, **7**) was the most potent in this category. It was found to possess higher potency and lesser toxicity than aminopyrine and phenylbutazone (Takaya *et al.*, 1979).



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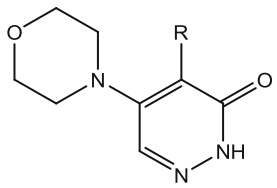
There are reports of synthesis of 4,6-diaryl-3-pyridazinones and their evaluation as anti-inflammatory, analgesic, and antipyretic. It was observed that inclusion of arylpiperazinomethyl moiety at position 2 in the

pyridazinone ring enhanced the potency of the compounds (Rubat *et al.*, 1989; Santagati *et al.*, 1985a, b).

Among the earlier study on pyridazinone derivatives related to aminopyrine containing pyridazinone nucleus was the synthesis of 4-alkoxy-2-methyl-5-morpholino-3(*2H*)-pyridazinones (**19**). These compounds were found to possess good anti-inflammatory and analgesic properties (Sato, 1979).



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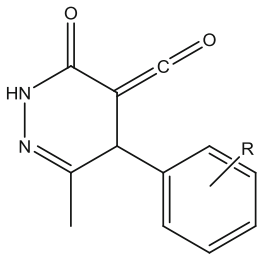
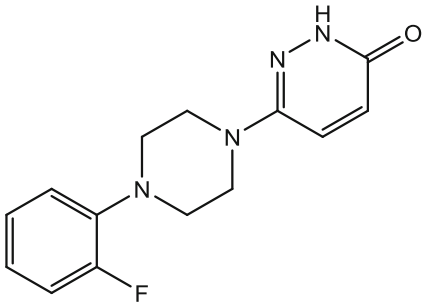
Synthesis of 3(*2H*)-pyridazinone derivatives was reported possessing good analgesic, antipyretic, and anti-inflammatory activities. The analgesic activity of these compounds was higher than phenylbutazone and was devoid of ulcerogenic action (Santagati *et al.*, 1985a, b).

A series of 4-carbomyl-5-aryl-6-methyl-4,5-dihydropyridazin-3(*2H*)-ones (**20**) (Wang *et al.*, 2007) were also synthesized and evaluated for anti-inflammatory and analgesic properties. Only one compound showed anti-inflammatory activity but had shorter duration than that of indomethacin, which was taken as reference drug. On the other hand, many derivatives had displayed significant analgesic properties.



20

Synthesis of various 6-substituted-3(*2H*)-pyridazinones was carried out, and the compounds were evaluated for anti-inflammatory and analgesic activities. The compound 6-[4-(2-fluorophenyl)piperazin-1-yl]-3(*2H*)-pyridazinone (**21**) exhibited anti-inflammatory activity similar to indomethacin. The SAR of these compounds confirmed the influence of substitution at position 6 in the 3(*2H*)-pyridazinone ring toward the anti-inflammatory–analgesic potency of the molecules (Gokce *et al.*, 2004).



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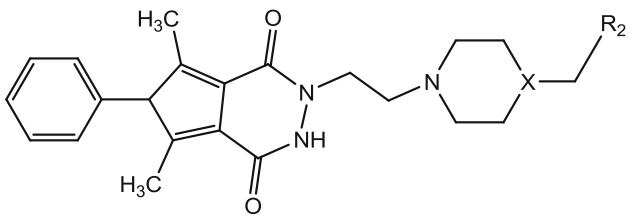
Literature reports synthesis of some pyridazinone derivatives and biheterocyclic derivatives made with pyridazinone ring having 4-arylpiperazinylalkyl substituents attached to the lactam nitrogen of pyridazinone (**22**) (Biancalani *et al.*, 2009a, b; Giovannoni *et al.*, 2003; Dogruer *et al.*, 2000). These compounds were found to have notable analgesic property. To further investigate the role of heterocyclic substituent attached to the pyridazinone lactam nitrogen, toward their analgesic property, Malinka et al. (2011) carried out design and synthesis of compounds containing arylpiperazinylpropyl chain linked to 4-*O* atom of a tautomeric form of pyrrolopyridazinone. These compounds were evaluated for their analgesic potency using hot plate method (for central analgesia) and writhing test (for peripheral analgesia). ASA (aspirin) and morphine were used as standards in these tests. From the results, it was revealed that substitution of pyrrolidinone ring with pyridazinone ring in pyrrole-3,4-dicarboximides increased the peripheral analgesic property of the compound, whereas replacement of the 4-arylpiperazinylalkyl moiety from lactam *N*-2 to 4-*O* atom of the hydroxyl group of tautomeric form of pyrrolopyridazinone diminishes the analgesic activity.



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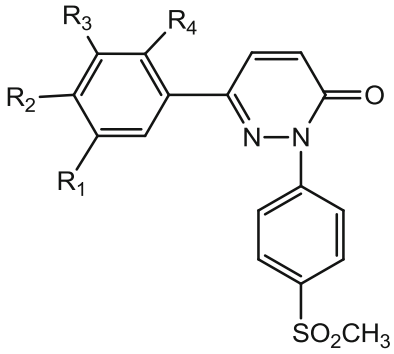
In one of the recent studies carried out by Syed *et al.*, some 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(*2H*)-one derivatives (**23**) were synthesized and evaluated in vivo for anti-inflammatory activity in carrageenan-induced rat paw edema, using etoricoxib as standard drug. The

compounds have shown mild-to-moderate anti-inflammatory activity. These compounds were also tested for their ulcerogenic potential and were found to be safe from the point of view of ulcer induction (Ovais *et al.*, 2013). The same group has also evaluated 6-aryl-2-(*p*-sulfamoylphenyl)-4,5-dihydropyridazin-3(*2H*)-ones for similar anti-inflammatory activity and their ulcerogenic potential, and this series was also found to be potent anti-inflammatory and low ulcer induction potential (Bashir *et al.*, 2012).

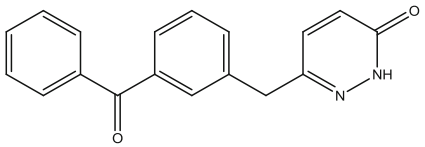


23

COX inhibitors

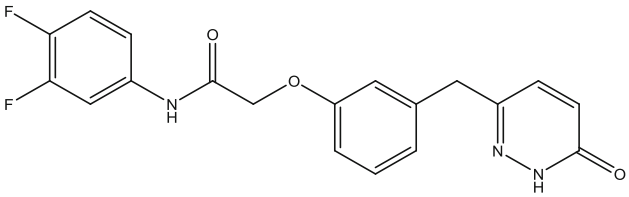
Cyclooxygenase (COX) is the key enzyme in the manifestation of inflammation and pain, and it catalyzes the conversion of arachidonic acid into prostaglandin H_2. NSAIDS (nonsteroid anti-inflammatory drugs) which are COX inhibitors are widely used in the treatment for pain and inflammation. The major side effects of these drugs are ulceration in gastrointestinal tract and hemorrhage (Allison *et al.*, 1992). The cyclooxygenase exists in two isoforms, COX-1 and COX-2. COX-2 is the enzyme which is activated in response to various pro-inflammatory stimuli (Kurumbail *et al.*, 1996). The major structural difference in the two isoforms of the enzyme lies in the active site where COX-1 contains isoleucine residue (Ile523) which is replaced by a valine residue in COX-2 (Val523). This difference in single amino acid accounts for the differences in the polarity, binding kinetics, and selectivity of the COX-2 inhibitors toward its isoenzyme (Bombardier, 2002). Thus, selective COX-2 inhibitors have been found to have lesser gastrointestinal side effects, and since COX-1 is not inhibited, its cytoprotective action helps in healing (Ferreira *et al.*, 1971; Murry and Brater, 1993; Dannhardt and Kiefer, 2001). In the last decade, many COX-2 inhibitors have reached the market (Penning *et al.*, 1997), few of them are rofecoxib (Talley *et al.*, 2000), celecoxib (Li *et al.*, 1996), valdecoxib (Friesen *et al.*, 1998), and etoricoxib (Li *et al.*, 2003).

In search of novel selective cyclooxygenase inhibitors, the compounds bearing pyridazinone moiety such as the syntex compound (**24**) RS-57067 (**25**) and benzylpyridazinone derivatives (**26**) (Biancalani *et al.*, 2006; Beswick *et al.*, 2004; Chintakunta *et al.*, 2002) have come into light. The various derivatives such as 3-*o*-substituted benzyl pyridazinone (Li *et al.*, 2003; Okcelik *et al.*, 2003), 4-phenyl, and 4-(2-chlorophenyl)-6-(5-chloro-2-oxo-3*H*-benzoxazol-7-yl)-3(*2H*)-pyridazinone (**27**) (Harris *et al.*, 2004) were also found to be selective cyclooxygenase inhibitors.



SYNTEX COMPOUND

24



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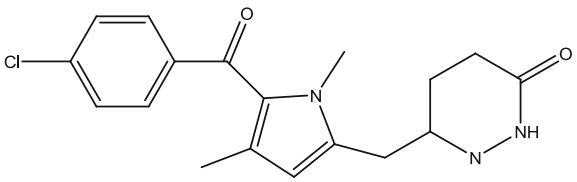
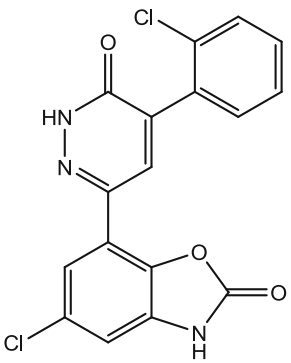


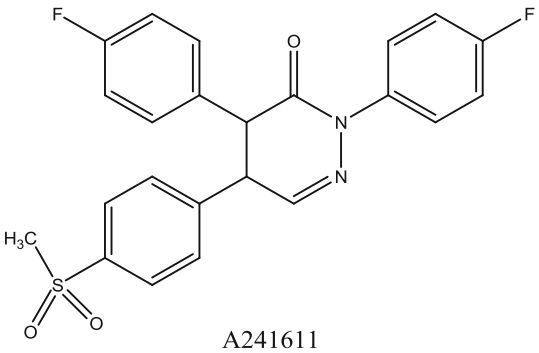
RS-57067

26



27

In 2004, Harris et al. reported vicinally disubstituted pyridazinones as potent and selective COX-2 inhibitors. The compound A-241611 (**28**) was discovered as an early lead from the series, and it showed both acute and chronic anti-inflammatory profiles in rat models. But this compound suffered from low aqueous solubility and hence lower rate of elimination. A further research in this field gave a 4-butoxy-substituted compound, A-282904 (**29**), which had good anti-inflammatory and analgesic potency as a COX-2 inhibitor in comparison with A-241611. But it still suffered from poor solubility. Synthesis of another derivative using additional alcohol to the terminal carbon of the alkoxy side chain gave a good compound ABT-963 (([2-(3,4-difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-*2H*-pyridazin-3-one], **30**). This compound was a selective and potent COX-2 inhibitor with a better solubility profile when compared with the other two previous compounds and even with established drugs celecoxib and rofecoxib. Because of its improved solubility, it had shown improved pharmacokinetic profile. ABT-963 reduced the prostaglandin E_2 levels after oral administration, which is responsible for its anti-inflammatory effect, and also reduced nociception in hyperalgesic models in dose-dependent manner. Its high selectivity toward COX-2 inhibitors showed its effectiveness as anti-inflammatory in arthritic models also.



A241611

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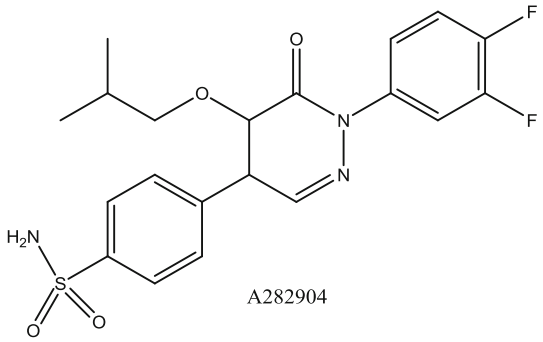

A282904

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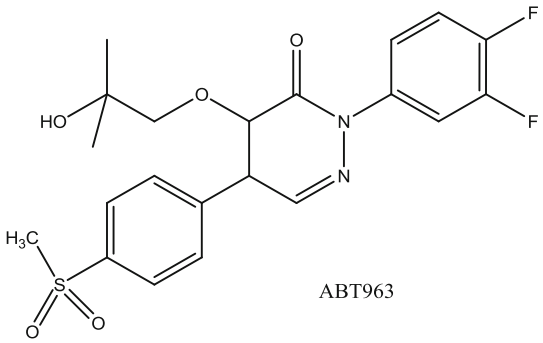
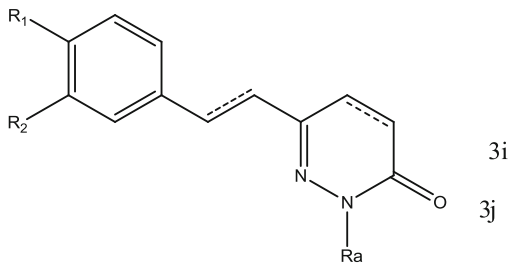


ABT963

30

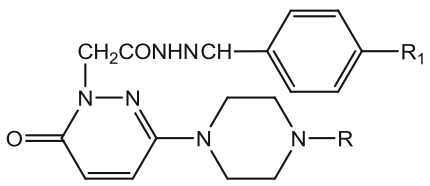
In one of the studies, a series of pyridazinone derivatives were synthesized by linking the aryl and biphenyl moieties at position 6 using two carbon spacer in between (**31**). Such compounds exhibited good anti-inflammatory activity along with better gastrointestinal protectivity. The results had shown that using ethyl spacer between two dihydropyridazinone ring and aryl moiety gave the compounds with higher activity when compared to the ethenyl analogs (Gokce *et al.*, 2001).



	R1	R2	Ra
3i	Ph	H	H
3j	-OCH2CH2O-		H

31

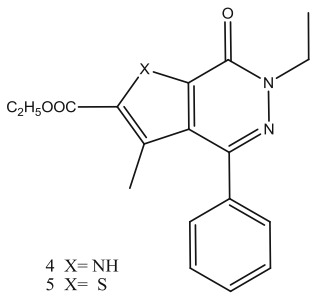
Some of the pyrazolone derivatives have been found to possess analgesic and anti-inflammatory activities such as dipyrone and phenylbutazone, but the side effects associated with them have limited their clinical usefulness. The 3(*2H*)-pyridazinone derivatives which are structurally related to pyrazolone have been widely reported in the literature as analgesic and anti-inflammatory compounds devoid of side effects (Gokce *et al.*, 2005; Dündar *et al.*, 2007; Sato *et al.*, 1981). One such compound is emofazone (**7**), it possess anti-nociceptive property which is neither mediated by prostaglandin nor through opiod receptors (Viaud *et al.*, 1995; Rohet *et al.*, 1996). A number of studies have confirmed that the attachment of aryl piperazinyl side chain to the lactam nitrogen in the pyridazinone ring lends the molecule analgesic activity (Giovannoni *et al.*, 2003; Rubat *et al.*, 1992; Piaz *et al.*, 2003; Santagati *et al.*, 1985a, b; Banoglu *et al.*, 2004). This analgesic potency can further be increased by inserting a spacer carbon chain between the lactam nitrogen and the amine moiety (Gökce *et al.*, 2009b). Keeping these points in mind, Gokce *et al.*, (2009a) designed and synthesized 6-(substituted-arylpiperazinyl)-3(*2H*)-pyridazinone derivatives bearing different substituents at position 2 in the pyridazinone ring. The compounds belonging to 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(*p*-substituted benzal)hydrazone derivatives (**32**) were evaluated for analgesic and anti-inflammatory activities using carrageenan-induced writhing and rat paw edema tests, respectively, taking phenylbenzoquinone as standard. They were also tested for their irritative and ulcerogenic potential on gastric mucosa. 6-[4-(3-Chlorophenyl)piperazine]-3(*2H*)-pyridazinone-2-acetyl-2-benzal hydrazone, 6-[4-(4-chlorophenyl)piperazine]-3(*2H*)-pyridazinone-2-acetyl-2-benzalhydrazone, and 6-[4-(pyridyl)piperazine]-3(*2H*)-pyridazinone-2-acetyl-2-benzal hydrazone derivatives were found to possess better analgesic–anti-inflammatory activity, and cytoprotective effect in comparison with the reference compound acetyl salicylic acid (Piaz *et al.*, 1998).



32

Asthma/COPD

The treatment regimen for chronic obstructive pulmonary disease (COPD) and asthma, although dependent on the severity of the diseases, mainly depends on corticosteroids and β2-agonists (Gaga *et al.*, 2007). In cases of mild-to-moderate asthma, a combination of inhalation corticosteroids and long-acting β2-agonist (LABA) is employed now days. However, corticosteroids when taken in high doses over a prolonged period of time can produce several severe side effects (US FDA Web site). Similarly, LABA has also been reported to possess certain potential adverse effects in their post-approval clinical trials from 2011 by US FDA (Chung, 2006). Thus, there is a dire need of some other category drug in the management of these respiratory diseases. Inhibitors for the phosphodiesterase (PDE) IV enzyme family have stolen a considerable interest as compounds with the mixed action having anti-inflammatory and bronchodilatory activities; they act by increasing the intracellular c-AMP levels and inducing smooth muscle relaxation (Torphy *et al.*, 1998). A good PDE IV inhibitor can be an appropriate substitute for β2-agonist and corticosteroids. Rolipram was one such compound but could not make it to the market because of low potency and side effects such as nausea, vomiting, and headache. Roflumilast (**35**) is another drug which has been approved by US FDA in 2011 and acts as selective, long-acting PDE IV inhibitor. Pyridazinones have also been developed as PDE IV inhibitors, particularly compounds such as syntex agents **24**, **33,** and **34** (Giembycz *et al.*, 2008).



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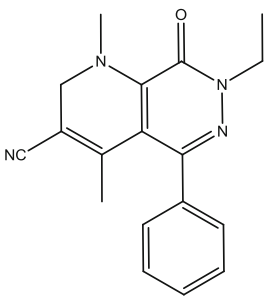

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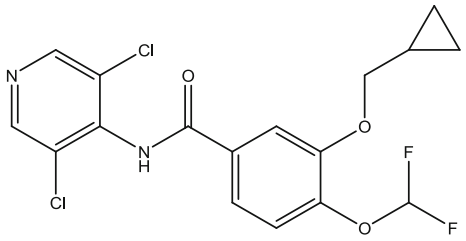
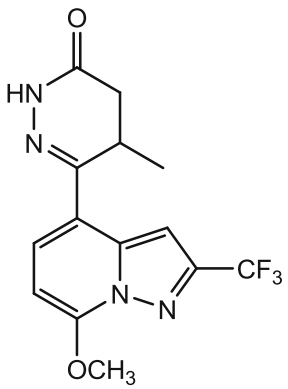


35

Another inhibitor in phosphodiesterase series is PDE III inhibitors, which have been found to be superior to PDE IV inhibitors in mediating the relaxation of airway passage (Ochiai *et al.*, 2011). Hence, either a combination of PDE III and IV inhibitors or dual inhibitors (PDE III/IV) offer a better therapeutic response in comparison with the individual selective agents.

Working on these lines, Ochiai et al. (2012) have synthesized (−)-6-[7-methoxy-2- (trifluoromethyl)pyrazolo[1,5-a]pyridin-4-yl]-5-methyl-4,5-dihydro-3(*2H*)-pyridazinone (KCA-1490, **36**) as a dual PDE III/IV inhibitor. This compound possessed anti-inflammatory and bronchodilatory activity and had an improved therapeutic window over the existing drug roflumilast (Bristol *et al.*, 1984). When the compounds in KCA-1490 series were studied for SAR, it was observed that 5-methyldihydropyridazinone subunit was essential for the PDE III inhibitory activity.

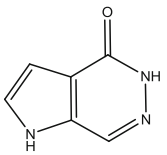


KCA1490

36

Anticancer activity

Pyrrole[2,3-*d*]pyridazine is one of the rarely reported moiety. Pyrrole[2,3-*d*]pyridazin-4-ones (**37**) (Marquet and Bisagni, 1968) have been reported in the literature as inhibitors of human cancer cell proliferation and pyrrole[2,3-*d*]pyridazin-7-ones (**38**) as carbohydrate-modified nucleosides which are active as antiviral and antiproliferative agents (Meade *et al.*, 1997). Another work has been reported by Murineddu et al. (2002) on 1-methyl-2-phenyl- and 1,3-dimethyl-2-phenyl-substituted pyrrole[2,3-*d*]pyridazinones as cytotoxic agents were tested in vitro at NCI in preclinical antitumor screening program against 60 human tumor cell lines. Significant activity was found for indenopyrrole[2,3-*d*]pyridazinone **39** (X=CH_2) and for benzo[g]pyridazin[4,5-b]indol-7-one, **40** (X=CH=CH).



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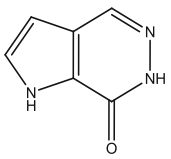

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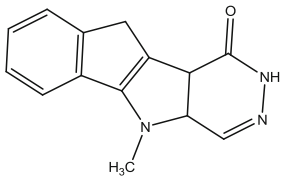

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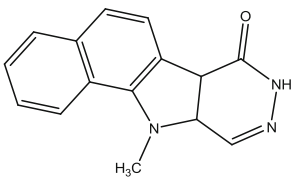
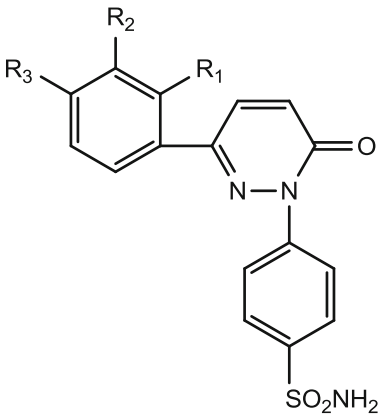


40

A new class of 6-aryl-2-(*p*-sulfamylphenyl)-pyridazin-3(*2H*)-ones (**41**) was designed and synthesized. They were tested against human cancer cell line. Of all the compounds evaluated, the compound bearing R1=R2=H and R3=C_2H_5 substitution was found to possess remarkable activity against non-small-cell lung and leukemia cell lines. In acute toxicity studies also, this compound has shown good intraperitoneal tolerance (Rathish *et al.*, 2012).

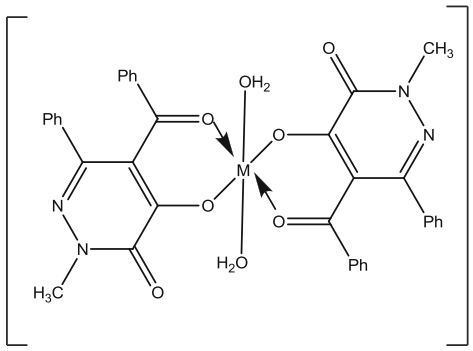


41

In another study, the antiproliferative potential of a series of 23 compounds bearing substituted aryl-pyridazin-3(*2H*)-one moiety was tested against 60 human cancer cell lines. One of the compounds bearing an ethyl substitution at position R2 in the ring displayed promising antiproliferative activity against 20 cell lines (Ovais *et al.*, 2013).

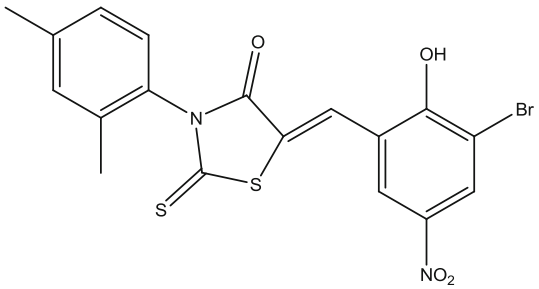
Antimicrobial activity

Various metal complexes of 5-benzoyl-4-hydroxy-2-methyl-6-phenyl-*2H*-pyridazin-3-one (**42**) were synthesized using Cd(II) and Ni(II) by Sonmez et al. These complexes have shown activity against gram-positive *S. aureus* and gram-negative *Pseudomonas putida* and two yeasts (*Candida albicans* and *C. tropicalis*). Sortase A (SrtA) is an enzyme which attaches the surface proteins in *S. aureus* to the cell wall. This enzyme helps in the transpeptidation process of the cell wall synthesis. Any molecule which inhibits this enzyme would hence be a powerful anti-infective agent as it would inhibit transpeptidation ultimately not allowing cell wall synthesis of the microorganism. In an attempt to identify SrtA inhibitors, high throughput screening of around 30,000 compounds was carried out, which lead to the identification of three molecules **43**–**45** that could be developed into anti-infective agents. The pyridazinone and pyrazolethione analogs were found to be significant in structure–activity relationship studies. These molecules showed better activity than the already existing synthetic or natural compounds and held good potential to be explored further (Sonmez *et al.*, 2006).



M(II) COMPLEX

42



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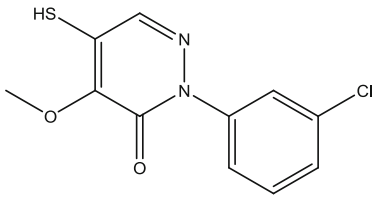

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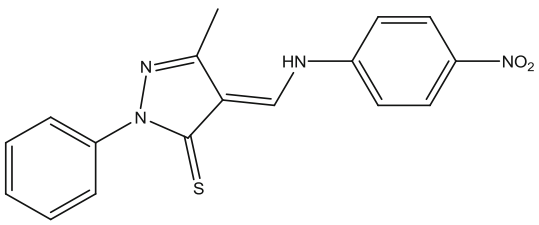
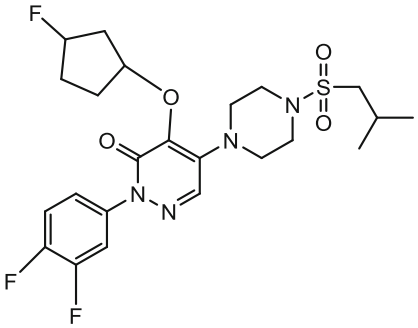


45

Antifungal agent

β-1,3-Glucan synthase (GS) is the target enzyme for the development of many antifungal agents. Echinocandins are a class of semisynthetic natural products that act as GS inhibitor but can only be given parenterally (Walker *et al.*, 2011). In an attempt to develop novel small molecules as antifungal agents, a class of piperazinyl–pyridazinones (**46**–**49**) was discovered as GS inhibitor. These classes of compounds have shown oral efficacy against *C. glabrata* infection in murine model and were found to be superior than echinocandins (Ton-That *et al.*, 2004).



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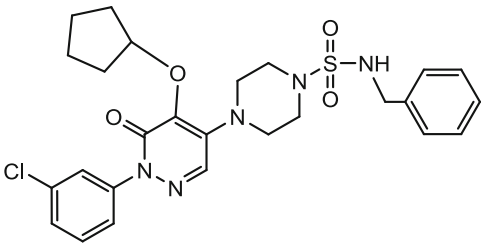

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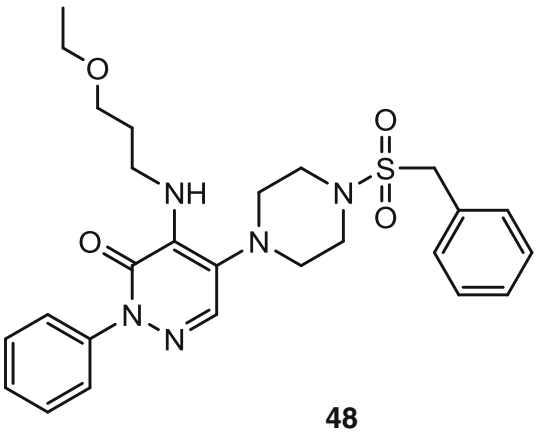

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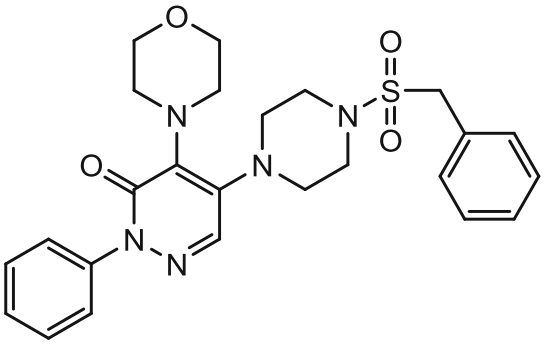
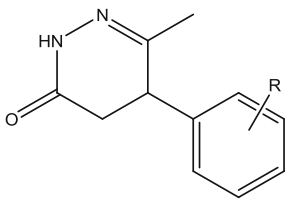


49

Antiplatelet activity

Formation of thrombus in the coronary artery is the primary cause for the development of angina, stroke, myocardial infarction, and peripheral artery disease (Sureea *et al.*, 2009). Owing to the better understanding of the role of platelets in vascular injuries, new approaches for the better and efficacious antiplatelet agents are coming into light. Aspirin, clopidogrel, ticlopidine, and sulfinpyrazole are among various therapeutic strategies developed to inhibit platelet function. A series of 5-aryl-6-methyl-4,5-dihydropyridazin-3(*2H*)ones (**50**) and related 5-aryl-6-methyl-pyridazin-3(*2H*)ones (**51**) were synthesized and evaluated for their pharmacological profile. Some of them displayed significant antithrombotic and antiulcer properties (Pinna *et al.*, 1988).



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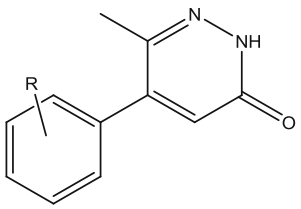
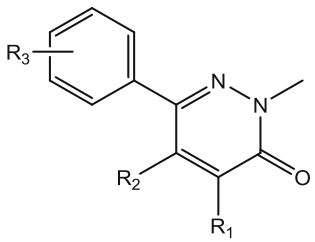


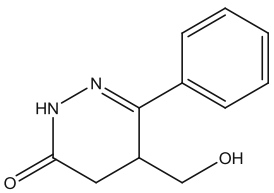
51

In late 90s, a lot of work can be found on pyridazinones acting as platelet aggregation inhibitors. A series of 4,5-functionalized-2-methyl-6-(substituted phenyl)-3(*2H*)-pyridazinones (**52**) were synthesized and evaluated as platelet aggregation inhibitors in human platelet-rich plasma. The compounds had shown good activity in sub-micromolar range (Fuster *et al.*, 1992).



52

In search of new antiplatelet agents in a series, 6-phenyl-3(*2H*)-pyridazinones were developed with a diverse range of substituent in the position 5. These compounds were evaluated for their potential to inhibit platelet aggregation. These modifications confirmed that the group at position 5 in 6-phenyl-3(*2H*)-pyridazinones system influences both variations in antiplatelet activity and mechanism of action (Coelho *et al.*, 2004). In another work, 6-phenyl-5-hydroxymethyl-4,5-dihydro-3(*2H*)-pyridazinone (**53**) and 6-thienyl-5-hydroxymethyl-4,5-dihydro-3(*2H*)-pyridazinones (**54**) were found to inhibit platelet aggregation induced by thrombin (IC_{50} = 0.25 and 0.26 mm, respectively) or by the calcium ionophore ionomycin (IC_{50} = 0.42 and 0.43 mm, respectively; Pinna *et al.*, 1988).



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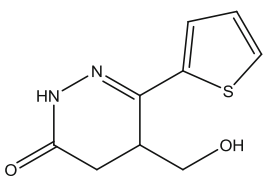
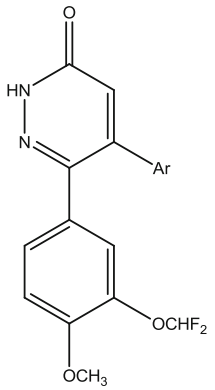


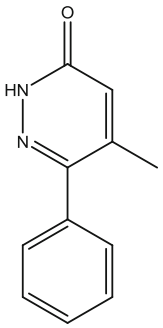
54

Glycoprotein (IIB/IIIA) receptor antagonist is a new class which has been identified as antiplatelet agents. Amrinone and milrinone (2(1H)-pyridones), zardaverine (**55**), and pimobendan (**5**) (3(*2H*)-pyridazinones) are clinically used PDE III inhibitors (**56**). A number of 6-aryl-3(*2H*)-pyridazinone derivatives substituted at position 5 have been synthesized, and their mechanism of action is found to be based on their capacity to inhibit calcium ion influx, which is required for the activation of platelet aggregation. The substitutions at position 5 greatly influence the potency of the molecule, like the presence of electron-withdrawing groups at position 5, e.g., CHO, COOME, and CH_2OCOCH_3 enhance the activity (Dal Piaz *et al.*, 1997).



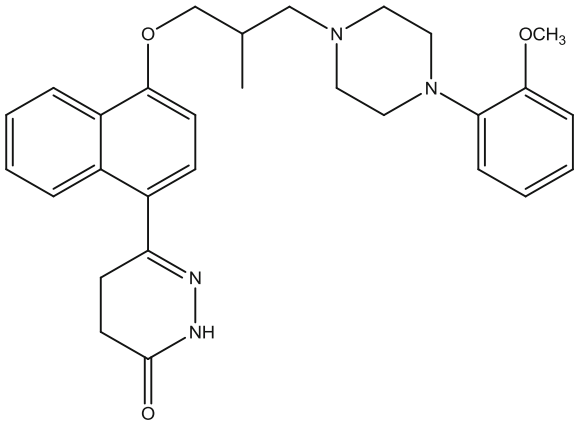
Zardaverine

55



56

Coelho et al. have prepared 5-substituted-6-phenyl-3(*2H*)-pyridazinones (**57**) and reported antiplatelet activity along with SAR. The compounds such as "**6c**" and "**6f**" were found to be particularly interesting (Schneider *et al.*, 1979). In a study conducted by Cherng et al., a new pyridazinone derivative PC-09 (**58**) was synthesized and found to be a good antiplatelet aggregating agent. Upon investigation, it was revealed that PC-09 has multiple modes of action, i.e., it causes inhibition of thromboxane A2 formation, reduction in mobilization of intracellular calcium, and platelet surface GPIIB/IIIA expression along with increasing cyclic AMP levels by inhibiting cyclic AMP phosphodiesterase (Cherng *et al.*, 2006).



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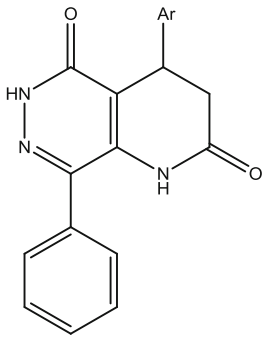
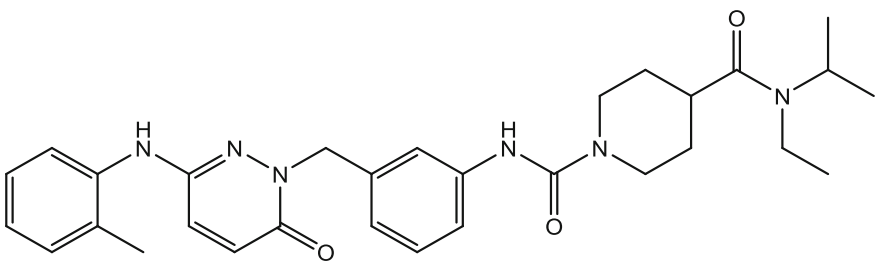


58

Antidiabetic

Benzenesulfonylurea substituted 15 novel pyridazinone derivatives "(**3a–o**)" were synthesized from their corresponding sulfonamides derivatives via novel carbamates. Their blood sugar lowering effect was evaluated using glucose tolerance test at the dose of 20 mg/kg (p.o.) Thirteen of these compounds have shown good decrease in blood sugar levels of the rat models (Rathish *et al.*, 1997).

pyridazinone by HTS as a novel acetylcholinesterase (AchE) inhibitor. By SAR development, compound **59** stood out as displaying high ache inhibitory activity and AchE/butyrylcholinesterase (BuchE) selectivity in vitro. Docking studies revealed that **59** might interact with the catalytic active site (CAS) and the peripheral anionic site (PAS) simultaneously. Based on this novel binding information, 6-*o*-tolylamino and *N*-ethyl-*N*-isopropylacetamide substituted piperidines were disclosed as new PAS and CAS binder (Xing *et al.*, 2013).



59

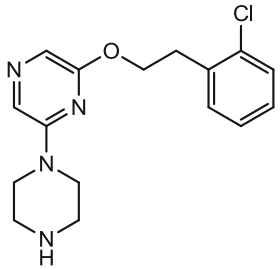
Acetylcholinesterase inhibitors

Alzheimer's disease (AD) is a complex neurodegenerative disorder of the central nervous system. Acetylcholinesterase (AchE), a serine protease, is responsible for acetylcholine hydrolysis. The hydrolysis of acetylcholine results in the termination of nerve impulses at the cholinergic synapses and neuromuscular junction. Among the various approaches for treating AD, inhibition of AchE is still prevailing in treating or alleviating the symptoms of AD. Xing et al. have identified 2,6-disubstituted

HT agonist

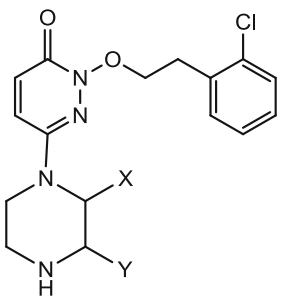
5-HT is instrumental in regulating mood, sleep, sexuality, and appetite. The 5-HT receptor subtype $5HT_{2c}$ is present in brain, and their agonists have potential for the treatment for sexual dysfunction, obesity, schizophrenia, and urinary incontinence. Certain pyridazinone derivatives were synthesized, and their SAR was established as $5HT_{2c}$ receptor agonist for urinary incontinence. The SAR was developed by using the known non-selective 5-HT_{2c} agonist meta-chlorophenyl piperidine (**60**). The compound **61** has shown

good in vivo efficacy in preclinical models of stress urinary incontinence (Charlotte *et al.*, 2009).



m-CPP

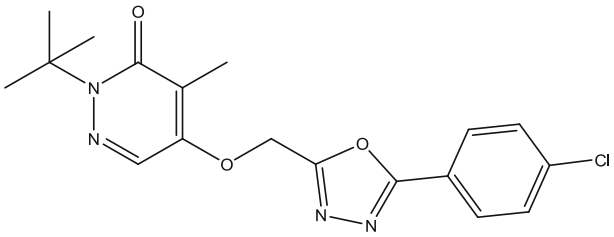
60



61

Antifeedant

Oxadiazolyl 3(*2H*)-pyridazinone (ODP, **62**) was developed and evaluated as antifeedant and compared with toosendanin, an insecticide extracted from the bark of *Melia toosendan*. The insect growth regulatory and antifeedant activity were checked on the larvae of the armyworm, Pseudaletia separata walker (Lepidoptera: Noctuidae). This compound was found to inhibit the activities of the enzymes such as trypsin, chymotrypsin, and alpha amylase in the fifth instar of the larvae (Cao *et al.*, 2003; Asif, 2013a, b).



62

Conclusion

Pyridazinone, although a simple basic nucleus, holds a lot of potential. With basic prior understanding of SAR, this moiety can be utilized effectively as a lead in many of known pharmacodynamic fields such as antihypertensives, COX inhibitors, antimicrobial, antitubercular, antidiabetic, antiplatelet, anticancer, antidepressant–anxiolytic, anticonvulsant, bronchodilatory, antifeedant, 5-HT agonists, and many other properties. A number of drugs in the market have pyridazinone nucleus/moiety in their structures such as indolidan, pimobendan, levosimendan, emorfazone, and zardaverine. The molecule has been studied well, and a good amount of SARs has been established for various series, but it still holds potential for further exploitation in various known and unknown fields.

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