

## Review Article

# Overview on Emorfazone and Other Related 3(2H) Pyridazinone Analogues Displaying Analgesic and Anti-Inflammatory Activity

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## Keywords

- Pyridazinone
- Analgesic
- Anti-inflammatory

## Abstract

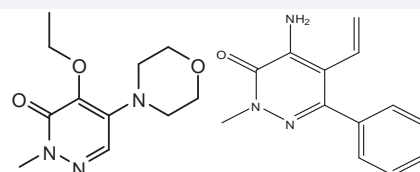
A series of structurally varied derivatives of 3(2H)-pyridazinone were tested for their analgesic and anti-inflammatory activity by using different test models. The analgesic and anti-inflammatory activity of the compounds were found to be significant as compare with reference drugs. Some of the 3(2H)-pyridazinone derivatives are having analgesic and anti-inflammatory activities. Pyridazine derivatives, Emorfazone is a non-steroidal analgesic anti-inflammatory drug which is clinically used for ailments such as pain, inflammation and rheumatoid arthritis. Various pyridazine derivatives also exhibited non-steroidal analgesic anti-inflammatory activity.

## INTRODUCTION

The majority of currently known non-steroidal anti-inflammatory and analgesic drugs (NSAIDs), i.e, aspirin and ibuprofen, mainly act peripherally by blocking the production of prostaglandins through inhibition of cyclooxygenase (COX) enzymes, COX-1 and COX-2, to varying extents [1]. These drugs tend to produce side effects such as gastrointestinal ulceration and suppression of renal function due to inhibition of the constitutive COX-1, which is responsible for the production of prostaglandins (PGs), responsible for gastro protection and vascular homeostasis [2-4]. Therefore, the main trend nowadays in pain therapy focuses on improved nonsteroidal analgesics which are effective as an analgesic but devoid of the side effects which are inherent to traditional NSAIDs. In terms of this aspect, many studies have been focussed on 3(2H)-pyridazinones, which are characterized to possess good analgesic and anti-inflammatory activities and also very low ulcerogenicity [5-9]. Among the various pyridazinone derivatives, 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone) is being marketed in Japan as an analgesic and anti-inflammatory drug [10,11]. The 4-amino-2-methyl-6-phenyl-5-vinyl-3(2H)-pyridazinone (Figure 1) was seven-fold more potent than emorfazone (Figure 1) [12-14] in bringing about analgesic and anti-inflammatory response. Additionally, 2-substituted 4, 5-dihalo-3(2H)-pyridazinone derivatives with high analgesic activity and with no ulcerogenic side effects [15]. Subsequently, 2-substituted 4,5-functionalized 6-phenyl-3(2H)-pyridazinone

derivatives have also been reported to bear potent analgesic activity with negligible general side effects as those of currently used NSAIDs [16]. In the meantime, 3-O-substituted benzyl pyridazinone derivatives were shown to exhibit in vitro potent anti-inflammatory activity [14,17]. As a continuation of work for the development of improved NSAIDs; which are effective but devoid of the well-known side-effects linked with the obligatory use of NSAIDs, we also got interested in 3(2H)-pyridazinones [18-21], which resulted in good analgesic and anti-inflammatory activities.

Purpose: Non steroidal anti-inflammatory drugs (NSAIDs) constitute an important class of drugs with therapeutic applications. Treatment of inflammatory disorders likes rheumatoid arthritis (RA) and osteoarthritis (OA) starting from the classic drug to the recent rise and fall of selective COX-2 inhibitors. Efforts to discover drug to treat inflammation



Emorfazone 1: isomers of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone

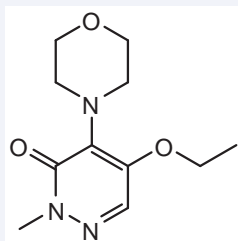
Figure 1

continues to be an important drug design challenge. This review traces the origins of NSAIDs with pyridazine moieties, their mechanism of action at the molecular level such as cyclooxygenase (COX) inhibition, development of selective COX-2 inhibitors, their adverse cardiovascular effects and some recent developments targeted to the design of efficient anti-inflammatory drugs with less side effects.

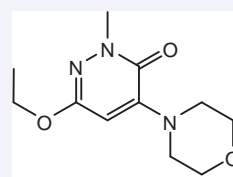
### Analgesic and anti-inflammatory activity of pyridazinone analogues

A number of nonsteroidal anti-inflammatory drugs (NSAIDs) are available for the treatment of pain syndromes; their chronic use for treatment of pain concomitant with inflammation limits their therapeutic use since they cause gastrointestinal and renal side effects. Therefore, the main trend nowadays in pain therapy focuses on improved nonsteroidal analgesics that are effective as an analgesic but devoid of the side effects inherent to traditional NSAIDs. In recent years, the dual inhibition of cyclooxygenase (COX) and 5-lipoxygenase enzymes for treatment of inflammation and pain has been introduced as a novel therapeutic target. In addition, many studies also focused on pyridazine derivatives for developing potent and safer NSAIDs without gastric side effects. Among these compounds, (emorfazone) is currently being marketed in Japan as an analgesic and anti-inflammatory drug. Subsequently synthesized some pyridazinone derivatives and reported that these compounds showed potential analgesic activity [22-27]. The position isomers of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone or **1**), an analgesic anti-inflammatory drug, 5-ethoxy-2-methyl-4-morpholino-3(2H)-pyridazinone (Figure 2), 6-ethoxy-2-methyl-4-morpholino-3(2H)-pyridazinone (Figure 3) and 6-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (Figure 4) were exhibited analgesic and anti-inflammatory activities. The compound **4** exhibited the most strong activity among these compounds, various 6-alkoxy- or 6-allyloxy-2-alkyl- or 2-cyclohexyl- or 2-phenyl-5-substituted amino-3(2H)-pyridazinones were evaluated for their analgesic and anti-inflammatory activities. The 2-methyl-5-morpholino-6-propoxy-pyridazin-3(2H)-one and 4-methyl-5-morpholino-6-n-propoxy-3(2H)-pyridazinone (Figure 5a,5b) and 2-methyl-5-morpholino-6-n-butoxy-3(2H)-pyridazinone and 4-methyl-5-morpholino-6-n-butoxy-3(2H)-pyridazinone (Figure 6a,6b) and 6-ethoxy-2-ethyl-5-morpholino-3(2H)-pyridazinone (Figure 7) were shown to be more potent in analgesic and antipyretic activities than analgesic and anti-inflammatory drugs (emorfazone, aminopyrine, mepirizole, tiaramide hydrochloride, phenylbutazone, mefenamic acid) [28].

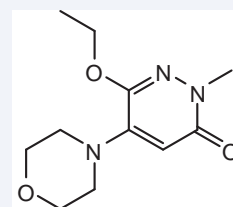
A series of 4-amino-3(2H)-pyridazinones substituted at



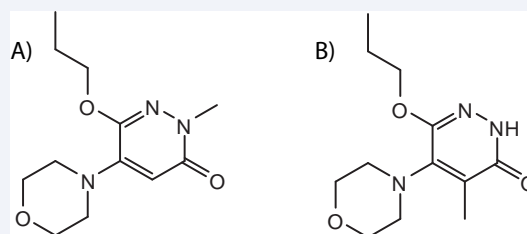
**Figure 2** 5-ethoxy-2-methyl-4-morpholino-3(2H) -pyridazinone.



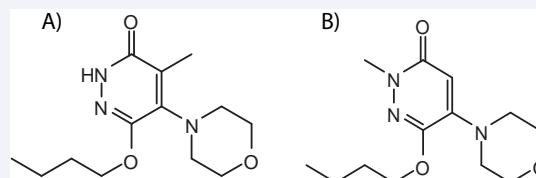
**Figure 3** 6-ethoxy-2-methyl-4-morpholino-3(2H)-pyridazinone.



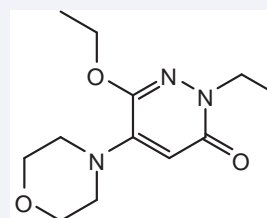
**Figure 4** 6-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone.



**Figure 5 a)** 2-methyl-5-morpholino-6-propoxy-pyridazin-3(2H)-one. **b)** 4-methyl-5-morpholino-6-n-propoxy-3(2H)-pyridazinone



**Figure 6 a:** 2-methyl-5-morpholino-6-n-butoxy-3(2H)-pyridazinone. **b:** 4-methyl-5-morpholino-6-n-butoxy-3(2H)-pyridazinone.



**Figure 7** 6-ethoxy-2-ethyl-5-morpholino-3(2H)-pyridazinone.

position 2 with arylpiperazinyl alkyl groups and analogues were evaluated as antinociceptive agents in the mice abdominal constriction model. Some of these compounds dosed at 100 mg/kg s.c. significantly reduced the number of writhes induced by the noxious stimulus. One showed 100% inhibition of writhes and was able to protect all the treated mice from the effect of the

chemical stimulus and this compound was almost 40-fold more potent than the structurally related Emorfazone [29] (Figure 8a,8b,8c). Effects of emorfazone (M 73101) on thermic edema in rats, oral use of emorfazone (100 and 200 mg/kg) significantly inhibited the edema formation resulting from immersing the rat paws in a water bath. It was found that in the 15-min period from 15 to 30 min after immersing the highest amount of bradykinin-like substance was obtained, and the release of kininogen, kinin-forming enzyme and kininase was markedly increased. Emorfazone showed a significant inhibitory action against release of bradykinin-like substance and kininogen and a tendency to decrease the release of kinin-forming enzyme. However, emorfazone had no direct effect on the content of kininogen, kinin-forming enzyme and kininase activity in rats' plasma. It is suggested that kininogen and kinin-forming enzyme released into the extravascular space may be of importance for the biosynthesis of bradykinin-like substance, and that the inhibitory effect of emorfazone on the release of bradykinin-like substance into the extravascular space may be involved in the mechanism of analgesic and anti-inflammatory action [30]. Effects of M 73101 on the nociceptive responses induced by the liminal dose of bradykinin (BK alone-induced response), the combined use of the subliminal dose of BK and prostaglandin E (PGE-potentiated response) and the electrical stimulation of the sensory nerve were explored. The BK and PGE were injected into the femoral artery of dogs and the right carotid artery of rats. In lightly anesthetized dogs, M 73101 (5-20 mg/kg, i.v.), aminopyrine (30 mg/kg, i.v.) and aspirin (50 mg/kg, i.v.) inhibited the vocalization response induced by BK alone but did not by the electrical stimulation of the saphenous nerve. Distinct morphine HCl, these agents showed a blocking action on the saphenous nerve activity evoked by BK. These three drugs differed from each other with respect to the action on the PGE-potentiated response; M 73101 inhibited the PGE-potentiated response to the same extent as in the case of the BK alone-induced response, while aminopyrine was less active in inhibiting the PGE-potentiated response than BK alone-induced response and aspirin showed no action on the PGE-potentiated response. Mode of action of M 73101 on BK-induced nociception and main site of anti-nociceptive action of M 73101 may be in the periphery, and that its action may be not due to inhibition of PGs-synthesis or release [31]. The mechanism of the elevation of serum corticosterone level by M73101 and its participation in the anti-inflammatory action is investigated. M73101 when

given to rats i.p. at doses of 50-200 mg/kg, caused an increase in serum and adrenal corticosterone in a dose-dependent manner. Oral use of 200 mg/kg of M73101 also elevated the serum corticosterone level. Such action of M73101 was fully abolished by adrenalectomy, hypophysectomy, or the pretreatment with pentobarbital and morphine. In vitro study showed that M73101 had no direct effect on adrenocortical function. The response to M73101 must be mediated through the release of ACTH from the adenohypophysis, which is probably due to the secretion of corticotropin releasing factor from the hypothalamus. M73101 at an oral dose of 200 mg/kg significantly reduced the volume of exudative fluid and the number of leucocytes in carrageen in-induced pleurisy of intact rats. The inhibitory action of this drug on cell mobilization decreased by adrenalectomy but not on exudative fluid, indicating that anti-inflammatory actions of M73101 may be due in part to pituitary-adrenocortical stimulation [32]. Analgesic, anti-inflammatory and other related actions of M73101 were examined in animals. Analgesic activity of M73101 was more potent than that of other anti-inflammatory drugs except for aminopyrine in phenylquinone test in mice. The M73101 showed the most potent analgesic activity among the drugs tested in rats. The mode of analgesic action of M73101 similar to aminopyrine and possessed potent inhibitory activities on acute inflammatory edema and suppressed the permeability of capillary vessels. The M73101 inhibited histamine release from isolated rat mast cells and rat skin by the condensation product of N-methyl-homoanisylamine formaldehyde, and leucocyte emigration in carrageen in rat pleurisy. The M73101 was much less active than phenylbutazone and other anti-inflammatory drugs in causing gastric lesion. The M73101 was found to be superior to mepirizole, tiaramide, benzydamine, phenylbutazone and aspirin [33]. The M73101 reduced locomotor activity in mice and rats and prolonged sleeping time induced by hexobarbital in mice. There were no facts of cataleptogenic action, anti-tremorine action and antagonistic effect on reserpine-induced hypothermia in mice. The M73101 did not inhibit seizures induced by maximal electroshock (MES) and pentylenetetrazol (PTZ) but slightly inhibited the seizure induced by strychnine (STR) in mice. Moreover, M73101 reduced only the monosynaptic action potential in intact and spinal cats, indicating that this compound exerts an inhibitory action on spinal function. These properties of M73101 on the central nervous system (CNS) are similar to those seen with aminopyrine though the potency was weaker.

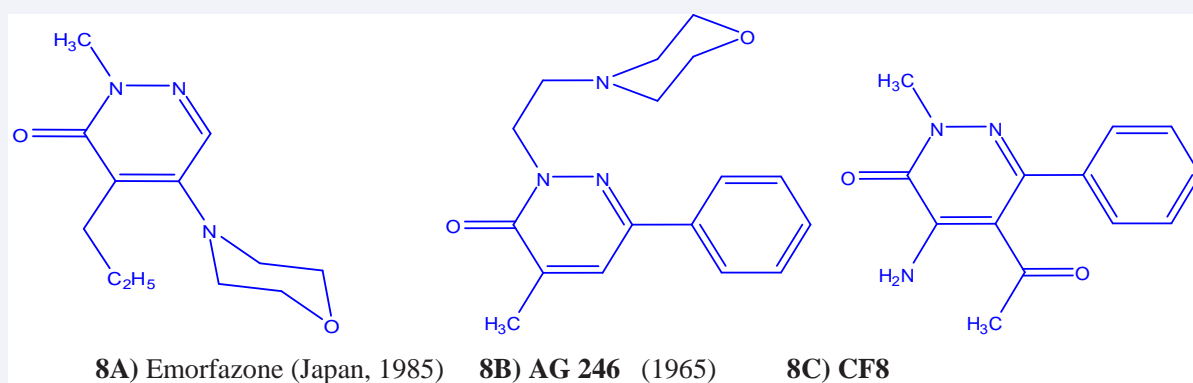


Figure 8

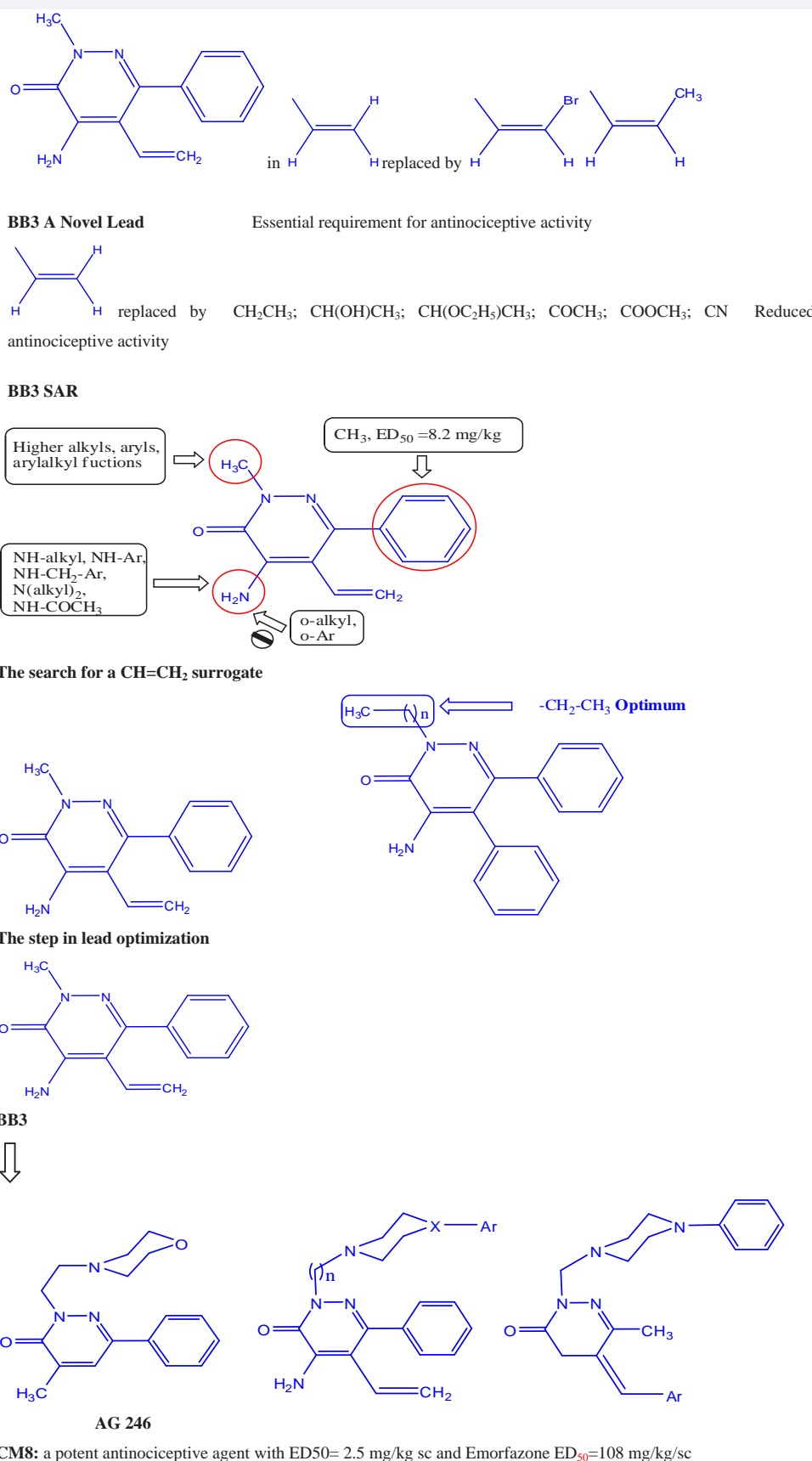


Figure 9 Analgesic antiinflammatory drug its mechanism.

M73101 like aminopyrine showed no marked activity on the motor function [34-36] (Figure 9).

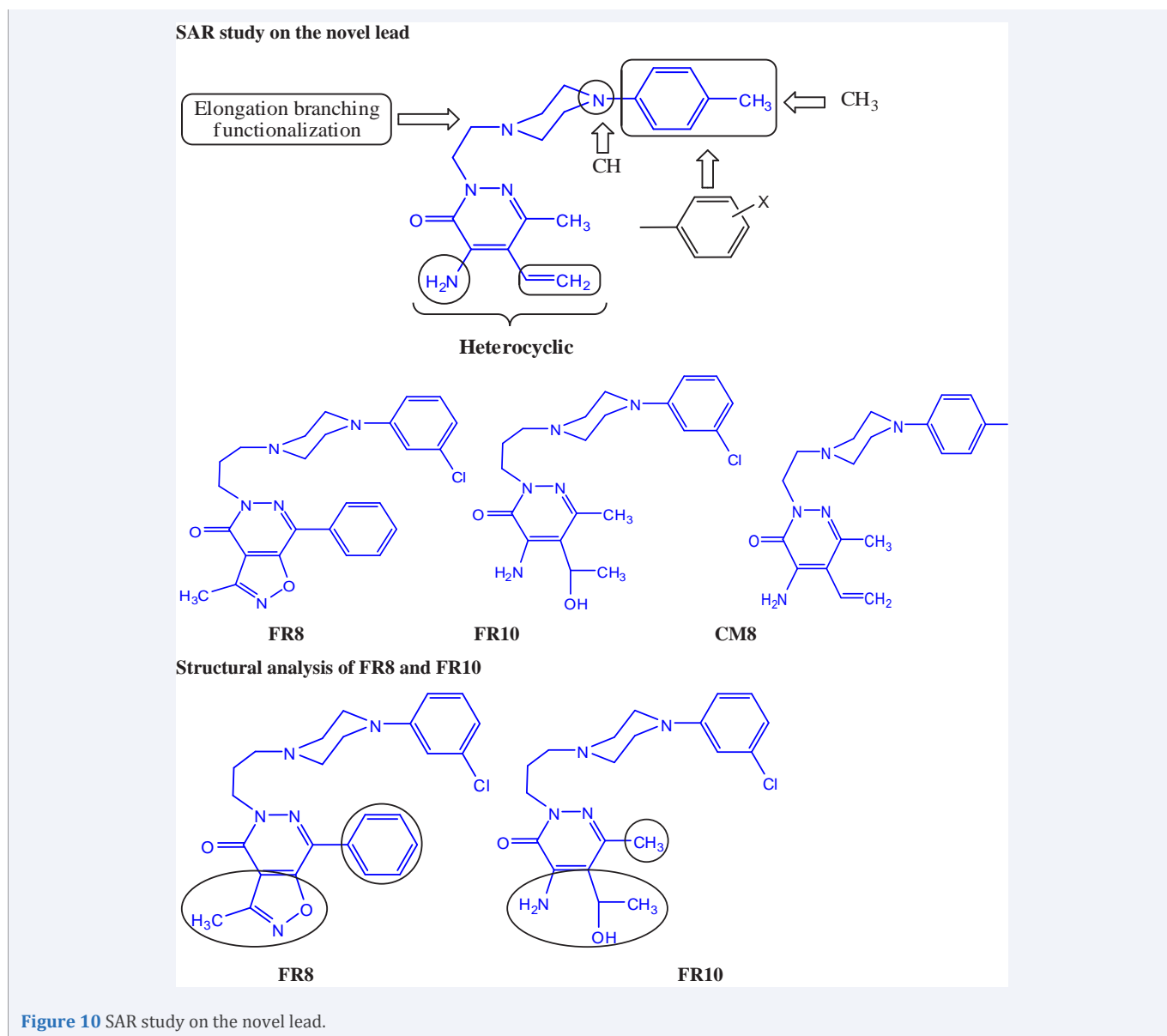
The effect of M7310U, a new non-steroidal analgesic anti-inflammatory agent (NSAIDs), on liver microsomal drug-metabolizing enzymes was investigated. Rats were treated orally with M73101 (100, 200, 500 mg/kg), henylbutazone (PZ, 200 mg/kg), aminopyrine (AM, 100 mg/kg) or phenobarbital sodium (PB, 100 mg/kg) once daily for 2 weeks and then were observed for 2 weeks during which treatment was not given. On treatment with M73101, PZ, AM and PB, the liver enlarged but was restored to normal 1 week after the last administration. The rate of increase in the case of M73101 was lower than that seen with the reference compounds. M73101 markedly increased the content of microsomal protein, cytochrome P-450 or b5 and NADPH cytochrome C reductase, aniline hydroxylase and AM demethylase activity, but these increments returned to the normal level 1 week after the last administration. The serum concentration of M73101 after repeated administration (200 mg/kg, p.o.) for 1 week was lower than that after a single administration. Furthermore, M73101 increased Vmax for both aniline hydroxylase and AM demethylase, whereas it increased Km only for aniline hydroxylase. M73101 did not enhance the lipid peroxidation. The enlargement of rat liver seen with M73101 was due to the induction of drug-metabolizing enzymes and that this agent can probably be classified as a phenobarbital-type inducer [37]. Male and female dogs, aged 17-21 months, were administered oral M 73101 (0, 60, 120 and 240 mg/kg/day), a new analgesic and anti-inflammatory drug, for 27 weeks, and following recovery test was carried out for 5 weeks. Dead animals were not found throughout the experimental period. Body weight gain and food and water consumption were not affected due to M 73101 administration. Except for a slight increase of vomiting in the highest dose, there were no abnormal symptoms. Biochemical examination showed the slight increase in serum alkaline phosphatase activity and free cholesterol level. Pathological examination revealed a dose-dependent increase of liver weight and hypertrophy of hepatocytes due to proliferation of smooth endoplasmic reticulum. In addition, mitochondria became irregularly large in the highest dose. There were no abnormal findings in the gastro-intestinal tracts except for an erosion of gastric mucosa, which was noted in a female dog treated 240 mg/kg/day of M 73101. From these results, it was suggested that the maximum non-toxic dose was 60 mg/kg/day or less, and the greatest safety dose was 120 mg/kg/day in beagle dogs [38]. General pharmacological actions of M73101, a new NSAID were investigated in mice, rats, guinea pigs, rabbits, cats and dogs. Intravenous administration of M73101 produced a slight transient fall in blood pressure, an increase in heart rate and a respiratory stimulation, but no remarkable change in the electrocardiogram. The contraction induced by epinephrine in the isolated ear vessels of rabbits relaxed by M73101. In the isolated trachea of guinea pigs, M73101 relaxed the contraction induced by histamine. Furthermore, M73101 inhibited the broncho-constriction by histamine but not by bradykinin in guinea pigs. These properties of M73101 on the tracheal smooth muscle were similar to those seen with aminopyrine but different from those seen with aspirin which inhibited only the contraction by bradykinin in vivo, suggesting that M73101 is a compound with properties similar to basic non-steroidal anti-inflammatory

drugs. M73101 inhibited the intestinal propulsion in mice and also the gastrointestinal movement in rats and dogs. Moreover, M73101 showed a spasmolytic activity on the isolated ileum of guinea pigs, but such was not due to any specific antagonistic action on the chemical mediators. On the other hand, M73101 had no effect on the isolated uterus and vas deferens of rats. M73101, unlike aminopyrine and phenylbutazone, slightly increased urine volume and electrolytes excretion in rats, indicating that this compound probably does not produced edema. M73101 showed no significant pharmacological activities on the blood sugar level, blood coagulation, platelet aggregation, met hemoglobin formation and local irritation [34]. The anti-inflammatory activity and the mode of action of M73101, a new NSAID, were explored in animals and compared with those of reference drugs. M73101 inhibited the increase in vascular permeability induced by acetic acid and its activity was more potent than that of phenylbutazone. M73101 showed a marked inhibitory effect against rat paw edema induced by various phlogistic agents (carrageen in, dextran, histamine, serotonin and bradykinin) and the activities were equal to or more potent than those of aminopyrine, mepirizole and tiaramide HCl. M73101 also inhibited the edema induced by mustard, scalding and anti-rat rabbit serum in rats. In addition, the anti-edematous effect of M73101 on carrageen in-induced rat paw edema was not influenced by spinalectomy or adrenalectomy, indicating that the anti-inflammatory action of M73101 was not mediated by the CNS and the adrenals. Local and oral use of M73101 inhibited significantly the leucocyte migration into the fluid of CMC pouch in rats and the activity was more potent than phenylbutazone, suggesting that the anti-inflammatory effect of M73101 was due to the direct action at the inflamed site. On the other hand, M73101 did not show any marked activities on the experimental chronic inflammatory models. From these results, it is suggested that M73101 may be useful for clinical application as a analgesic, anti-inflammatory drug with remarkable anti-inflammatory activity. The mechanism of the anti-inflammatory action of M73101 probably involves inhibition of an increase in vascular permeability and leucocyte migration [34]. It was observed that neutralization of the NSAIDs accomplished by preparing pyridazine derivatives resulted in compounds with good analgesic and anti-inflammatory activity and with no gastric side effects in animal models. Based on this approach, certain pyridazine derivatives showed superior analgesic activity compared to the reference compound aspirin used in the assays. Other research also indicated that the presence of substituted phenylpiperazine moiety had a positive influence on their analgesic activity. Thus, emorfozone template in the structure, which is well established for analgesic and anti-inflammatory activity, indicates that the preparation of certain derivatives might be important for good analgesic activity. Therefore, results demonstrate that the presence of certain pyridazine analogues might contribute to their analgesic activity.

Analgesic antiinflammatory drug its mechanism does not depend on opiod and prostaglandin system in replaced by  $\text{CH}_2\text{CH}_3$ ;  $\text{CH}(\text{OH})\text{CH}_3$ ;  $\text{CH}(\text{OC}_2\text{H}_5)\text{CH}_3$ ;  $\text{COCH}_3$ ;  $\text{COOCH}_3$ ; CN Reduced antinociceptive activity.

It is still active as antinociceptive agents, different structure activities relationship and probably different mechanism of action. Specific opioids,  $\alpha_2$  adrenergic, nicotinic and GABA-B antagonists



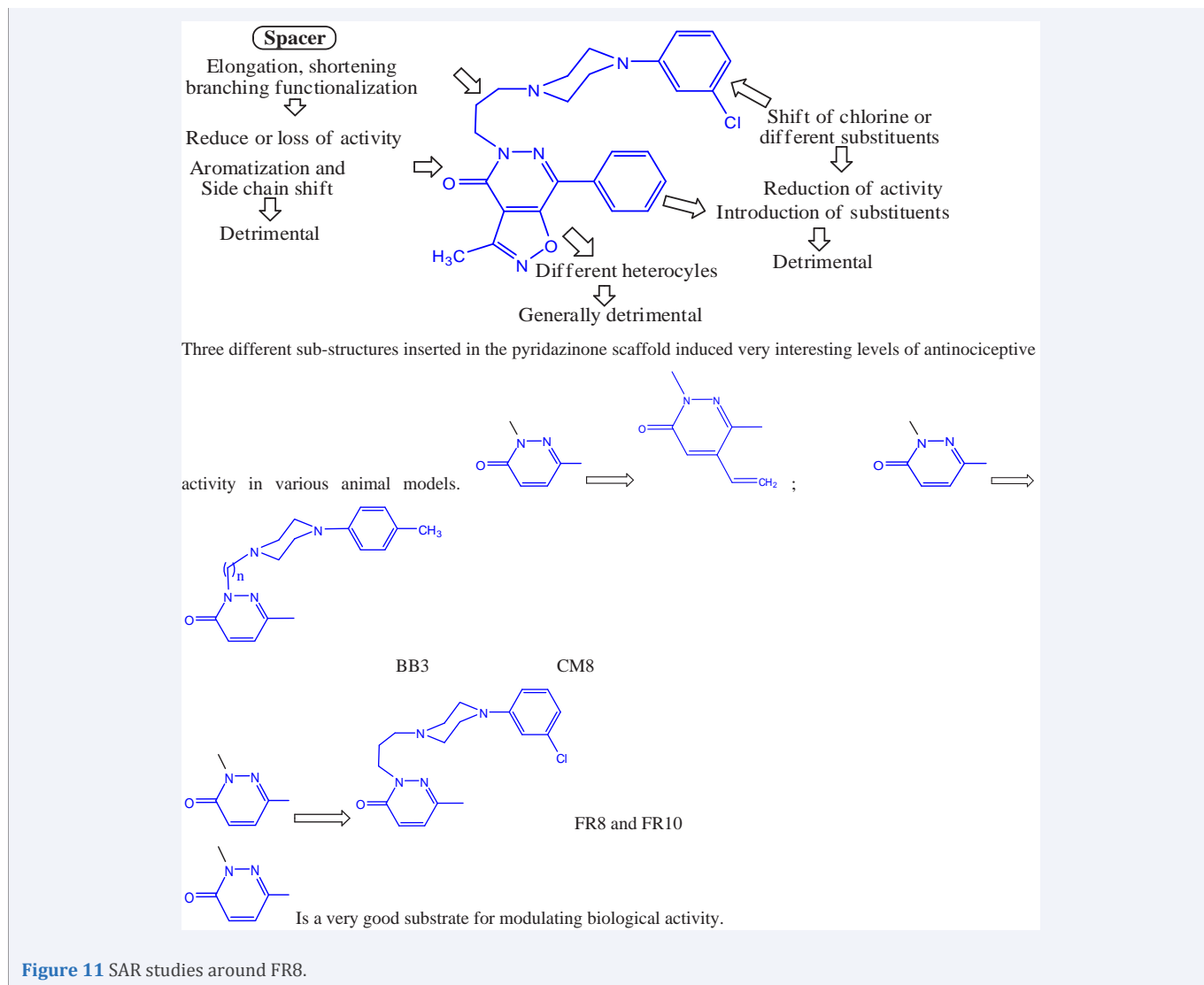


their pharmacological activities. Therefore, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years. Recently, it has been reported that a considerable number of 3(2H)-pyridazinone derivatives bearing analgesic pyridazinone ring have been tested for their pharmacological activities. Among these compounds, emorfazone is an analgesic and anti-inflammatory compound marketed as pentoil and nandron [40,41]. It is known that an edema produced by carrageenan is a biphasic event and it is reported that the inhibitory effects of agents which act on the first stage of the carrageenan-induced hind paw inflammation are attributable to the inhibition of the chemical mediators such as histamine, serotonin and bradykinin. The second stage of the edema might be related to the arachidonic acid (AA) metabolites, since it is inhibited by aspirin, indometacin and other COX inhibitors [42,43]. These compounds exhibited considerable anti-inflammatory activity both in the first and second phases of edema and the activity did show a gradual increase in the second

phase of the edema, indicating that these compounds might exert their anti-inflammatory activities through the mechanisms that involve the inhibition of chemical mediators such as histamine and serotonin and also presumably the COX isoforms. Some recent studies for developing safer analgesic and anti-inflammatory drugs which inhibit COX-2 enzyme have concentrated on well-established NSAID templates such as indometacin [44] and meclofenamic acid [45]. The neutralization of the NSAIDs accomplished by preparing pyridazinone derivatives resulted in compounds that selectively inhibited COX-2 but not COX-1 with good analgesic and anti-inflammatory activity and with no gastric side effects in animal models.

## CONCLUSION

Based on the above findings, various 3(2H)-pyridazinones were investigated for their analgesic and anti-inflammatory activity. These types of compounds results might lead to further studies for developing better compounds with potent analgesic



**Figure 11** SAR studies around FR8.

and anti-inflammatory activities. The preparation of distinct pyridazine derivatives based on this initial screening study is currently under investigation. The ring substitutions and the presence of side chain that is linked to the pyridazinone ring improved the analgesic and anti-inflammatory activity along with nil or very low ulcerogenicity. These types of compounds might lead to further studies for developing better candidates with potent analgesic and anti-inflammatory activities.

## FOOTNOTE

The some of the recent advances toward developing effective anti-inflammatory agents (NSAIDs,) with COX1/COX2 inhibitors activities. A great progress has been made toward developing novel anti-inflammatory compounds. The design and development of safe, effective and economical treatment for treating inflammatory conditions still presents a major challenge.

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