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Review Article

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

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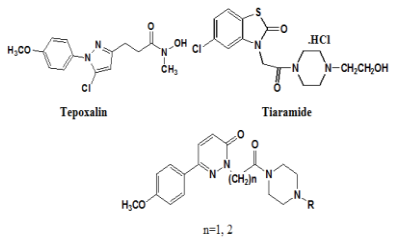
GRAPHICAL ABSTRACT



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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.

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 asthey 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-lypoxygenase enzymes has beenused 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].

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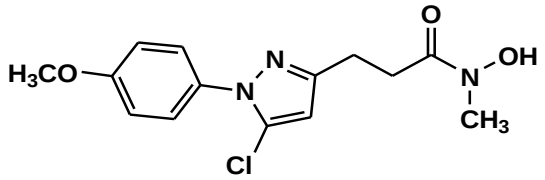


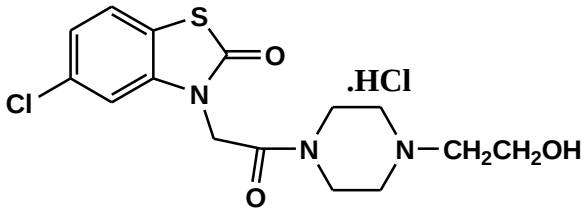
Fig. 1. Structure of Tepoxalin

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

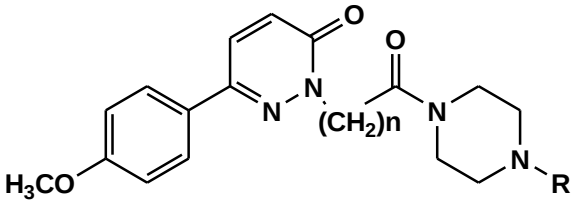
The [6-(4-methoxyphenyl)-3(2H)-pyridazinone-2-yl]acetamide and propanamide derivatives have revealed some analgesic activity [7,8]. The NSAIDs are useful for the treatment of inflammation, pain, and fever. The clinical effects of NSAIDs are based on the inhibition of cyclooxagenase (COX) enzymes, catalyzingthe 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 antipyrine 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 involvedin 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 antipyrine 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)-pyridazinone) 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 moieties 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** haveshowed potential analgesic activity [33]. The 6-piperazinyl-3(2H)-pyridazinones exhibited high analgesic and anti-inflammatory activities [34]. The incorporation of a thienyl ring as a bioisostere of the aryl ring with



Tiaramide (**1**)



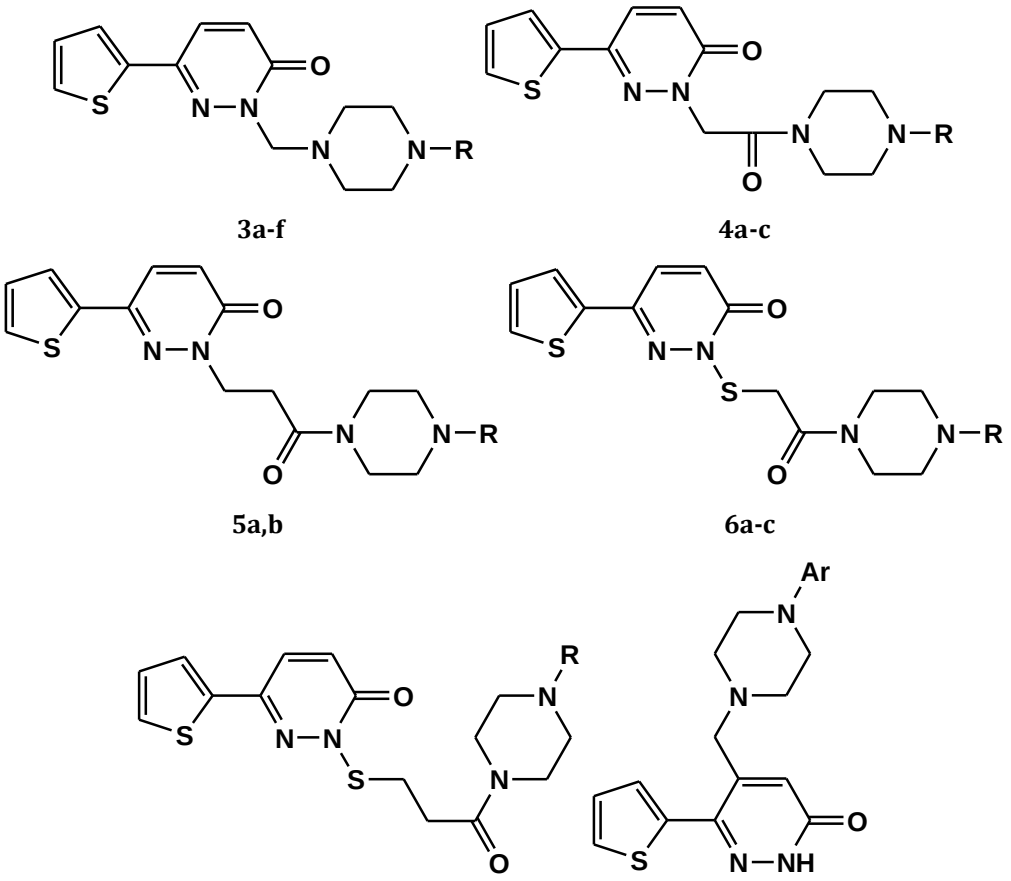
2a n=1 **2b** n=2

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-Ssubstituted 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-ylcarbonylethyl)]-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-ylcarbonylethylthio]-6-(thien-2-yl) pyridazines (**7a,**b) and 5-(4-substituted piperazin-l-yl-methyl)-6-(thien-2-yl)-2H-pyridazin-3-ones (**8a,b**) were exhibited anti-inflammatory activity [35].



3a-f **4a-c**

5a,b **6a-c**

7a,b **8a**Ar=4F-C6H4; **8b**Ar=2-Pyridyl

Fig. 3. Structure of various piperazine and thiophene containing pyridazine derivatives having anti-inflammatory and analgesic activities**.**

Table 1. Piprazine containing pyridazine derivatives.

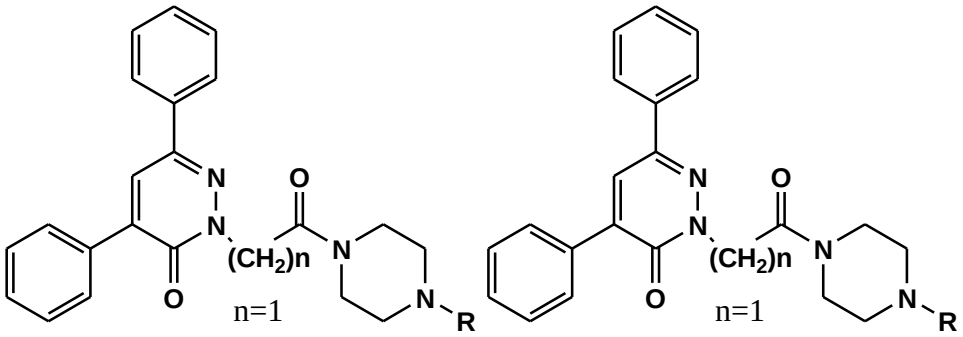
Compound	R	Compound	R	Compound	R
3a	C_6H_5	**3b**	2-F-C_6H_4	**3c**	$CH_2C_6H_4$
3d	2-pyridyl	**3e**	CH_3	**3f**	C_2H_5
4a,6a	4-F-CH_3	**4b,6b**	2-pyridyl	**4c,6c**	C_2H_5
5a,7a	CH_2-C_6H_4	**5b,7b**	C_6H_5		

These compounds had strong antiflammatory 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 exhibitedless 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 beenillustrated 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.

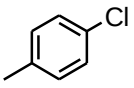
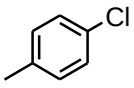
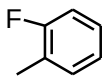
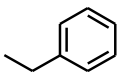
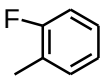
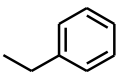
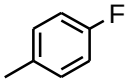
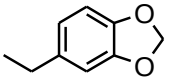
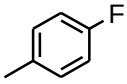
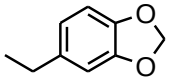
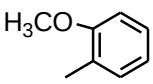
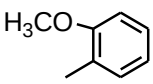
A series of 2-(6-oxo-3,5-diphenyl-6H-pyridazin-1-yl)-acetamides(**8a-g**) and 3-[6-oxo-3,5-di-phenyl-6Hpyridazin-1-yl)-propanamides(**9a-g**) were exhibited analgesic and anti-inflammatory activities. All compounds except for **8g** were more potent than aspirin in a *p*-benzoquinone–induced writhing test at 100 mg/kg dose. Compounds **8b**, **8c** and **8e** had the highest anti-inflammatoryactivity, andcompound **8e** showed the highest analgesic and anti-inflammatory activities with noulcerogenic side effects [36].



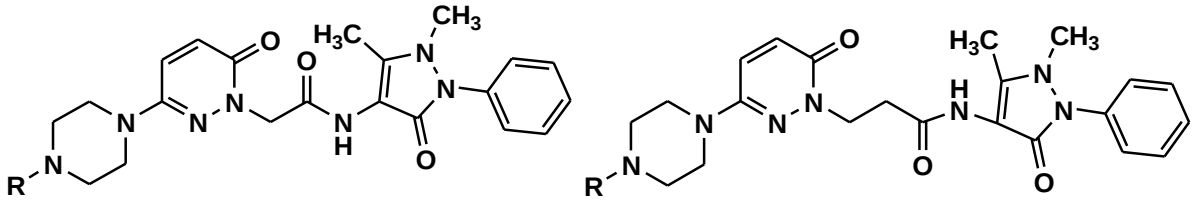
Compounds 8a-8g **Compounds 9a-9g**

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

Table 2. Piprazine amide containing pyridazine derivatives.

Compd	R	Compd	R	Compd	R	Compd	R
8a		*8e*		*9a*		*9e*	
8b		*8f*		*9b*		*9f*	
8c		*8g*		*9c*		*9g*	
8d				*9d*			

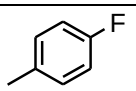
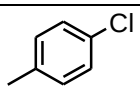
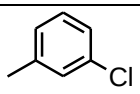
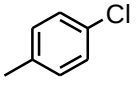
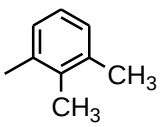
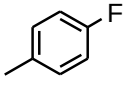
Analgesic activity of the compounds was assessedusing a p-benzoquinone (PBQ)-induced writhing test. All compounds showed significant analgesic activity at 100 mg/kg dose level (55.6 to 82.7%). All compounds except for **8g** were more potent than aspirin. Four compounds (**8a, 8c**, **8e** and **9f)** 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** depictedan 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 asit 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 isno difference in terms of the NSAIDs activity in theacetamide and propanamide derivatives. However the more active compounds in terms of anti-inflammatoryactivity were found in acetamides. Substitutions on the phenyl ring of the phenylpiperazinemoiety by *o*- or *p*-fluoro groups or a 2-pyridyl group increased NSAIDs activity of acetamide derivatives markedly.



10a-d **10f-h**

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

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

Compd	R	Compd	R	Compds	R	Compds	R
10a		**10c**		**10e**		**10g**	
10b		**10d**		**10f**			

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(2*H*)-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 testin mice and sufficientlysensitive to detect the effect of analgesics that are less active than aspirin.The compounds withphenylpiperazine**10a** and 4-(2,3-dimethylphenyl)piperazine**10d** at the 6 position of the pyridazine ring revealedanalgesic activities higher than aspirin. Compounds **10c, 10e,** and **10g** were approximately equipotent to aspirin at thesame dose of 100 mg/kg.Analgesic activities of derivatives **10a-g** seem to be sensitive to electronic effects of the substituent atthe sixth position of the pyridazine ring. While the substituted piperazine or piperidine derivatives showedpotent 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 hybridmolecules, 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 ringis incorporated to antipyrine via an acetylenic amide bond revealed higher analgesic activity than derivatives **10g** possessing propionic amide bonds.The [6-(4-methoxyphenyl)-3(2*H*)-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 ofcarrageenan into the rat paw may cause inflammation,(resulting from plasma extravasations), which increased the tissue waterand plasma protein exudation along with neutrophil extravasations [41-44].

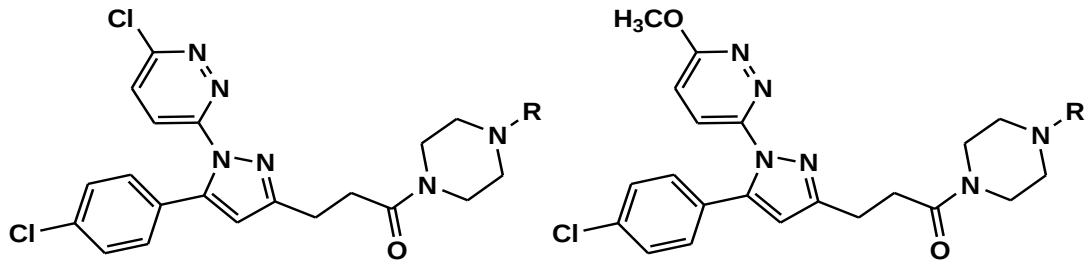
Compound **10c** showed remarkably potent anti-inflammatory activity, indicating that COX inhibition is basically related to the anti-inflammatory activities. Analgesic activity of compounds was also showed a correlation with its anti-inflammatory activity.

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 substitutionin the phenyl ring of the phenylpiperazine moiety caused both analgesic and anti-inflammatory activitiesto 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 weakdamage 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 knowndrugsincluding, 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 relativelyequipotent analgesic activity toaspirin. The analgesic activity of **11h**, and **11i**was found to besignificant [45].These findings stimulated us to search for new compounds with a 1,5-diaryl substitution patternwitha 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.

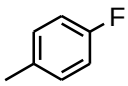
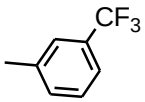
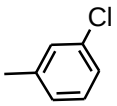
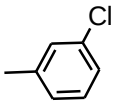
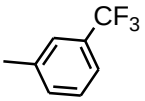
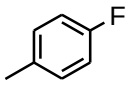
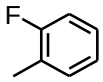
Analgesic activity of the amide derivatives **11a-i**wereassessedin mice, compounds having 4-(3-chlorophenyl)piperazine**11b**, and 4-(3-trifluoromethylphenyl)piperazine**11e**in the amide portion where the pyridazine is substitutedwith chlorine atom at the 6 position and compounds having 4-(3-chlorophenyl)piperazine**11h**,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



11a-e **11f-i**

Fig. 6. . Structure of various piperazine and pyrazolyl containing pyridazine derivatives having anti-inflammatory and analgesic activities**.**

Table 4. Structure of pyrazole ring containing pyridazine derivatives

Compd	R	Compd	R	Compd	R	Compd	R
11a		**11d**		**11f**		**11h**	
11b		**11e**		**11g**		**11i**	
11c							

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**showeda reducing effect on analgesic activity when compared to **11h**.

To develop safer NSAIDs, the studied have focused on preparingthe amide derivatives of well-established NSAID templates with free carboxylic acidsuch asindometacin 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-(5-methyl-3-phenylpyrazole-1-yl)-3(2*H*)-pyridazinone-2-yl] acetamides [50-51], certain amide derivatives including 4-fluorophenylpiperazine, 4-phenylpiperazine, 4-(2-pyridyl)piperazine,4-methoxy-phenyl, and the *N*-octyl in the amide portion were showed more significant analgesic activity compared to the aspirin. The [6-(4-methoxy-phenyl)-3(2*H*)-pyridazinone-2-yl]acetamide and propanamide derivatives, the highest analgesicactivity was observed with 4-fluorophenylpiperazine derivative in the amide portion of the compounds. The presence of substituted phenylpiperazinemoiety at the amide side chain of the pyridazinone ring had a positive influence on their analgesiceffect [52,53].Amidation of 3-(1-(6-chloro/methoxy-pyridazine-3-yl)-5-(4-chlorophenyl)-1H-pyrazole-3-yl)propanoic acids bearing the 1,5-diarylpyrazole, has beenwell established for analgesic and anti-inflammatory activity [54,55],indicatingthat the amide derivatives of free carboxylic acid derivatives might be important for good analgesic activity.

Conclusion

Theinitial results exhibited that the presence of arylpiperazine and aromatic aminesubstituents in the amide portion might contribute to their analgesic activity. These compoundsmight lead to further studies for developing novel drug molecules with potent analgesic and anti-inflammatory activities.It

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 assessthe effect of the synthesized molecules on inflammatory test models and COX-2 selective inhibitory actions.

Conflict of interests

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

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