Review Article

General study of pyridazine compounds against cyclooxygenase enzyme and their relation with analgesic, anti-inflammatory and anti-arthritic activities

Abstract

There is increased focus on developed non-steroidal anti-inflammatory drugs (NSAIDs) containing a pyridazine nucleus. The NSAIDs are one of the most commonly used medications worldwide to inhibit cyclooxygenase (COX-1 and COX-2) enzyme in varying extent by inhibiting prostaglandin (PGEs) synthesis for the treatment of pain, inflammation, arthritis and edema. Their routine and long-term use causes gastrointestinal (GIT) and renal toxicities. In order to minimize these side-effects, selective COX-2 inhibitors are prepared with an improved GIT and renal safety profile relative to other NSAIDs. The recent development toward the effective NSAIDs agents causes dual COX and lipooxygenase inhibitory effects because COX-2 inhibitors cause cardiovascular problems. The literature stimulated these above findings. Our attention has been focused on the series of pyridazine or other derivatives that were reported or will be reported in the future as anti-inflammatory, analgesic, anti-arthritic as well as anti-edemic agent.

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Introduction

Pyridazine and their Derivatives

During the past few decades, increasing interest in the synthesis and properties of pyridazines and pyridazinones has been observed. These show a wide spectrum of biological activities, as described in the literature. A substantial number of pyridazines and pyridazinones have been reported to possess antimicrobial, antitubercular, analgesic and anti-inflammatory, antipyretic, antifeedant, herbicidal, antiplatelet, anticancer, cardiovascular and neurological disorder and other anticipated biological and pharmacological activities.[1-7] In particular, a considerable number of substituted pyridazines and pyridazinones are well known as anti-inflammatory and analgesic agents associated with non-narcotic properties.[8-12]

In terms of this aspect, many studies have been focused on pyridazinones, which are characterized to possess good analgesic and anti-inflammatory, antiplatelete activities and also very low or nil nephrotoxicity and ulcerogenicity. In order to minimize these side-effects, there is increased focus on developing non-steroidal anti-inflammatory drugs (NSAIDs). Stimulated by these above findings, our attention has been focused on the series of pyridazine and pyridazinone derivatives that were reported as having antinociceptive and anti-inflammatory activities.

Non-Steroidal Anti-Inflammatory and Analgesic

The mostly NSAIDs mainly act peripherally by blocking the production of prostaglandins through inhibition of cyclooxygenase (COX) enzymes, i.e. COX-1 and COX-2, to varying extents. These drugs produce various side-effects, such as gastrointestinal (GIT) irritation or ulceration and suppression of renal function damage. The opioid agonists produce side-effects such as respiratory depression, constipation and physical dependence, as well as of the GIT problems. These GIT problems are due to inhibition of the constitutive COX-1, which is responsible for the production of prostaglandins, responsible for gastroprotection and vascular homeostasis. On the other hand, morphine-like

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opioid agonists also produce various side-effects such as respiratory depression, constipation and physical dependence as well as the GIT problems. In view of this fact, research has been directed in the recent years at designing compounds devoid of these side-effects. Moreover, some studies for developing selective COX-2 inhibitors, but not COX-1, because selective COX-2 inhibitors has confirmed the utility in the treatment of inflammatory pain with an improved GIT safety profile relative to other NSAIDs. They also reduced the edema. These selective COX-2 inhibitors may have utility in the treatment of the pain and inflammation associated with arthritis. The COX-2 enzyme is induced by mediators of inflammation, such as lipopolysaccharides, interlukin-1, rheumatoid synovial endothelial cells, monocytes and macrophages. Recent studies have indicated that COX-2 plays specific functions in reproduction, renal physiology, bone resorption and neurotransmission. Prostaglandins (PGs) such as PGE2 and PGI2 produced via the COX-2 pathway magnify the degree of inflammation initiated by other mediators of inflammation, such as histamine and bradykinin, leading to increased vascular permeability and edema. COX-2 is not detectable in normal tissue but is detectable after induction by inflammatory stimuli. Selective COX-2 inhibitors exhibit good anti-inflammatory and analgesic activities in various animal models.[13-17]

Traditional NSAIDs prescribed to control pain and treat inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) produce their anti-inflammatory and analgesic effects by non-selective (COX-1 and COX-2) inhibition of COX activity.

Thereafter, researchers focused their efforts on the design of selective COX-2 inhibitors in order to develop superior anti-inflammatory and analgesic agents with reduced adverse effects compared with traditional NSAIDs. On the basis of adverse cardiovascular effects and progress made in the development of novel anti-inflammatory agents, a significant reduction in GIT and cardiovascular adverse effects has been noticed. In the recent years, the inhibition of COX-2 enzyme for the treatment of inflammation and pain has been introduced as a novel therapeutic target with lipooxygenase (LOX) inhibitor.[14,17,18]

The objective of this review is to discuss the pyridazine and pyridazinone compounds having anti-inflammatory, analgesic, anti-RA and anti-OA agents having reduced GIT and cardiovascular adverse effects as PGs or COX inhibitor, selective COX-2 inhibitors and their COX-1/COX-2 selectivities. The recent rise and fall of selective COX-2 inhibitors has provided an enthralling evolution. Efforts to discover an ultimate magic moiety to treat inflammation continue to be an important drug design challenge. The selective COX-2 inhibitors exhibited cardiovascular adverse effects, and some recent developments targeted the design of effective anti-inflammatory, analgesic and arthritis agents with reduced or without side-effects.

PG Biosynthesis

PGs are produced via the COX pathway. PGs are the important physiological and pathological mediators implicated in a number of therapeutic areas, including inflammation, pain, pyrexia, cancer, glaucoma, male sexual dysfunction, osteoporosis, cardiovascular disease, labor and asthma. In the COX pathway, the two known COX isoforms catalyze the biosynthesis of PGs, thromboxanes (TxA) and other eicosanoids.[17-19]

COX and the GIT

It has been shown that COX-1 but not COX-2 is expressed constitutively throughout the GIT. PGs such as PGE2 and PGI2 produced by COX-1 are known to exhibit cytoprotective effects on the GIT mucosa by reducing gastric acid secretion by the parietal cells in the stomach, increase mucosal blood flow and stimulate the release of viscous mucus. Selective COX-2 inhibitors are efficient anti-inflammatory agents with less GIT toxicity due to their selective inhibition of COX-2 and sparing action on COX-1. It has also been reported that during the GIT ulcer formation process, COX-2 may be induced and that it could play a role in the GIT healing. Clinical trials indicate that short-term GIT safety benefits occur with selective COX-2 inhibitors compared with traditional NSAID therapy.[17-19]

Analgesic and Anti-inflammatory Action of Pyridazine Derivatives

Many researchers have been interested in pyridazinones for the development of potential analgesic and anti-inflammatory activities.[20-23] Among them, 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone) is marketed as pentoil and nandron in Japan as an analgesic and anti-inflammatory agent,[24] which was launched at the beginning of the last decade. Moreover, it has been reported that 4-amino-2-methyl-6-phenyl-5-vinyl-3(2H)-pyridazinone was seven-fold more potent than emorfazone. Later it was synthesized and the antinociceptive activities of 2-substituted-4,5-functionalized 6-phenyl-3(2H)-pyridazinones were evaluated, and it was observed that some were more potent than emorfazone.[25] 4,5-dihaloderivatives, the 5-arylidene and 4-carbamoylpyridazinones and a series of 3-oxo-5-benzylidene-6-methyl-(4H)-2-substitutedpyridazines[26] that have emerged in the recent past are of particular interest.

Additionally, 2-substituted 4,5-dihalo-3(2H)-pyridazinone derivatives have a high analgesic activity, with no ulcerogenic side-effects.[27] Subsequently, 6-phenyl-3(2H)-pyridazinone derivatives and 2-substituted 4,5-functionalized (amino and ethylene group) 6-phenyl-3(2H)-pyridazinone derivatives have also been reported to bear a potent analgesic activity

with negligible general side-effects.[26,28] In the meantime, 3-*O*-substituted benzyl pyridazinone derivatives were shown to exhibit an *in vitro* potent anti-inflammatory activity.[29] The structurally diverse amide derivatives of [6-(3,5-dimethyl-4-chloro-1-pyrazolyl)-3(2H)-pyridazinone] acetic acid are used as *in vivo* analgesic and anti-inflammatory compounds. In these compounds, the heterocyclic ring substitutions at position six, and the presence of the acetamide side chain that is linked to the lactam nitrogen of pyridazinone ring at position two of the pyridazinone ring improved the analgesic and anti-inflammatory activity along with nil or very low ulcerogenicity.[30] [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl] acetamide and propanamide derivatives and derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl] propanoic acids reported that these compounds showed a potential analgesic activity. Moreover, some studies for developing COX-2 inhibitors have concentrated on the pyridazine derivatives and found that neutralization of these NSAIDs by preparing pyridazine derivatives resulted in compounds that selectively inhibited COX-2 but not COX-1.[14]

Most 4,6-diphenyl-2-[3-(4-arylpiperazin-1-yl)propyl]-3(2H) -pyridazinone derivatives, inspired from tradazone, an antidepressant drug, were more potent than acetaminophen and noramidopyrine in a *p*-benzoquinone-induced writhing test. 6-(4-methoxyphenyl)-3(2H)-pyridazinone derivatives carrying acetamide and propanamide moieties at position two of the pyridazinone ring and 1-[3-[6-(4-methoxyphenyl)-3(2H)-pyridazinon-2-yl] propanoyl]-4-(4-fluorophenyl) piperazine had a significant analgesic activity. 6-substituted-3(2H)-pyridazinones, 6-[4-(4-fluorophenyl)]piperazine-3(2H)- pyridazinone, with a derivative activity is an analgesic agent. 4,6-diphenyl-3(2H)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonylalkyl moieties on the nitrogen atom in position two of the pyridazinone ring was investigated as an analgesic and anti-inflammatory.[14,31]

Some novel heterocyclic-fused pyridazinones that inhibit Phosphodiesterase-4 (PDE4) are effective anti-inflammatory agents, although some adverse effects are observed.[29] These effects have forced researchers to find new PDE4 inhibitors with less-adverse effects. The 5-methyl-6-p.cyanophenyl-4,5-dihydro-3(2H)-pyridazinone corresponding to a 4,4a-dihydro-5H-indeno[1,2-c]-3-pyridazinonic structure (II), as well as other members having structure (II), exhibited anti-inflammatory properties.[32]. The study of some new 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal) hydrazone derivatives exhibited more potent activities than the standard drugs aspirin and indimethacin for analgesic and anti-inflammatory activities, respectively. None of the compounds showed a gastric ulcerogenic effect compared with the reference NSAIDs.[33] A series of structurally diverse amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl] propanoic acids [Figure 1] was found to have an approximately equipotent analgesic activity to aspirin.[14]

A series of structurally diverse amide derivatives of [6-(3,5-dimethyl-4-chloro-pyrazole-1-yl)-3(2H)-pyridazinone-2-yl]acetic acid [Figure 2] showed analgesic and anti-inflammatory activities, although some compounds were found to be equipotent to aspirin and indometacin.[31]

Some novel compounds of 2-(4-substituted piperazin-l-ylmethyl)-6-(thien-2-yl)-2H-pyridazin-3-ones, 2-(4-substituted piperazin-l-ylcarbonylmethyl)-6-(thien-2-yl)-2H-pyridazin-3-ones, 2-[2-(4-substituted piperazin-l-ylcarbonylethyl)]-6-(thien-2-yl)-2H-pyridazin-3-ones, 3-(4-substituted piperazin-l-ylcarbonyl methyl thio)-6-(thien-2-yl) pyridazines, 3-[2-(4-substitutedpiperazin-l-ylcarbonylethylthio]-6-(thien-2-yl)pyridazines and 5-(4-substituted piperazin-l-ylmethyl)-6-(thien-2-yl)-

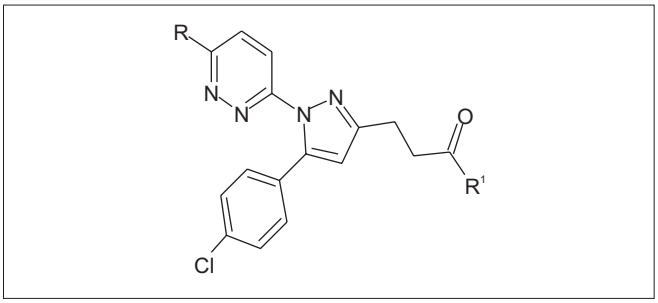

Figure 1: R=Cl, R^1=Amino phenyl derivatives, piprazine derivatives, amino alkyl derivatives

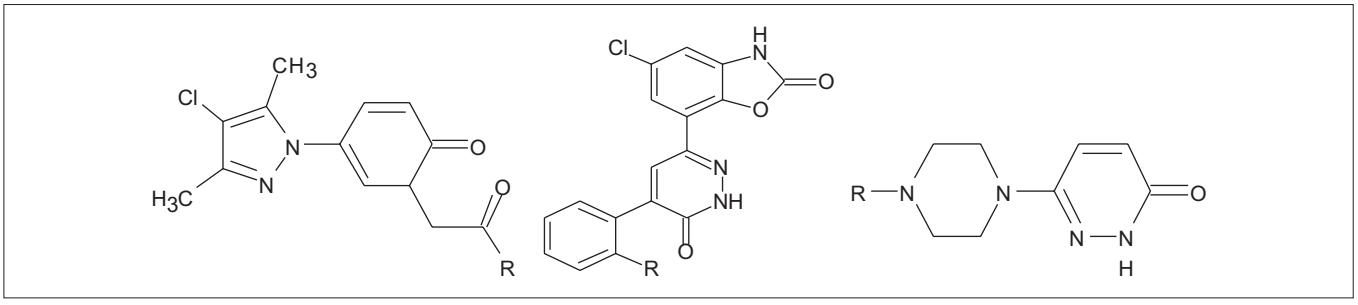

Figure 2: R=Derivatives of phenyl piprazine, pyridinyl piprazine, amino alkyl, amino ethyl benzene and amino pyridine

2H- pyridazin- 3-ones series showed significant anti-inflammatory activity [Figure 3].[16]

Some 3 - oxo -5-benzylidene - 6 - methyl - (4H) - 2 - substituted pyridazines were shown to exert anti-inflammatory and antinociceptive effects.[27]

A new series of 2-(6-oxo-3,5-diphenyl-6H-pyridazin-1-yl)-acetamides and 3-[6-oxo-3,5-diphenyl-6Hpyridazin-1-yl)-propanamides [Figure 4] were more potent than aspirin at a 100 mg/kg dose, and had a good anti-inflammatory activity with less ulcerogenic side-effects.[14]

A variety of 6-phenyl/(4-methylphenyl)-3(2H)-pyridazinon-2-propionamide were shown to possess analgesic and anti-inflammatory activities. 6-Phenyl-3(2H)-pyridazinon-2-yl-[4-(4-fluorophenyl) piperazinyl] propanamide was the most active agent among these compounds. Acetylsalicylic acid and indometacin were used as reference drugs. None of the compounds showed a gastric ulcerogenic effect compared with the reference NSAIDs.[33]

Recent studies have shown that the pyridazinone ring can serve as an excellent core template for designing selective COX-2 inhibitors. Structure–activity relationship studies employing pyridazinones have shown that *N*-substitution is a requirement for COX-2 selectivity, as exemplified. In the *N*-benzyl series, the isopropoxy compound showed excellent *in vitro* selective COX-2 inhibition and *in vivo* activity.[17]

A number of pyridazinone derivatives bearing an arylpiperazinyl alkyl chain series were most interesting and potent, a value about three- to four-fold higher with respect to morphine.[34]

Vicinally disubstituted pyridazinones as potent and selective COX-2 inhibitors [Figure 5], ABT-963 (2-(3,4-Difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methane sulfonyl-phenyl)-H-pyridazin-3-one), [Figure 5] have excellent selectivity (ratio of 276, COX-2/COX-1) in human whole blood, improved aqueous solubility as compared with celecoxib and rofecoxib, high oral anti-inflammatory potency *in vivo* and gastric safety in the animal studies. ABT-963 reduced PGE2 production and reduced the edema. ABT-963 has utility in the treatment of the pain and inflammation associated with arthritis.[20]

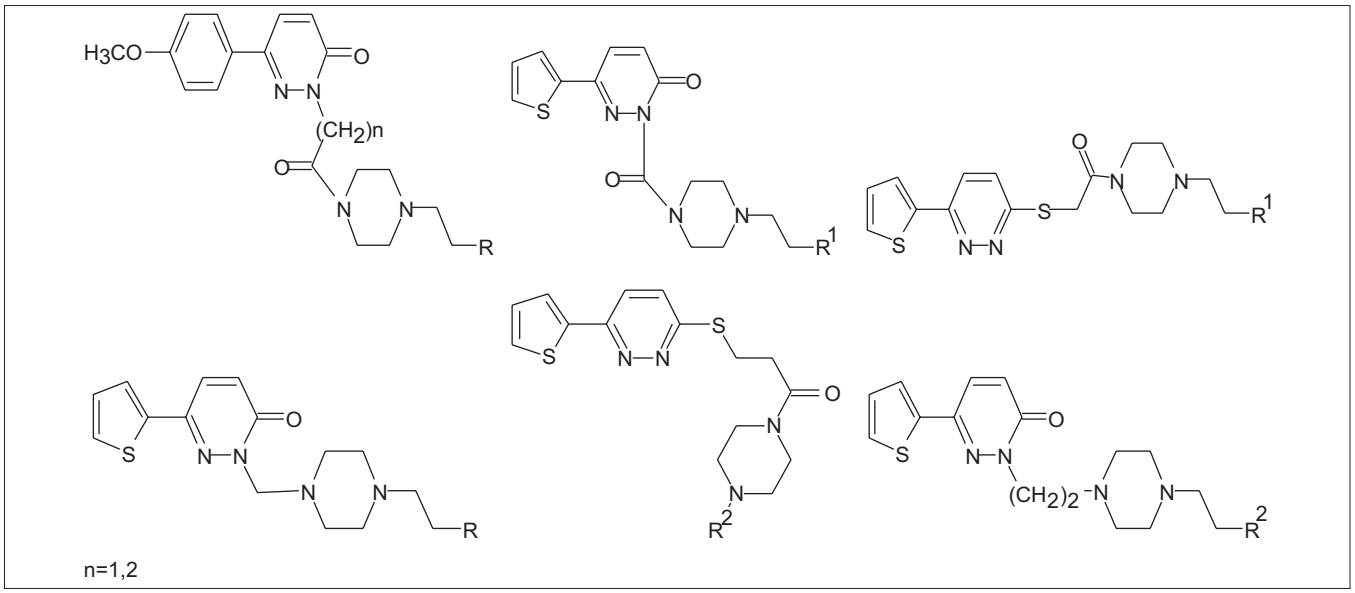

Figure 3: R=CH_3, C_2H_5, C_6H_5, $CH_2C_6H_4$, p-FC_6H_4, 2-pyridyl; R^1=4-F-CH_3, 2-pyridyl, C_2H_5; R^2=$CH_2C_6H_4$, C_6H_5

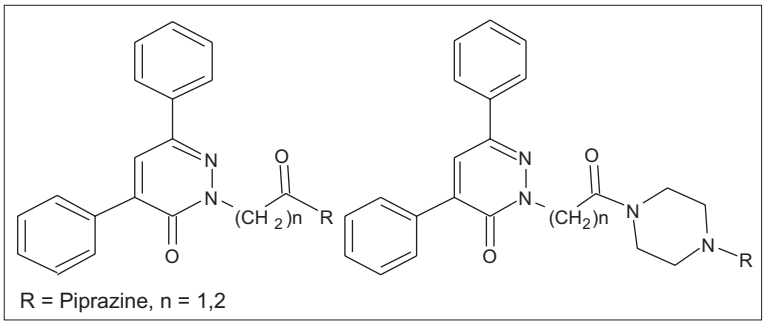

Figure 4: 4,6-diphenyl-3(2H)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonylalkyl moieties

Among the various pyridazinone derivatives, emorfazone as an analgesic and anti-inflammatory drug was without any ulcerogenic side-effects. Moreover, it has been reported that some other pyridazine derivatives were more effective than emorfazone, such as 4-amino-2-methyl-6-phenyl-5-vinyl-3(2H)-pyridazinone (seven-fold more potent than emorfazone) and 2-substituted 4,5-dihalo-3(2H)-pyridazinone derivatives, with a high analgesic activity and with no ulcerogenic side-effects.[29]

In analgesic and anti-inflammatory compounds, replacement of $CH=CH_2$ by CH_2CH_3, $CH(OH)CH_3$, $CH(OC_2H_5)CH_3$, $COCH_3$, $COOCH_3$ or CN (BB3) enhanced the pain threshold [Figure 6].[26]

In place of methyl group- higher alkyls, aryls, aralkyls functions, in place of amino grp NH-alkyls, NH-Ar, NH-CH2-Ar, N(Alkyl)2, NH-Ac inhibit the action by O-alkyl, O-Ar. Phenyl is replaced by methyl. Methyl is replaced by (CH2)n- CH_3 But, CH_2-CH_3 has optimum activity [Figure 7].[35]

Discussion

NSAIDs are used in treating various inflammatory conditions such as RA and OA. The most currently used NSAIDs drugs mainly act peripherally by blocking the production of PGs through inhibition of enzyme PGs or COX-1 and COX-2 enzymes to varying extents for the treatment of pain and inflammation. Their routine and long-term use causes GIT irritation and suppression of renal function. The new approaches for developing new compounds with fewer side-effects resulted in developing compounds that are effective inhibitors of COX-2 as well as the 5-LOX enzyme. Further studies conclusively demonstrated that selective COX-2 inhibitors may tip the natural balance between prothrombotic TxA2 and antithrombotic PGI2, potentially increasing the possibility of a thrombotic cardiovascular event. Recent studies have indicated that COX-2 plays specific functions in reproduction, renal physiology, bone resorption and neurotransmission. PGs such as PGE2 and PGI2 produced via the COX-2 pathway magnify the degree of inflammation initiated by other mediators of inflammation, such as histamine and bradykinin, leading to increased vascular permeability and edema. Selective COX-2 inhibitors exhibit good anti-inflammatory and analgesic activities in various animal models. Various pyridazine derivatives showed selective and non-selective NSAID activity with different substituted structures.[37-44] The development of NSAIDs encompasses the major chemical classes of selective COX-2 as well as LOX inhibitors. The recent advances lead to the development of effective anti-inflammatory and analgesic agents such as dual-COX/LOX inhibitor therapy.[14,20,26]

Conclusion

The rapid discovery of selective COX-2 inhibitors can be attributed to the rational drug design approach. However, the cardiovascular side-effects associated with selective COX-2 inhibitors highlights the pitfalls that may be encountered in the drug discovery paradigm. COX/LOX inhibitor therapies represent novel approaches directed toward the development of effective anti-inflammatory therapy. A great deal of progress has been made toward developing

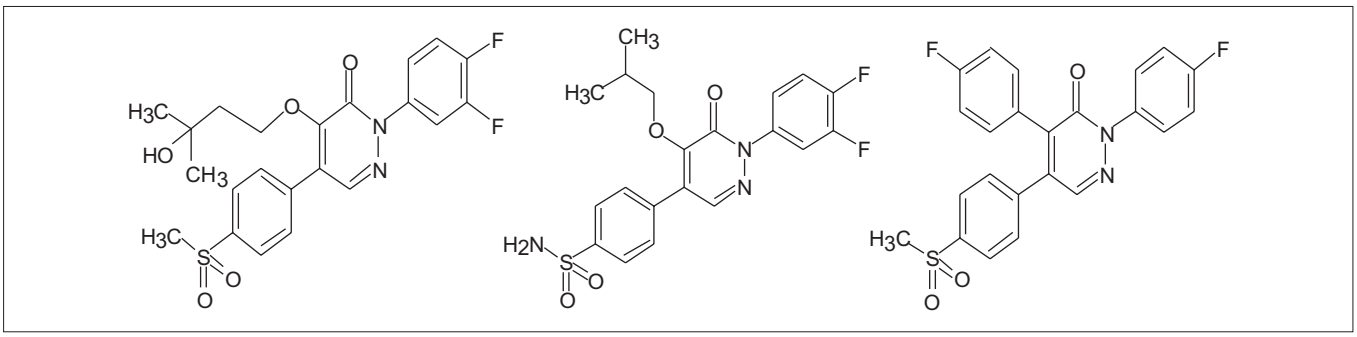

Figure 5: (ABT-963) (A-282904) (A-241611)

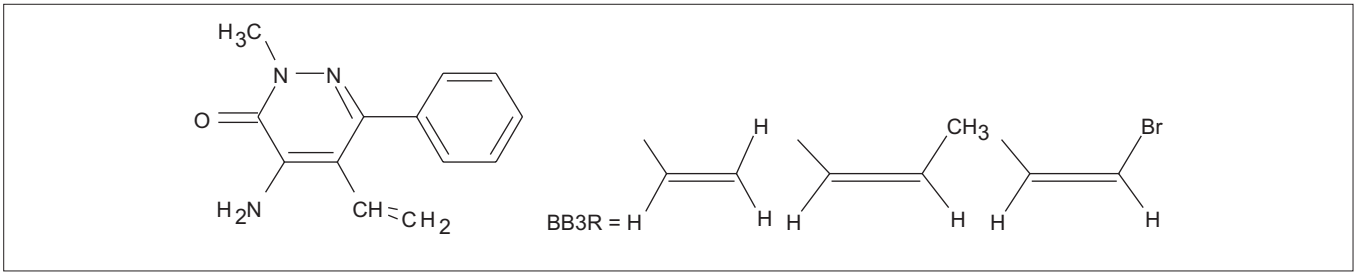

Figure 6: BB3

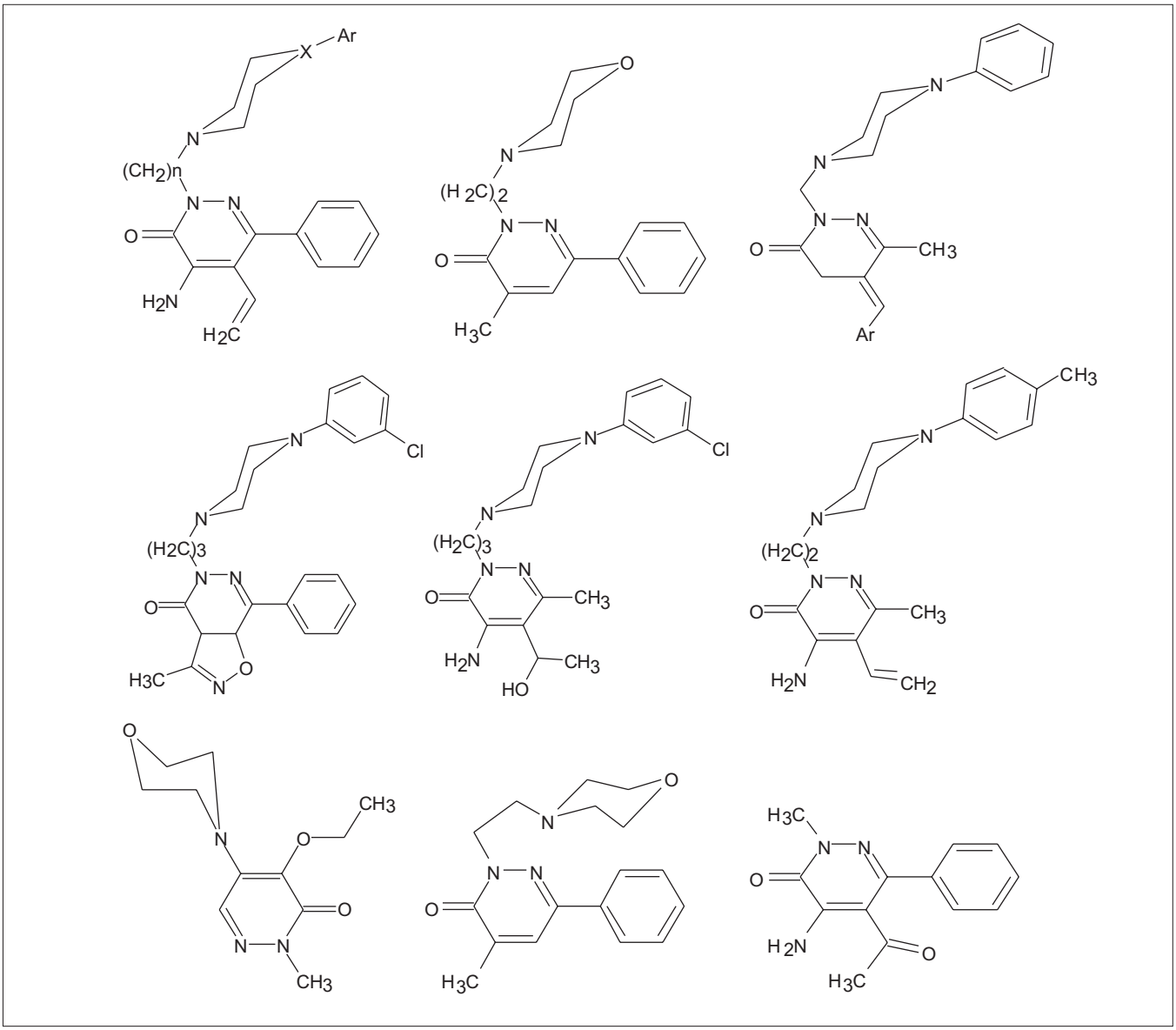

Figure 7: BB3 AG 246, FR8 FR10 CM8, Emorfazone AG 246 CF8[26,35,36] reported some pyridazine-containing structures with analgesic and anti-inflammatory effects

novel anti-inflammatory and analgesic agents that contain pyridazine moieties. In spite of the tremendous advances in the last decade, the design and development of a safe, effective and economical therapy for treating inflammatory and analgesic conditions still presents a major challenge.

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