A Review on Analgesic and Anti-Inflammatory Activities of Various Piperazinyl Containing Pyridazine Derivatives

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ABSTRACT

Most currently used nonsteroidal anti-inflammatory drugs (NSAIDs) have some restrictions for therapeutic use since they may cause gastrointestinal and renal side effects that are undividable from their pharmacological activities. In this review various piperazinyl containing pyridazine derivatives were studied for their analgesic and anti-inflammatory activities and their side effects. Synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemistry.

KEYWORDS

Pyridazine; Analgesic; Anti-inflammatory; Piperazinylpyridazines

Introduction

Although various nonsteroidal anti-inflammatory drugs (NSAIDs) are available for the treatment of pain, their chronic use for treatment of pain associated with inflammation limits their therapeutic use as they may cause gastrointestinal (GIT) and renal side effects [1]. Nowadays pain therapy focuses on improved non-steroidal analgesics that are effective as an analgesic but devoid of the side effects of traditional NSAIDs. The dual inhibition of COX and 5-lipoxygenase enzymes has been used for treatment of inflammation and pain, introduced as a novel therapeutic target. One of the examples of dual acting analgesic and anti-inflammatory molecules was tepoxalin (figure 1), is a diarylpyrazole derivative [2]. Many studies have focused on pyridazine derivatives for developing potent and safer NSAIDs without the gastric side effects [3-5].
Fig. 1. Structure of Tepoxalin

Among these compounds, 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyrazinone (emorfazone) is being marketed as an analgesic and anti-inflammatory drug [6].

The [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetamide and propanamide derivatives have revealed some analgesic activity [7,8]. The NSAIDs are useful for the treatment of inflammation, pain, and fever. The clinical effects of NSAIDs are based on the inhibition of cyclooxygenase (COX) enzymes, catalyzing the rate-limiting step in the metabolism arachidonic acid (AA) to prostaglandin H2 (PGH2). The PGH2 is further metabolized to prostanoids, PGs and thromboxane-A2 (TxA2). Various physiological effects of PGs include inflammatory reactions, blood pressure (BP) change, platelet aggregation, induction of labour and increasing pain and fever. Effectiveness of NSAIDs in the therapy of inflammation and pain is often limited by GIT side effects including, ulceration and bleeding [9-14]. Developing safer NSAIDs with no side effects has been the goal of many researchers. Antipyrine was the first pyrazolin-5-ones used as an analgesic and antipyretic and anti-inflammatory drugs. Bioactive antipyrene derivatives have been tested as potent anti-inflammatory, analgesic, antipyretic, and antimicrobial activities [15-17]. Pyridazinone derivatives possess diverse biological properties as anti-inflammatory, analgesic, antimicrobial and antiviral activities have been attracting widespread attention. In designing new bioactive drugs, besides the design and development of new drugs, there is another approach involved in the synthesis of hybrid molecules. Combination of various pharmacophores with different mode of actions in the same structure may lead to drugs having more efficiency in pharmacological activity [18]. Diverse biological properties of the compounds containing antipyrine and pyridazinone ring have prompted to design and synthesize the hybrid compounds which incorporating two scaffolds in a single molecule. To identify new molecules that may be of value in designing potent, selective and less toxic analgesic and anti-inflammatory drugs. Preparing new antipyrene derivatives contain pyridazinone moiety as hybrid molecules with analgesic and anti-inflammatory activities were also tested for the irritative and ulcerogenic effects on the gastric mucosa. Various compounds with a pyridazinone ring have been prepared for their pharmacological activities [19]. Various pyridazinone derivatives bear analgesic activity, among these compounds, emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2H)-pyrazinone) is an NSAIDs, marketed as pentoil and nandron [20,21]. Most 4,6-diphenyl-2-[3-(4-arylpiperazin-1-yl)propyl]-3(2H)-pyridazinone derivatives were prepared by inspiration from Trazodone (an antidepressant drug), were more potent than acetaminophen and noramidopyrine in a p-benzoquinone-induced writhing test [22]. The 2-substituted-4,5-dihalo-3(2H)-pyridazinones had high analgesic activity. The 6-(4-methoxyphenyl)-3(2H)-pyridazinones carrying acetamide and propanamide moiety at position 2 of the pyridazinone ring and 1-[3-[6-(4-methoxyphenyl)-3(2H)-pyridazinon-2-yl]propanoyl]-4-(4-fluorophenyl)piperazine had the significant analgesic activity [23]. The 6-substituted-3(2H)-pyridazinones reported that the
6-[4-{4-fluorophenyl}]piperazine-3(2H)-pyridazinones were showed the efficient analgesic activity [24]. The 4,6-diphenyl-3(2H)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonylalkyl moieties on the nitrogen atom in the 2-position of the pyridazinone ring were exhibited analgesic and anti-inflammatory activity. Cyclooxygenases (Cox-1 and Cox-2) catalyze the prostaglandin (PG) formation and they are the major targets of NSAIDs [25]. Inhibition of PGs by NSAIDs reduces inflammation, pain and fever. However, these drugs have serious side effects including, GIT and kidney damage [26].

The aim of this study is to develop new NSAIDs with no side effects. Many researchers have studied the effect of substitution of selected aromatic rings in current NSAIDs with alternative hetero aromatic rings. Various 2-benzoxazolinones and 2-benzothiazolinones were showed significant analgesic activity [27]. A common feature of some compounds is that the lactam nitrogen is substituted by a piperazinyl alkyl moiety [28] such as Tiaramide (1) which has strong anti-inflammatory activity with mild side effects and 2H-pyridazin-3-ones for developing potent and safer NSAIDs without gastric side effects [29].

Pyridazinones bearing an aryl-piperazine moiety at the side chain on the lactam nitrogen of the ring have significant analgesic effect [30-32]. They were also exhibited significant analgesic activity if they bear a carbon chain between the lactam nitrogen and the amine component of the side chain. The [6-(4-methoxyphenyl)-3(2H) pyridazinon-2-yl]acetamide 2a and propionamide 2b have showed potential analgesic activity [33]. The 6-piperaziny1-3(2H)-pyridazinones exhibited high analgesic and anti-inflammatory activities [34]. The incorporation of a thieryl ring as a bioisostere of the aryl ring with

Fig. 2. Structure of Tiaramide and amide derivative of pyridazinone.

the pyridazinone ring, a substituted piperazinyl moiety was linked at either position 2 (lactam nitrogen)-through a methyl, acetyl or propionyl spacer -or at position 5, through a methyl linkage. The 3-Substituted piperazinyl acetyl and propionylpyridazines exhibited some anti-inflammatory activity.

Anti-Inflammatory and Analgesic Activities of PiperazinylPyridazineDerivatives

A series of 2-(4-substituted piperazin-l-ylmethyl)-6-(thien-2-yl)-2H-pyridazin-3-ones (3a-f), 2-(4-substituted piperazin-l-ylcarbonylmethyl)-6-(thien-2-yl)-2H-pyridazin-3-ones (4a-c), 2-[2-(4-substituted piperazin-l-ylcarbonylthioyl]-6-(thien-2-yl)-2H-pyridazin-3-ones (5a,b), 3-(4-substituted pipera-zin-l-ylcarbonylmethylthio)-6-(thien-2-yl)pyridazines (6a-c) and 3-[2-(4-substituted piperazin-l-yl-methyl)-6-(thien-2-yl)-2H-pyridazin-3-ones (8a,b) were exhibited anti-inflammatory activity [35].
Fig. 3. Structure of various piperazine and thiophene containing pyridazine derivatives having anti-inflammatory and analgesic activities.

Table 1. Piprazine containing pyridazine derivatives.

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<td>3a</td>
<td>C₆H₅</td>
<td>3b</td>
<td>2-F-C₆H₄</td>
<td>3c</td>
<td>CH₂C₆H₄</td>
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<tr>
<td>3d</td>
<td>2-pyridyl</td>
<td>3e</td>
<td>CH₃</td>
<td>3f</td>
<td>C₂H₅</td>
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<td>4a,6a</td>
<td>4-F-CH₃</td>
<td>4b,6b</td>
<td>2-pyridyl</td>
<td>4c,6c</td>
<td>C₂H₅</td>
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<tr>
<td>5a,7a</td>
<td>CH₂-C₆H₄</td>
<td>5b,7b</td>
<td>C₆H₅</td>
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These compounds had strong antiinflammatory activity compared to about 50% seen with the indomethacin. Compound 3b with a piperazinyl methyl group linked to the lactam nitrogen showed a low anti-inflammatory effect. Compound 4c to be the man exception as it caused no reduction in edema. In compound 7b, phenyl piperazine is linked to pyridazine by a propionyl link was showed superior anti-inflammatory effect than indomethacin.
Compound 5b with a propionyl moiety attached to the lactam nitrogen exhibited less potent than its S-analogue, 7b. The propionamides 7b and 5b were found to be more potent than the acetamide derivatives 6c and 4c[33,35]. These compounds have been illustrated by a piperazinyl methyl moiety at the 5-position of the pyridazin-3-one. The 6-thien-2-yl pyridazine derivatives represent a highly promising group for the development of anti-inflammatory drugs. A series of 2-(6-oxo-3,5-diphenyl-6H-pyridazin-1-yl)-acetamides (8a-g) and 3-(6-oxo-3,5-di-phenyl-6Hpyridazin-1-yl)-propanamides (9a-g) were exhibited analgesic and anti-inflammatory activities. All compounds except for 8g were more potent than aspirin in a p-benzoquinone–induced writhing test at 100 mg/kg dose. Compounds 8b, 8c and 8e had the highest anti-inflammatory activity, and compound 8e showed the highest analgesic and anti-inflammatory activities with no ulcerogenic side effects [36].

Fig. 4. Structure of various piperazine and diphenyl containing pyrazine derivatives having anti-inflammatory and analgesic activities.

Table 2. Piprazine amide containing pyridazine derivatives.

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<td>8f</td>
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Analgesic activity of the compounds was assessed using a p-benzoquinone (PBQ)-induced writhing test. All compounds showed significant analgesic activity at 100 mg/kg dose level (55.6 to 82.7%). All compounds except for 8g were more potent than aspirin. Four compounds (8a, 8c, 8e and 9f) exhibited more than 80% analgesic activity. Compound 8e was the most potent analgesic and anti-inflammatory activity with no ulcerogenic side effects. The significant analgesic activity was also seen at the 50 mg/kg dose level in lesser degrees (15.9-50.2%). Compounds 8f, 8g, 9f and 9g depicted an ulcerogenic effect even at a half dose. The inhibitory effects of agents are attributable to inhibition of the release of chemical mediators such as histamine and serotonin. The second stage of the Hind paw edema may be related to arachidonic acid (AA) metabolites as it is inhibited by aspirin and other arachidonateCOX inhibitors [37]. Pyridazinonederivatives bearing acetamide moieties (8a-8g) were showed potent anti-inflammatory activity, but compounds 8b, 8c and 8e had the most potent anti-inflammatory activity. None of these compounds showed ulcerogenic side effects. There is no difference in terms of the NSAIDs activity in the acetamide and propanamide derivatives. However the more active compounds in terms of anti-inflammatory activity were found in acetamides. Substitutions on the phenyl ring of the phenylpipazinemoiety by o- or p-fluoro groups or a 2-pyridyl group increased NSAIDs activity of acetamide derivatives markedly.

Fig. 5. Structure of various piperazine and pyrazolone containing pyridazine derivatives having anti-inflammatory and analgesic activities.

Table 3. Structure of phenyl)-3(2H)-pyridazinone-2-ylacetamide and propionamides.

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<td></td>
<td>10c</td>
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As for the ulcerogenic effects, compounds 8g and 9g caused severe damage to the GIT mucosa at 100mg/kg dose. Compounds 8b, 8c and 8e possessing the highest anti-inflammatory activity, were safe in terms of ulcerogenic effects. Compounds possessing inhibitory activity higher than 70% in the PBQ-induced writhing test were studied. Some antipyrine/pyridazinone hybrids, 6-(4-substituted phenyl)-3(2H)-pyridazinone-2-ylacetamide and propionamides (10a-g) were exhibited vivo analgesic and anti-inflammatory activities. The compounds 10a, 10c, and 10d were equally or more potent analgesic and anti-inflammatory agents than aspirin and indomethacin, respectively. Most of the compounds were found to be non-ulcerogenic [38].

Analgesic activities of the compounds (10a-g) were tested by p-benzoquinone-induced writhing test in mice and sufficiently sensitive to detect the effect of analgesics that are less active than aspirin. The compounds withphenylpiperazine10a and 4-(2,3-dimethylphenyl)piperazine10d at the 6 position of the pyridazine ring revealed analgesic activities higher than aspirin. Compounds 10c, 10e, and 10g were approximately equipotent to aspirin at the same dose of 100 mg/kg. Analgesic activities of derivatives 10a-g seem to be sensitive to electronic effects of the substituent at the sixth position of the pyridazine ring. While the substituted piperazine or piperidine derivatives showed potent analgesic activities (except 10f), the derivatives possessing phenyl or methylphenyl groups have diminished analgesic activities [38].

Amide derivatives of well-known NSAID drugs with free carboxylic acid for developing new NSAIDs with reduced side effects showed good analgesic and anti-inflammatory activity [39,40]. To achieve the hybrid molecules, pyridazinone was linked to the antipyrine through an acetylenic or propionic amide bond. The acetamides have been found more potent than propionamides. The 4-fluorophenylpiperazine and benzylpiperidine derivatives, compounds 10c and 10e in which the pyridazinone rings are incorporated to antipyrine via an acetylenic amide bond revealed higher analgesic activity than derivatives 10g possessing propionic amide bonds. The [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetamide and propanamide derivatives, the highest analgesic activity was observed with acetamide 4-fluorophenylpiperazine derivative in the amide portion of the compounds. In vivo anti-inflammatory activities of the compounds were assessed in mice at 100 mg/kg body weight [26]. The edema formed is a multi-mediated case divided into 2 phases. The first phase is mediated by release of histamine and serotonin for 1 h followed by the kinin-mediated increased vascular permeability up to 2.5 h whereas the second phase (3 and 4 h after carrageenan injection) is mainly mediated by release of PGs and PGs-associated leukocytes into the site of edema. Subcutaneous injection of carrageenan into the rat paw may cause inflammation, resulting from plasma extravasations, which increased the tissue water and plasma protein exudation along with neutrophil extravasations [41-44].

Compound 10c showed remarkably potent anti-inflammatory activity, indicating that COX inhibition is basically related to the anti-inflammatory activities. Analgesic activity of compounds was also showed a correlation with its anti-inflammatory activity.

Compound 10c has strongly inhibited the peripheral pain response in the mice. Compounds 10b, 10h, produced poor anti-inflammatory activity. When the chemical structures of the active compounds are...
taken into consideration, para-fluoro substitution in the phenyl ring of the phenylpiperazine moiety caused both analgesic and anti-inflammatory activities to increase in antipyrine/pyridazinone hybrids possessing acetylenic amide bond. Moreover, acute toxicity and gastric ulcerogenic effects of the compounds were tested. As for the ulcerogenic effects of the compounds, compounds 10a, 10c, and 10h caused weak damage to the GIT mucosa at 100 mg/kg dose. The other compounds had no ulcerogenic side effect. The analgesic and anti-inflammatory activities of 10c are comparable to those of known drugs including aspirin and indomethacin (without inducing any GIT damage). A series of structurally diverse amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl]propanoic acids were tested for their in vivo analgesic activity. All the compounds exhibited relatively equipotent analgesic activity to aspirin. The analgesic activity of 11h, and 11i was found to be significant [45]. These findings stimulated us to search for new compounds with a 1,5-diaryl substitution pattern with a central pyrazole ring. Some pyridazine derivatives have potent analgesic and anti-inflammatory activities [46-49] and pyridazine ring have one of the aryl substituents about the central pyrazole ring, the presence of the propanamide side chain that linked to the 3 position of the pyrazole ring to determine the contribution to the analgesic activity. The amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1H-pyrazole-3-yl]propanoic acids and present the initial results of in vivo analgesic activity of the amide derivatives.

Analgesic activity of the amide derivatives 11a-e were assessed in mice, compounds having 4-(3-chlorophenyl)piperazine 11b, and 4-(3-trifluoromethylphenyl)piperazine 11e in the amide portion where the pyridazine is substituted with chlorine atom at the 6 position and compounds having 4-(3-chlorophenyl)piperazine 11h, 4-phenylpiperazine 11o in the amide portion in 6-methoxypyridazines were showed activity higher than aspirin.

![Fig. 6. Structure of various piperazine and pyrazolyl containing pyridazine derivatives having anti-inflammatory and analgesic activities.](image-url)
Table 4. Structure of pyrazole ring containing pyridazine derivatives

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Among the tertiary amide derivatives, the 3-chlorophenylpiperazine 11h and phenylpiperazine 11i derivatives in which the pyridazine ring is substituted with a methoxy group with higher but not significantly different analgesic activity compared with that of the aspirin. Introducing a chloro substituent at the 6 position of the pyridazine ring 11b showed a reducing effect on analgesic activity when compared to 11h.

To develop safer NSAIDs, the studied have focused on preparing the amide derivatives of well-established NSAID templates with free carboxylic acids such as indometacin and meclofenamic acid. It was observed that, neutralization of the NSAIDs accomplished by preparing amide derivatives resulted in compounds with good NSAIDs activity and with no gastric side effects. Based on this approach, [6-(4-methoxy-phenyl)-3(2H)-pyridazinone-2-yl]acetamide and propanamide derivatives, the highest analgesic activity was observed with 4-fluorophenylpiperazine derivative in the amide portion of the compounds. The presence of substituted phenylpiperazine moiety at the amide side chain of the pyridazinone ring had a positive influence on their analgesic effect [52,53]. Amidation of 3-[1-(6-chloro/methoxy-phenyldiazinone-3-yl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl)propanoic acids bearing the 1,5-diarylpyrazole, has been well established for analgesic and anti-inflammatory activity [54,55], indicating that the amide derivatives of free carboxylic acid derivatives might be important for good analgesic activity.

**Conclusion**

The initial results exhibited that the presence of arylpiperazine and aromatic amine substituents in the amide portion might contribute to their analgesic activity. These compounds might lead to further studies for developing novel drug molecules with potent analgesic and anti-inflammatory activities.
was found that, the presence of arylpiperazine substituents at the pyridazine ring in pyridazinone may contribute to their analgesic and anti-inflammatory activities. Further studies should be conducted to assess the effect of the synthesized molecules on inflammatory test models and COX-2 selective inhibitory actions.

References


Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.


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