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Review Article

The Study of Pyridazine Compounds on Prostanoids: Inhibitors of COX, cAMP Phosphodiesterase, and TXA_2 Synthase

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The pyridazine moiety is an important structural feature of various pharmacological active compounds. Synthetic pyridazine compounds have been reported as effective antiprostaglandins (PGs), 5-lipoxygenase (5-LOX), and antiplatelet agents, that is, inhibitors of prostaglandin or cyclooxygenase (COX-I & COX-II) enzyme, platelet cAMP phosphodiesterase, and thromboxane A2 (TXA_2) synthase. These compounds are selective and nonselective COX inhibitors and showed analgesic, anti-inflammatory, and antipyretic activity. Pyridazine compounds with antiplatelet agents inhibited TXA_2 enzyme. Pyridazines also exhibited antirheumatoid activity. These pyridazine compounds hold considerable interest relative to the preparation of organic intermediates and other anticipated biologically active compounds.

1. Introduction

Most biologically active compounds are heterocyclic in nature. Due to this finding, nitrogen heteroatom containing compounds are becoming more popular in the current research and so is development of new more potent drugs and newer derivatives of existing or currently used drugs with minimum or without adverse effects. In this paper, our attention has been focused on pyridazine derivatives such as anti-PGs, antiplatelets, and antirheumatic agents. Pyridazinone compounds exhibited various types of biological activities [1]. These activities depend upon the changes of substitutional groups in pyridazine ring system resulting in different fruitful biological activities. Recently, a considerable number of pyridazine compounds have been reported to possess antimicrobial, analgesic, anti-inflammatory, antifeedant, herbicidal, antiplatelet, anticancer, antisecretory, antiulcer, antidepressant, neuroleptic, sedative-hypnotic, anticonvulsant, immunosuppressant, cardiotonic, vasodilator, antiarrhythmic, hypocholesterolaemic, and other anticipated biological properties [2–5]. Various derivatives of pyridazine are found to be associated with significant industrial as well agricultural uses. The biological activity of pyridazine derivatives stimulated the vigorous growth of investigations of this moiety. Over the past few years, a number of pyridazine derivatives have been applied as antithrombotic, anti-PGs, and antiplatelets agents [6–9].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have huge therapeutic value in the management of pain and inflammation. These compounds inhibit the cyclooxygenase enzymes (COX-1 and COX-2), which catalyze the conversion of arachidonic acid (AA) to PGs and thus prevent the formation of PGs and 5-lipoxygenase (5-LOX) also [10–12]. COX-1 is constitutive isoform and is found in the gastrointestinal tract, kidney, and platelets and is believed to be responsible for the maintenance of physiological homeostasis such as gastrointestinal integrity and renal function. On the other hand, COX-2 is induced by many kinds of inflammatory mediators and plays an important role in the PGs biosynthesis associated with inflammatory responses. Inhibition of both COX-1 and COX-2 by classical NSAIDs leads to a decrease in all PGs synthesis, which accounts for the beneficial anti-inflammatory and analgesic effects of NSAIDs as well as the gastrointestinal side effects. COX-2 was discovered in the brain, spinal cord, and kidney as well as many organs, suggesting that this isoenzyme may play a more complex physiological role than was expected [13, 14]. So, there is still a necessity to synthesize novel, potent COX-2 inhibitors with reduced side effects, compared with currently marketed COX-2 inhibitors. There are several classes of compounds

having selective COX-2 inhibitory activity. Many research groups have been interested in pyridazines for the development of potential analgesic and anti-inflammatory activities [15].

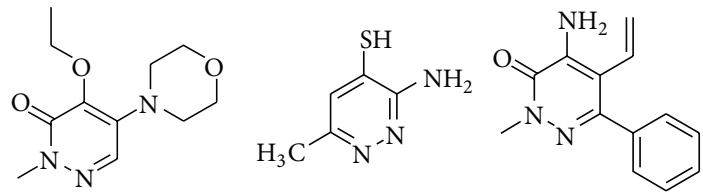
The antiplatelet drugs are administered as adjuncts to thrombolytic therapy, along with heparin, to maintain perfusion and to limit the size of the myocardial infarction. Recently, antiplatelet drugs have been found to be of new importance in preventing thrombosis in percutaneous coronary intervention procedures (angioplasty and stent). Administration of an antiplatelet drug increases the risk of bleeding. Aspirin inhibits platelet aggregation and prolongs bleeding time. It is useful for preventing coronary thrombosis in patients with unstable angina, as an adjunct to thrombolytic therapy, and in reducing recurrence of thrombotic stroke. It acetylates and irreversibly inhibits primarily COX-1 both in platelets, preventing the formation of TXA_2 , and in endothelial cells, inhibiting the synthesis of PGI_2 (anticoagulant, antiplatelet, and fibrinolytic (thrombolytic)). While endothelial cells can synthesize cyclooxygenase, platelets cannot [16–20]. The goal of therapy with aspirin is to selectively inhibit the synthesis of platelet TXA_2. Low concentrations of PGE_2 enhance and higher concentrations inhibit platelet aggregation. Both PGI_2 and PGD_2 inhibit the PA in human *in vitro*. TXA_2, the major product of COX-1 in platelets, induces PA. Perhaps more importantly, TXA_2 acts as an amplification signal for other, more potent platelet agonists such as thrombin and adenosine diphosphate (ADP). The actions of TXA_2 on platelets are restrained by PGI_2, which inhibits platelet aggregation by all recognized agonists. Several approaches have been used in the clinical application of eicosanoids. Enzyme inhibitors and receptor antagonists have been developed to interfere with the synthesis or effects of the "pathologic" eicosanoids (i.e., TXs and LTs). For example, knowledge of eicosanoid synthesis and metabolism has led to the development of new NSAIDs that inhibit COX (especially COX-2), with improved pharmacokinetics and pharmacodynamics. The dual inhibitors block both the COX (especially COX-2) and LOX pathways. The vasodilator effects of PGE compounds have been studied extensively in hypertensive patients. These compounds also promote sodium diuresis. The PGE and PGI_2 compounds are used in Raynaud's phenomenon and peripheral atherosclerosis. In the latter case, prolonged infusions have been used to permit remodeling of the vessel wall and to enhance regression of ischemic ulcers. Eicosanoids are involved in thrombosis because TXA_2 promotes PA and PGI_2 inhibits it. Aspirin inhibits platelet COX to produce a mild clotting defect [16–20].

2. Pyridazinone as Prostaglandin and Thromboxane Inhibitor

A number of nonsteroidal anti-inflammatory drugs (NSAIDs) cause the dual inhibition of cyclooxygenase or PGs and 5-lipoxygenase (5-LOX) enzymes for treatment of inflammation and pain and pyrexia has been introduced as a novel therapeutic target. In addition, many studies also focused on pyridazine derivatives for developing potent and safer NSAIDs as well as antiplatelets or antithrombotic and antiarthritic activities. Among the various pyridazinone compounds, 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (Emorfazone) (**1**) was marketed as Pentoil and Nandron in Japan and 3-amino-6-methyl-pyridazine-4-thiol (*ES-1007*) (**2**) marketed in Germany as an analgesic and anti-inflammatory drug [21]. Moreover, it has been reported that 4-amino-2-methyl-6-phenyl-5-vinyl-3(2*H*)-pyridazinone (**3**) was sevenfold more potent than Emorfazone [22, 23] in bringing about analgesic and anti-inflammatory response [24] (see Scheme 1).

A series of 4-amino-3(2*H*)-pyridazinones substituted at position 2 with arylpiperazinylalkyl groups and analogues were tested for their analgesic effect in the mouse abdominal constriction model. Several of the compounds dosed at 100 mg/kg s.c. significantly reduced the number of writhes induced by the noxious stimulus. One compound showed 100% inhibition of writhes and was able to protect all the treated animals from the effect of the chemical stimulus. Subsequent dose-response studies revealed one compound to be almost 40-fold more potent than the structurally related Emorfazone. A series of 2-substituted 4,5-functionalized 6-phenyl-3(2*H*)-pyridazinones showed that some compounds were more active than the reference drug, Emorfazone, in inhibiting the effects of the noxious chemical stimulus, *p*-phenylquinone. Subsequent dose-response studies revealed one compound to be almost sevenfold more potent than Emorfazone [25].

Some peptidomimetics containing 6-aryl-pyridazinone compounds exhibited antiplatelet activity. The antiplatelet effect of dihydro-pyridizinonyl-peptidomimetics has been superior to that of simple dihydropyridezinones. The presence of halogen (chlorine) in 4-aryl group and a methyl group in pyridazinone has been shown to potentiate the antiplatelet effect. Incorporation of a dihydropyridazinone system into a peptide chain has been found to enhance the overall efficiency and stability of compounds. A series of 2-(4-substituted-piperazin-l-ylmethyl)-6-(thien-2-yl)-2*H*-pyridazin-3-ones, 2-(4-substituted-piperazin-l-yl-carbonylmethyl)-6-(thien-2-yl)-2*H*-pyridazin-3-ones, 2-[2-(4-substituted-piperazin-l-ylcarbonylethyl)]-6-(thien-2-yl)-2*H*-pyridazin-3-ones, 3-(4-substituted-piperazin-l-yl-carbonylmethyl-thio)-6-(thien-2-yl)pyridazines, 3-[2-4-substituted-piperazin-l-ylcarbonyl-ethylthio]-6-(thien-2-yl)pyridazines, and 5-(4-substituted piperazin-l-ylmethyl)-6-(thien-2-yl)-2*H*-pyridazin-3-ones exhibited anti-inflammatory activity. Some 3-oxo-5-benzylidene-6-methyl-(4*H*)-2-substituted pyridazines showed analgesic and anti-inflammatory activity [26]. Vicinally disubstituted pyridazinones as potent and selective COX-2 inhibitors, the lead compound in the series, ABT-963, 2-(3,4-Difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-2*H*-pyridazin-3-one (**4**), have excellent selectivity (ratio of 276, COX-2/COX-1) in human blood, high oral anti-inflammatory potency *in vivo*, and gastric safety in the animal studies. ABT-963 reduced PGE_2 production and reduced analgesia and inflammation dose dependently. ABT-963 is a highly selective COX-2 inhibitor that may have utility in the treatment of the pain and inflammation associated with arthritis [27]. Some 2-(6-oxo-3,5-diphenyl-6*H*-pyridazin-1-yl)-acetamides (**5**) and



Emorfazone (1) ES-1007 (2) (3)

Scheme 1

3-[6-oxo-3,5-diphenyl-6*H*-pyridazin-1-yl)-propanamides were exhibited analgesic and anti-inflammatory activities more potent than reference drugs [28] (see Scheme 2).

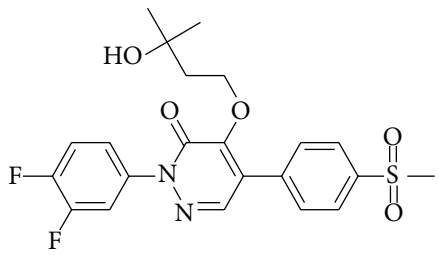
Recently, various compounds incorporating a 3(2*H*)-pyridazinone ring have been reported as analgesic and anti-inflammatory agents. Among these compounds, most 4,6-diphenyl-2-[3-(4-arylpiperazin-1-yl)propyl]-3(2*H*)-pyridazinone (**6**) derivatives were more potent than acetaminophen and noramidopyrine. In addition, 2-substituted 4,5-dihalo-3(2*H*)-pyridazinone derivatives had high analgesic activity. The 6-(4-methoxyphenyl)-3(2*H*)-pyridazinone (**7**) derivatives carry acetamide and propanamide moieties at position 2 of the pyridazinone ring and it was reported that 1-[3-[6-(4-methoxyphenyl)-3(2*H*)-pyridazinon-2-yl] propanoyl]-4-(4-fluorophenyl)piperazine (**8**) had the significant analgesic activity. Some compounds of 6-substituted-3(2*H*)-pyridazinones and the 6-[4-(4-fluorophenyl)]piperazine-3(2*H*)-pyridazinone series and 4,6-diphenyl-3(2*H*)-pyridazinones substituted by 4-arylpiperazin-1-yl-carbonyl-alkyl moieties on the nitrogen atom in position 2 of the pyridazinone ring exhibited analgesic and anti-inflammatory activity [29, 30]. A series of structurally diverse amide derivatives of 3-[1-(3-pyridazinyl)-5-phenyl-1*H*-pyrazole-3-yl]propanoic acids (**9**) exhibited *in vivo* analgesic activity, approximately equipotent to aspirin [31]. Some amide derivatives, [6-(4-methoxyphenyl)-3(2*H*)-pyridazinone-2-yl] acetamide (**10**) and propanamide, were reported as potential analgesic compounds. Moreover, some studies for developing COX-2 inhibitors have concentrated on the amide derivatives of currently used NSAIDs [30] (see Scheme 3).

A series of structurally diverse amide derivatives of [6-(3,5-dimethyl-4-chloro-pyrazole-1-yl)-3(2*H*)-pyridazinone-2-yl]acetic acid (**11**) exhibited *in vivo* analgesic and anti-inflammatory activity, equipotent to aspirin and indometacin as reference drug, respectively [32]. The antihypertensive 5-methyl-6-p-cyanophenyl-4,5-dihydro-3(2*H*)-pyridazinone (**12**) has been embodied in a rigid framework corresponding to a 4,4-dihydro-5*H*-indeno[1,2-c]-3-pyridazinonic structure. The resulting 7-cyano derivative was found to be devoid of antihypertensive activity. However this compound, as well as other members having structure, exhibited anti-inflammatory properties [33]. Some 6-substituted-3(2*H*)-pyridazinone-2-acetyl-2-(p-substituted benzal) hydrazone derivatives exhibited more potent analgesic activity than aspirin. Also these derivatives demonstrated anti-inflammatory activity as well as standard compound indomethacin. None of the compounds showed gastric ulcerogenic effect compared with reference NSAIDs. For reducing gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) a variety of 6-phenyl/(4-methylphenyl)-3(2*H*)-pyridazinon-2-propionamides (**13**&**14**) were tested *in vivo*. Compound 6-phenyl-3(2*H*)-pyridazinon-2-yl-[4-(4-fluorophenyl)piperazinyl] propanamide (**15**) was the most active one among the synthesized compounds. Also this compound exhibited the most potent anti-inflammatory activity; aspirin and indometacin were used as reference drugs. None of the compounds showed gastric ulcerogenic effect compared with the reference NSAIDs [34, 35] (see Scheme 4).

A number of pyridazinone derivatives bearing an arylpiperazinylalkyl chain were tested in a model of acute nociception induced by thermal stimuli in mice (tail flick). One compound was 4-fold more potent than morphine, suggesting a significant bioavailability. The same compound also showed high potency in the hot plate test [36].

3. Antiplatelets, Antithromboxanes, and Antiprostaglandins

Some compounds of 6-aryl-4,5-dihydro-3(2*H*)-pyridazinone series exhibited a strong antiplatelet action coupled with a hypotensive action. A series of 6-phenyl-3(2*H*)-pyridazinones bearing different substituents in position 5 of the pyridazinone ring exhibited new platelet-aggregation inhibitors [7]. The effects of 6-(2,3,4,5-tetrahydro-5-methyl-3-oxo-pyridazine-6-yl)-1,2,3,4-tetrahydro-1-methyl quinolin-2-one (Y-590) (**16**) on platelet phosphodiesterases (PDE). Compound Y-590 incubated with washed rabbit platelets did not affect the cyclic AMP (cAMP) content. But when added to the washed platelets 1.5 minutes before PGs-I2, it potentiated the ability of the latter to increase cAMP. Y-590 potently inhibited cAMP-PDE in rabbit platelets, but its inhibitory effect on cGMP-PDE was less potent. The concentration of Y-590 causing inhibition of cAMP-PDE was of the same degree as that inhibiting platelet aggregation. These results indicate that Y-590 is a selective inhibitor of cAMP-PDE which exerts its antiplatelet activity by inhibiting cAMP degradation in platelets [37]. The effects of 2-(2-dimethylaminoethyl)-5-benzylidene 6-methyl (2*H*,4*H*)-3-pyridazinone (**17**) were studied on the biosynthesis of TXA_2 and PGI_2 *in vitro* and TXA_2 and PGI_2 synthetase activity of heart tissue.



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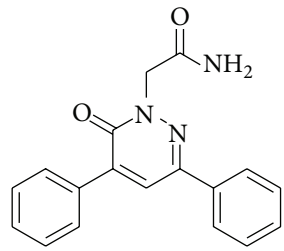

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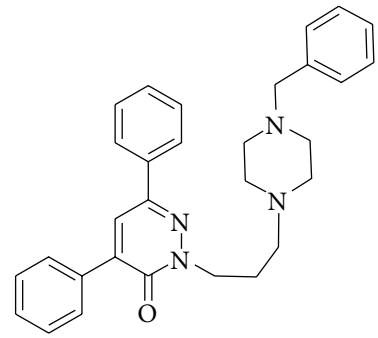

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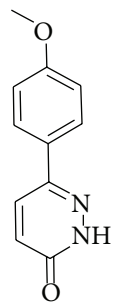
Scheme 2



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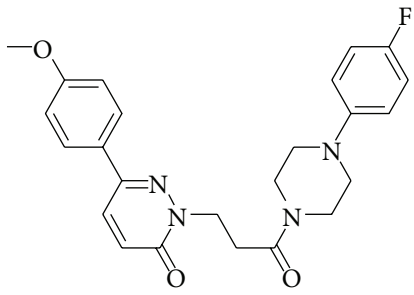

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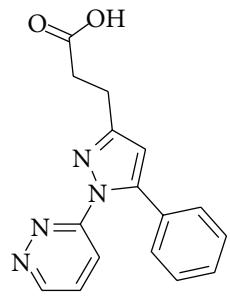

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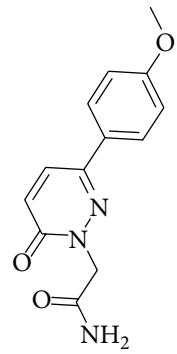

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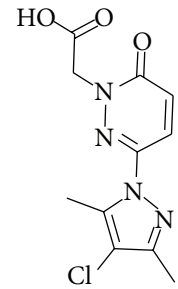
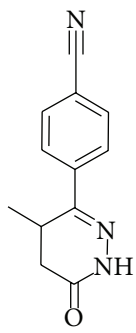


(11)

Scheme 3



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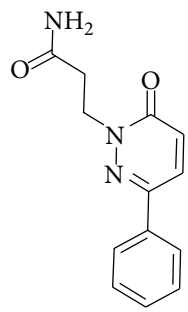

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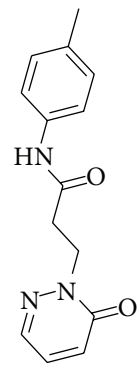

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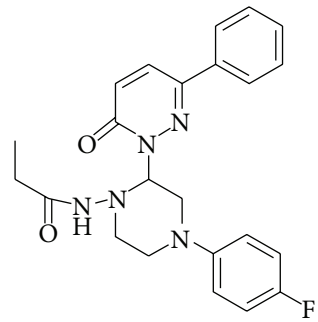

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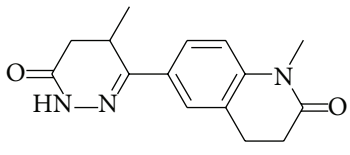
Scheme 4



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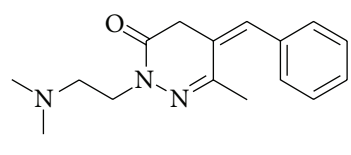

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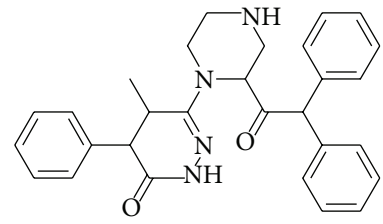


(18)

Scheme 5

Biosyntheses of TXA_2 and PGI_2 were carried out using arachidonic acid as a substrate and horse platelet and aorta microsomes as sources of TXA_2 and PGI_2 synthetases, respectively. TXB_2 and 6-keto PGF1α were determined by RIA. It did not significantly modify either the biosynthesis of PGI_2 *in vitro* or the PGI_2 synthetase activity of heart tissue. It did not significantly inhibit TXA_2 biosynthesis *in vitro* but markedly reduced the TXA_2 synthetase activity of heart tissue. Thus it behaves as a specific inhibitor of the TXA_2 synthetase activity of heart tissue and could have a beneficial use in therapeutics [38]. Compound 6-(α,α-diphenylacetylpiperazinyl)phenyl-5-methyl-4,5-dihydro-3-(2*H*)-pyridazinone (DMDP) (**18**) was shown to inhibit AA-, ADP- and PAF-induced rabbit platelet aggregation. At the concentration range of 1–500 μmol/L, the compound was found to depress TXB_2 content and to increase cAMP levels in washed rabbit platelets in a dose-dependent manner. These might be the mechanisms of the compound on the inhibition of rabbit platelets [39] (see Scheme 5).

A novel optically pure pyridazinone derivative was identified as a nonprostanoid PGI_2 agonist. It inhibited ADP-induced aggregation of human platelets and has high oral bioavailability (56%) with a long half-life (4.3 h) in rats [40]. The pyridazinone derivative zardaverine has been introduced as a potent bronchodilator. In addition, zardaverine exerts a positive inotropic action on the heart muscle *in vitro*. The actions of zardaverine are thought to be mediated via inhibition of phosphodiesterase (PDE) activity. The effects of zardaverine on the different PDE isozymes were investigated in several tissues. Zardaverine inhibited the cyclic GMP-inhibitable PDE III from human platelets and the rolipram-inhibitable PDE-IV from canine trachea and human polymorphonuclear (PMN) cells. Zardaverine affected the calmodulin-stimulated PDE I, the cyclic GMP-stimulated PDE II, and the cyclic GMP-specific PDE-V only marginally at concentrations up to 100 μM. Zardaverine inhibits the ADP-induced aggregation of human platelets. This inhibition was synergistically increased by activators of adenylate cyclase such as PGE_1 and forskolin. In human, zardaverine inhibited the zymosan-induced superoxide anion generation. Again, this effect was increased by activators of adenylate cyclase. Zardaverine is a selective inhibitor of PDE-III and PDE-IV isozymes [6]. In a series of 5-acyl-6-phenyl-2,4-substituted-3(2*H*)-pyridazinone derivatives, with a sulfur stereogenic center, had the most potent activity as human platelet aggregation inhibitor [41]. Compound PC-09, a new pyridazinone derivative, has antiplatelet activity *in vitro*. Pretreatment with PC-09 resulted in an inhibition on rabbit platelet aggregation and ATP release induced by AA, collagen, or thrombin. The THX-B2 formation caused by collagen or thrombin was markedly inhibited by PC-09, but there was no alteration in that caused by AA. The rise of platelet intracellular Ca^{+2} level stimulated by aggregation agonists and collagen-induced platelet membrane surface glycoprotein IIb/IIIa expression was also reduced by PC-09. In addition, PC-09 itself significantly increased the cAMP level through inhibiting cAMP PDE activity. These findings demonstrate that PC-09 is an inhibitor of platelet aggregation, which may be associated with mechanisms including inhibition of THX-A2 formation, intracellular calcium mobilization, and platelet surface GPIIb/IIIa expression accompanied by increasing cAMP level [42].

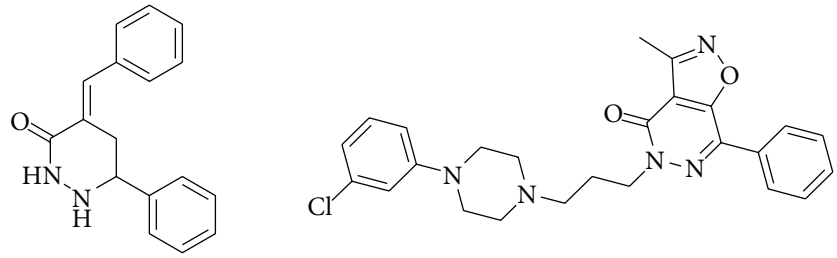
Many studies have been focused on 3(2*H*)-pyridazinones, which are characterized by possessing good analgesic and anti-inflammatory activities and also very low ulcerogenicity. Condensed 3(2*H*)-pyridazinones have become interesting structures for medicinal chemists. However, the biological properties of isoxazolo[4,5-d]pyridazin-4(5*H*)-ones, which are condensed 3(2*H*)-pyridazinone derivatives. One of the most extensive studies on biological activities of isoxazolopyridazinones was done by Giovannoni and coworkers. They evaluated the analgesic activities of a series of isoxazolo[3,4-d]- and isoxazolo pyridazinone derivatives. They reported that 5-{[4-(3-chlorophenyl)piperazine-1-yl]propyl}-3-methyl-7-phenylisoxazolo[4,5-d]pyridazin-4(5*H*)-one (**21**) showed higher analgesic activity than morphine. This interesting result prompted us to synthesize and screen the new NSAIDs [29, 30] (see Scheme 6).

The 6-phenyl-4-substituted benzylidene tetrahydropyridazin-3(2*H*)-one (**23**) derivatives exhibited significant analgesic activity [43]. 4,5-Dihydro-3(2*H*) pyridazinones such as CI-914, CI-930, and pimobendan along with tetrahydropyridopyridazine (endralazine) have been used as potent positive inotropes, antihypertensives, and platelet aggregation inhibitors. The pharmacophore models were computed to get useful insight into the essential structural features required for inhibiting phosphodiesterase-III in the heart muscles and blood vessels [44]. Some isoxazolo[4,5-d]pyridazin4(5*H*)-one derivatives exhibited analgesic activity, using morphine and diclofenac as references [45]. In the study, isoxazolo[4,5-d]pyridazin-4(5*H*)-one derivatives exhibited analgesic activities. Structure of 5-{[4-(3-chlorophenyl)-piperazine-1-yl]propyl}-3-methyl-7-phenylisoxazolo[4,5-d]pyridazin-4(5*H*)-one.

Some 2-[5,6-diphenyl-3(2*H*)-pyridazinone-2-yl]acetamide (**24**) and 3-[5,6-diphenyl-3(2*H*)-pyridazinone-2-yl]propanamide (**25**) derivatives showed *in vivo* analgesic and anti-inflammatory activities. Propanamide derivatives were found to be more potent than acetamide derivatives in terms of anti-inflammatory activity and some derivatives did not cause any gastric lesions and bleeding in stomachs of tested animals. Inhibitory activity of the active compounds on COX isoforms was also investigated by using *in vitro* human "whole blood assay" and it was found that these derivatives did not exert their analgesic and anti-inflammatory activities through COX inhibition and other mechanisms might be involved See Schemes 7–13.

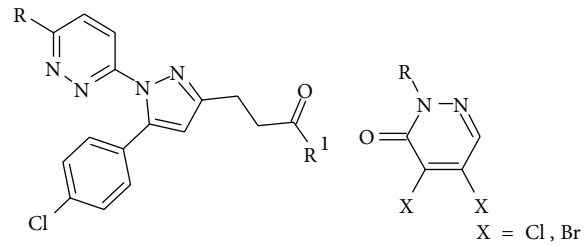
4. Overview of NSAIDs

The PGs and TXs have major effects on smooth muscle. Other important targets include platelets and monocytes, kidneys, the CNS, autonomic presynaptic nerve terminals, sensory nerve endings, endocrine organs, adipose tissue, and the eye (smooth muscle). Platelet-activating factors (PAF) generally contract gastrointestinal, uterine, and pulmonary smooth

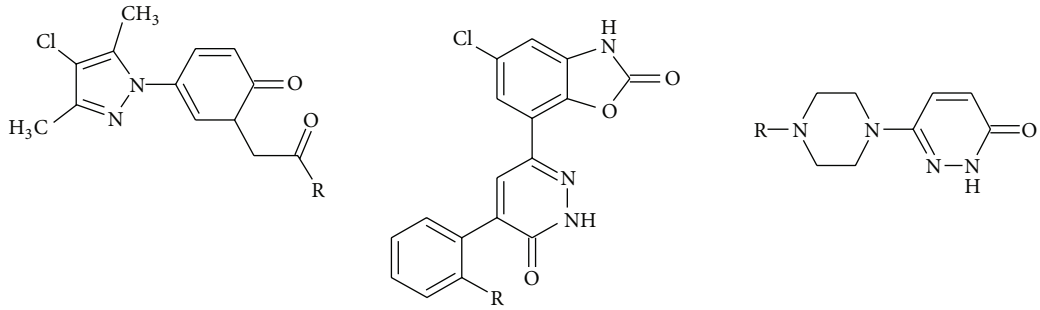


(23) **(21)**

Scheme 6

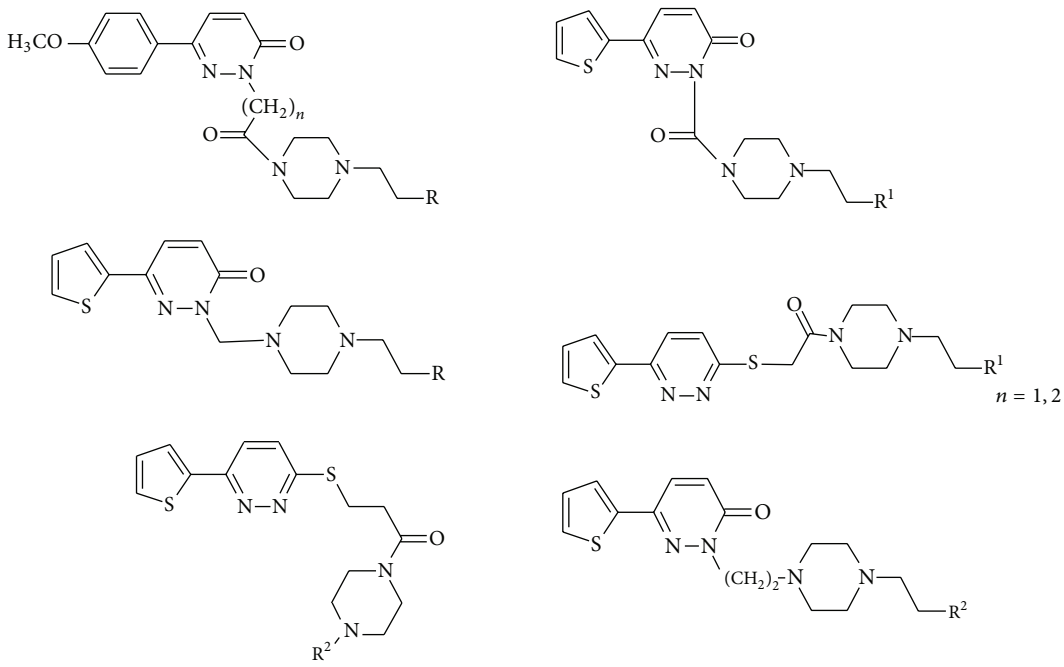


Scheme 7: R: Cl, R^1: amino phenyl derivatives, piperazine derivatives, and amino alkyl derivatives.

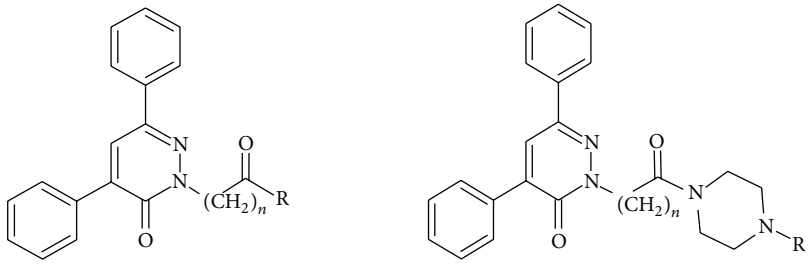


Scheme 8: R: derivatives of phenyl piperazine, pyridinyl piperazine, amino alkyl, amino ethyl benzene, and amino pyridine.

muscles. These contractions are inhibited by inhibitors of PG synthesis. PAF does not affect tracheal smooth muscle but contracts airway smooth muscle. Most evidence suggests that another autacoid (e.g., LTC_4 or TXA_2) mediates this effect of PAF. PAF also increases mucus secretion and the permeability of pulmonary microvessels. TXA_2 is a potent vasoconstrictor. PGF_2 is also a vasoconstrictor. Vasodilator PGs, especially PGI_2 and PGE_2, promote vasodilation by increasing cAMP and decreasing smooth muscle intracellular calcium. Most of the PGs and TXs activate gastrointestinal smooth muscle. Longitudinal muscle is contracted by PGE_2 and PGF_2, while circular muscle is contracted strongly by PGF_2 and weakly by PGI_2 and relaxed by PGE_2. Respiratory smooth muscle is relaxed by PGD_2 , PGE_1 , PGE_2, and PGI_2 and contracted by TXA_2 and PGF_2. Platelet aggregation (PA) is markedly affected by eicosanoids. PGE_1 and especially PGI_2 effectively inhibit aggregation, while TXA_2 is a potent PA. Platelets release TXA_2 during activation and aggregation, suggesting that thrombotic events such as myocardial infarction may result in the release of TXA_2. In fact, urinary metabolites of TXA_2 increase in patients experiencing a myocardial infarction even if they are receiving low-dosage aspirin. At this aspirin dosage, TXs synthesis is significantly inhibited only in platelets. This suggests that other cells may contribute to the increase in TXA_2; these other cells may be monocytes, since monocytes have a high capacity for sustained release of TXA_2. Neutrophils and lymphocytes synthesize little if any PGs, while monocytes have a substantial capacity for PGs and TXs synthesis through both constitutive and inducible COXs. Human eosinophils also seem to have a high capacity for PG and TXs synthesis. Both medulla and cortex of kidney synthesize PGs, the medulla considerably more than the cortex. In the normal kidney, this increases the synthesis of the vasodilator PGs. Therefore, patient response to a loop diuretic will be diminished if a COX inhibitor is administered concurrently. TXA_2 causes intrarenal vasoconstriction (antidiuretic-hormone- (ADH-) like effect), resulting in a decline in renal function. The normal kidney synthesizes only small amounts of TXA_2. However, in renal conditions involving glomerulonephritis, the inflammatory cells release substantial amounts of TXA_2. The TXA_2 synthase inhibitors should improve renal function in the patients. Hypertension is associated with increased TXA_2 and decreased PGE_2 and PGI_2 synthesis in some animal models. PGE_2 may

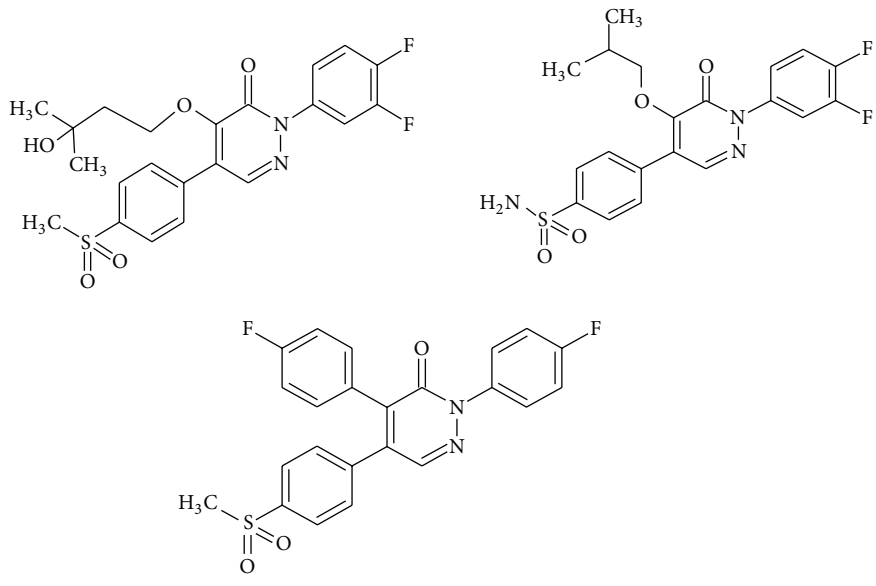


Scheme 9: R: CH_3, C_2H_5, C_6H_5, $CH_2C_6H_4$, p-FC_6H_4, 2-pyridyl; R^1: 4-F-CH_3, 2-pyridyl, C_2H_5; R^2: $CH_2C_6H_4$, C_6H_5.

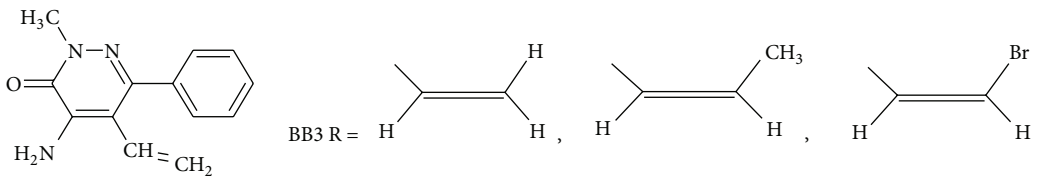


R = piperazine, $n = 1, 2$

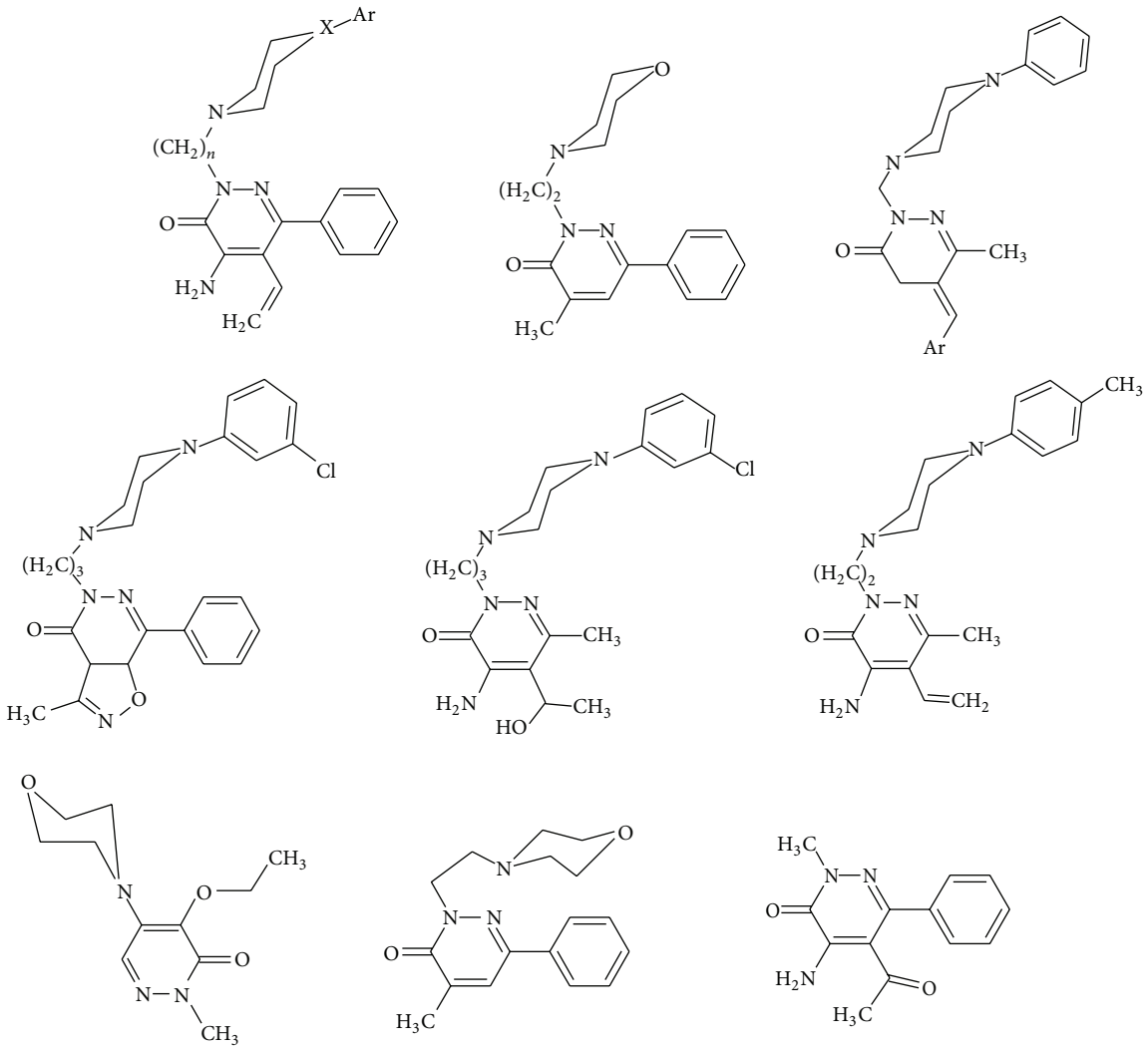
Scheme 10



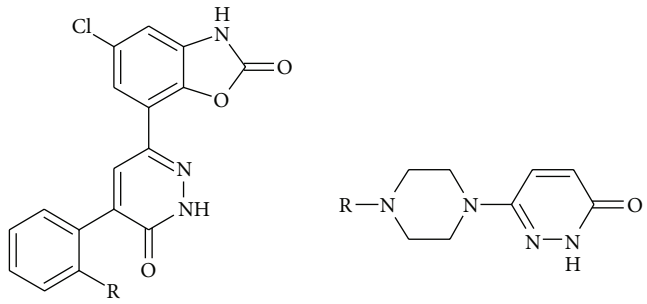
Scheme 11: ABT-963, A-282904, and A-241611.



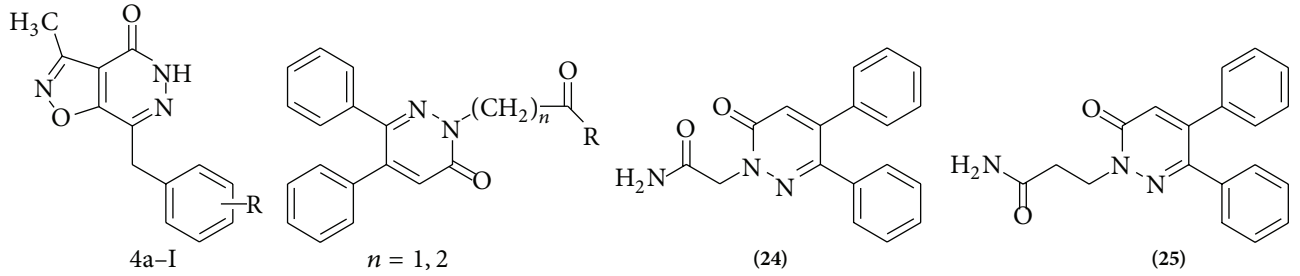
Scheme 12



Scheme 13: BB3 AG 246, FR8 FR10 CM8, and AG 246 CF8 reported some pyridazine-containing structures with analgesic and anti-inflammatory effects.



Scheme 14: R: derivatives of phenyl piperazine, pyridinyl piperazine, amino alkyl, amino ethylbenzene, and aminopyridine.



Scheme 15: R: -C_6H_5, -4-F-C_6H_4, -3Cl-C_6H_4, -CH_2-C_6H_5, -4Cl-C_6H_5, pyridyl, 2-F-C_6H_4, 5-ethyl-benzo[1, 3]dioxole.

also be involved in renal phosphate excretion. However, the physiologic role of this eicosanoid may be limited because the proximal tubule, the major site for phosphate transport, produces few PGs [46, 47].

The PGE compounds inhibit the release of norepinephrine from postganglionic sympathetic nerve endings. Moreover, NSAIDs increase norepinephrine release *in vivo*, suggesting that the PGs play a physiologic role in this process. Thus, vasoconstriction observed during treatment with COX inhibitors may be due to increased release of norepinephrine as well as to inhibition of the endothelial synthesis of the vasodilators PGE_2 and PGI_2. The NSAIDs (e.g., aspirin, indomethacin, and ibuprofen) block both PGs and TXs formation by inhibiting COX activity. The development of selective thromboxane synthase inhibitors and TXA_2 receptor antagonists has required considerable effort. They are being tested in the treatment of thromboembolism, pulmonary hypertension, and preeclampsia-eclampsia. Selective inhibitors of the lipoxygenase (LOX) pathway are also mainly investigational. With a few exceptions, NSAIDs do not inhibit LOX activity at concentrations that markedly inhibit COX activity. In fact, by preventing arachidonic acid (AA) conversion via the COX pathway, NSAIDs may cause more substrate to be metabolized through the LOX pathways, leading to an increased formation of the inflammatory leukotrienes. Even among the COX-dependent pathways, inhibiting the synthesis of one derivative may increase the synthesis of an enzymatically related product. Therefore, researchers are attempting to develop drugs that inhibit both COX and LOX [48–51].

5. Therapeutic Effects

All NSAIDs, including selective COX-2 inhibitors, are antipyretic, analgesic, and anti-inflammatory, with the exception of acetaminophen, which is antipyretic and analgesic but is largely devoid of anti-inflammatory activity. These drugs usually are effective only against pain of low-to-moderate intensity. Although their efficacy is much less than the opioids, NSAIDs lack the unwanted adverse effects of opiates in the CNS, respiratory depression, and physical dependence. The release of PGs by the endometrium during menstruation may cause severe cramps and other symptoms of primary dysmenorrhea; treatment of this condition with NSAIDs has been met with considerable success [52–54]. The selective COX-2 inhibitors are also efficacious in this condition. NSAIDs reduce fever in most situations, but not the circadian variation in temperature or the rise in response to exercise or increased ambient temperature. NSAIDs and selective COX-2 inhibitors suggest that COX-2 is the dominant source of PGs that mediate the rise in temperature evoked by bacterial LPS administration. This is consistent with the antipyretic clinical efficacy of both subclasses of NSAIDs. NSAIDs are used for the management of fever [55]. NSAIDs are used as anti-inflammatory agents in the treatment of musculoskeletal disorders, such as RA and osteoarthritis. A number of NSAIDs are used for the treatment of ankylosing spondylitis and gout. The use of NSAIDs for mild arthropathies, together with rest and physical therapy, generally is effective. When the symptoms are limited either to trouble sleeping because of pain or significant morning stiffness, a single NSAID dose given at night may suffice. PGs also have been implicated in the maintenance of patency of the ductus arteriosus, and some NSAIDs have been used in neonates to close the inappropriately patent ductus. Both COX-1 and COX-2 appear to participate in maintaining patency of the ductus arteriosus in fetal lambs, while in mice COX-2 appears to play the dominant role [56–59].

6. Other Clinical Uses

Mastocytosis is a condition in which there are excessive mast cells in the bone marrow, reticuloendothelial system, gastrointestinal system, bones, and skin. The PGD_2, released from mast cells in large amounts, has been found to be the major mediator of severe episodes of vasodilation and hypotension; this PGD_2 effect is resistant to antihistamines. However, tNSAIDs can cause degranulation of mast cells, so blockade with anti-H_1 and H_2 histamine receptors should be established before NSAIDs are initiated. Bartter's syndrome includes a series of rare disorders characterized by hypokalemic and hypochloremic metabolic alkalosis with normal blood pressure and hyperplasia. Fatigue, muscle weakness, diarrhea, and dehydration are the main symptoms. Renal COX-2 is induced and biosynthesis of PGE_2 is increased. Treatment with indomethacin, combined with potassium repletion and spironolactone, is associated with improvement in the biochemical derangements and symptoms. Selective COX-2 inhibitors also have been used in chemoprevention of cancer where the potential use of aspirin and/or NSAIDs is under active investigation. The studies showed that aspirin is associated with as much as a 50% decrease in the risk of colon cancer and other cancers.

NSAIDs have been used in familial adenomatous polyposis (FAP), an inherited disorder characterized by multiple adenomatous colon polyps developing during adolescence and the inevitable occurrence of colon cancer. Increased expression of COX-2 has been reported in multiple epithelial tumors, and in some cases the degree of expression has been related to prognosis [60–62].

7. Adverse Effects of Currently Used NSAID Therapies

Common adverse effects that complicated the therapy of currently used NSAIDs. Age generally is correlated with an increased probability of developing serious adverse effect of NSAIDs. The most common symptoms of NSAIDs are gastrointestinal, including anorexia, nausea, dyspepsia, abdominal pain, and diarrhea. These symptoms may be related to the induction of gastric or intestinal ulcers. Ulceration may range from small superficial erosions to full-thickness perforation of the muscularis mucosa. The ulceration can be accompanied by gradual blood loss leading to anemia or by life-threatening hemorrhage. The risk is further increased in those with *Helicobacter pylori* infection, heavy alcohol consumption, mucosal injury, and use of glucocorticoids. Although there is a perception that tNSAIDs vary considerably in their tendency to cause such erosions and ulcers, epidemiological studies suggest that combining low-dose aspirin (for cardioprotection) with other NSAIDs synergistically increases the likelihood of g.i.t adverse events. All of the selective COX-2 inhibitors have been shown to be less prone than equally efficacious doses of tNSAIDs to induce endoscopically visualized gastric ulcers [63]. While the COX-2-selective inhibitors are associated with a decreased incidence of g.i.t adverse events, the results were tempered by a fivefold increase in the incidence of MI, probably reflecting a cardiovascular hazard in predisposed individuals treated with selective COX-2 inhibitors together with a modest cardioprotective effect of naproxen. Gastric damage by NSAIDs can be brought about by at least two distinct mechanisms. Inhibition of COX-1 in gastric epithelial cells depresses mucosal cytoprotective PGs, especially PGI_2 and PGE_2. These eicosanoids inhibit acid secretion by the stomach, enhance mucosal blood flow, and promote the secretion of cytoprotective mucus in the intestine. Inhibition of PGI_2 and PGE_2 synthesis may render the stomach more susceptible to damage and can occur with oral, parenteral, or transdermal administration of aspirin or NSAIDs. There is some evidence that COX-2 also contributes to constitutive formation of these PGs by human gastric epithelium; products of COX-2 certainly contribute to ulcer healing in rodents. This may partly reflect an impairment of angiogenesis by the inhibitors. Indeed, coincidental deletion or inhibition of both COX-1 and COX-2 seems necessary to replicate NSAID-induced gastropathy in mice, and there is some evidence for gastric pathology in the face of prolonged inhibition or deletion of COX-2 alone. Another mechanism by which NSAIDs or aspirin may cause ulceration is by local irritation from contact of orally administered drug with the gastric mucosa. Local irritation allows backdiffusion of acid into the gastric mucosa and induces tissue damage. It also is possible that enhanced generation of LOX products (e.g., LTs) contributes to ulcerogenicity in patients treated with NSAIDs. Coadministration of the PGE_1 analog *misoprostol* or proton pump inhibitors (PPIs), which now are available over the counter in the USA, in conjunction with NSAIDs can be beneficial in the prevention of duodenal and gastric ulceration. While a combination of aspirin with a selective COX-2 inhibitor will undermine its distinction from a tNSAID with respect to serious GI complications, we do not know if the combination retains an advantage over aspirin plus a tNSAID [64–68].

7.1. Cardiovascular. NSAIDs, unlike aspirin, are not thought to afford cardioprotection [69]. Epidemiological evidence of cardioprotection is less impressive; it suggests about a 10% reduction in MI, compared to 20% to 25% with low-dose aspirin. This would fit with heterogeneity of response to naproxen. Controlled evaluation of naproxen in cardioprotection has not been performed, and naproxen should not be used as a substitute for aspirin for this purpose. Several groups have attached nitric-oxide-donating moieties to NSAIDs and to aspirin in the hope of reducing the incidence of adverse events. It seems likely that benefit may be attained by abrogation of the inhibition of angiogenesis by tNSAIDs during ulcer healing in rodents [70]. However, the clinical benefit of this strategy remains to be established. Similarly, LTs may accumulate in the presence of COX inhibition, and there is some evidence in rodents that combined LOX-COX inhibition may be a useful strategy. Combined inhibitors are under clinical evaluation [71]. Selective inhibitors of COX-2 depress PGI_2 formation by endothelial cells without concomitant inhibition of platelet TXs. Experiments in mice suggest that PGI_2 restrains the cardiovascular effects of TXA_2, affording a mechanism by which selective inhibitors might increase the risk of thrombosis. This mechanism should pertain to individuals otherwise at risk of thrombosis, such as those with rheumatoid arthritis, as the relative risk of myocardial infarction is increased in these patients compared to patients with osteoarthritis or no arthritis. The incidence of MI and stroke has diverged in such at-risk patients when COX-2 inhibitors are compared with tNSAIDs. Placebo-controlled trials have now revealed an increased incidence of MI and stroke in patients treated with rofecoxib, valdecoxib, and celecoxib consistent with a mechanism-based cardiovascular hazard for the class [72, 73]. All three drugs increase the risk of heart attack and stroke and will be labeled accordingly and restricted with respect to marketing directly to consumers. Patients at increased risk of cardiovascular disease or thrombosis are particularly prone to cardiovascular adverse events on these agents.

NSAIDs and COX-2 inhibitors have been associated with renal and renovascular adverse events [74]. NSAIDs have little effect on renal function or blood pressure in normal human. However, in patients with congestive heart failure, hepatic cirrhosis, chronic kidney disease, hypovolemia, and other states of activation of the sympathoadrenal or renin-angiotensin systems, PG formation becomes crucial in model systems and in humans [75]. NSAIDs are associated with loss of the PG-induced inhibition of both the reabsorption

of Cl^- and the action of ADH, leading to the retention of salt and water. The generation of vasodilator PGE_2 and PGI_2 to COX-2 raises the possibility that the incidence of hypertensive complications induced by NSAIDs in patients may correlate with the degree of inhibition of COX-2 in the kidney and the selectivity with which it is attained. Deletion of receptors for both PGI_2 and PGE_2 elevates blood pressure (BP) in mice, mechanistically integrating hypertension with a predisposition to thrombosis. Although this hypothesis has never been addressed directly, epidemiological studies suggest that hypertensive complications occur more commonly in patients treated with coxibs than those with tNSAIDs. NSAIDs promote reabsorption of K^+ as a result of decreased availability of Na^+ at distal tubular sites and suppression of the PG-induced secretion of renin. NSAIDs displayed hypersensitivity, manifested by symptoms such as vasomotor rhinitis with profuse watery secretions, angioedema, urticaria, bronchial asthma to laryngeal edema, bronchoconstriction, flushing, hypotension, and shock. Aspirin intolerance is a contraindication to therapy with any other NSAID because cross sensitivity can provoke a life-threatening reaction reminiscent of anaphylactic shock. Treatment of aspirin hypersensitivity is similar to that of other severe hypersensitivity reactions, with support of vital organ function and administration of epinephrine. Aspirin hypersensitivity is associated with an increase in biosynthesis of LTs, perhaps reflecting diversion of AA to LOX metabolism. The therapeutic use of the tNSAIDs has been limited by poor tolerability. Chronic users are prone to experience gastrointestinal irritation in up to 20% of cases. However, the incidence of these adverse events had been falling sharply in the population prior to the introduction of the COX-2 (coxibs). Because expression of COX-2 enzyme was regulated by cytokines and mitogens, it was proposed to be the dominant source of PG formation in inflammation and cancer. The COX was the predominant source of cytoprotective PGs formed by the g.i.t epithelium [76, 77]. Thus, selective inhibition of COX-2 was postulated to afford efficacy similar to tNSAIDs but with better tolerability. Subsequent crystallization of COX-1 and COX-2 revealed remarkable conservation of tertiary structure. However, one difference was in the hydrophobic channel by which the AA substrate gains access to the COX active site, buried deep within the molecule. This channel is more accommodating in the COX-2 structure and consequently exhibits wider substrate specificity than in COX-1. It also contains a side pocket that in retrospect affords a structural explanation for the identification in screens of the two enzymes *in vitro* of small molecule inhibitors that are differentially specific for COX-2 [78]. Although there were differences in relative hierarchies, depending on whether screens were performed using recombinantly expressed enzymes, cells, or whole blood assays, most tNSAIDs expressed similar selectivity for inhibition of the two enzymes. The inhibition of COX-2 (coxibs) and several older drugs (e.g., nimesulide, diclofenac, and meloxicam) exhibits relative selectivity for COX-2 inhibition. Rheumatoid disease (RA) is one of the common chronic inflammatory conditions and is a common cause of disability. The joint changes, which probably represent an autoimmune reaction, comprise inflammation, proliferation of the synovium, and erosion of cartilage and bone. The primary inflammatory cytokines IL-1 and TNF-α have major role in pathogenesis. The drugs most frequently used in therapy are the disease-modifying anti-RA drugs (DMARDs) and the NSAIDs—the former so called to point up the comparison with the NSAIDs—which reduce the symptoms of RA disease but do not retard the progress of the disease. Some immunosuppressants (e.g., azathioprine, ciclosporin) are also used as are the glucocorticoids. Disease-modifying drugs such as methotrexate, sulfasalazine, gold compounds, penicillamine, and chloroquine improve symptoms and can reduce disease activity in RA, such as reduction in number of swollen and tender joints, pain score, disability score, and rheumatoid factor. DMARDs are often referred to as second-line drugs, and some have a place in the treatment of other chronic inflammatory diseases [79–81].

7.2. Rheumatoid Arthritis. It appears to be an autoimmune disease caused primarily by activation of T cells, giving rise to T-cell-derived cytokines, such as IL-1 and TNF-α. Activation of B cells and the humoral response also are evident, although most of the antibodies generated are IgGs, apparently elicited by polyclonal activation of B cells rather than from a response to a specific antigen. Many cytokines, including IL-1 and TNF-α, have been found in the rheumatoid synovium. Glucocorticoids interfere with the synthesis and actions of cytokines, such as IL-1 or TNF-α. Although some of the actions of these cytokines are accompanied by the release of PGs TXA_2, COX inhibitors block only their pyrogenic effects. Many of the actions of the PGs are inhibitory to the immune response, including suppression of the function of helper T cells and B cells and inhibition of the production of IL-1. Thus, COX-independent effects may contribute to the efficacy of NSAIDs. Besides certain NSAIDs can directly inhibit the activation and function of neutrophils, perhaps by blockade of integrin-mediated neutrophil responses [82, 83].

7.3. Mechanism of Action and Therapeutic Effects of NSAIDs. The NSAIDs at low concentrations inhibited the enzymatic production of PGs. PGs participated in the pathogenesis of inflammation and fever. The PGs are released whenever cells are damaged and NSAIDs inhibit their biosynthesis. However, NSAIDs generally do not inhibit the formation of other inflammatory mediators, including other eicosanoids such as the LTs. At higher concentrations, NSAIDs also reduce the production of superoxide radicals, induce apoptosis, inhibit the expression of adhesion molecules, decrease nitric oxide synthase, decrease proinflammatory cytokines (e.g., TNF-α, IL-1), modify lymphocyte activity, and alter cellular membrane functions [84].

7.4. Inhibition of Prostaglandin Biosynthesis by NSAIDs. The NSAIDs usually are classified as mild analgesics. NSAIDs are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia). Bradykinin, released from plasma kininogen, and cytokines,

such as TNF-α, IL-1, and IL-8, appear to be particularly important in eliciting the pain of inflammation. These agents liberate PGs and probably other mediators that promote hyperalgesia. In general, NSAIDs do not affect either hyperalgesia or pain caused by the direct action of PGs. The analgesic effects of these agents are due to inhibition of PG synthesis. However, some data have suggested that relief of pain may occur *via* mechanisms other than inhibition of PG synthesis, including antinociceptive effects at peripheral or central neurons [75, 85].

The principal therapeutic effects of NSAIDs are to inhibit PGs synthesis. The first enzyme in the PG synthetic pathway is PG-G/H synthase, also known as cyclooxygenase (COX). This enzyme converts arachidonic acid (AA) to the unstable intermediates PGG_2 and PGH_2 and leads to the production of thromboxane A_2 (TXA_2) and a variety of PGs. Therapeutic doses of NSAIDs reduced PG biosynthesis in humans by COX inhibitors and showed anti-inflammatory activity. There are two forms of cyclooxygenase (COX-1 and COX-2). COX-1 is a primarily constitutive isoform found in most normal cells and tissues, while cytokines and inflammatory mediators that accompany inflammation induce COX-2 production. However, COX-2 also is constitutively expressed in certain areas of the kidney and brain and is induced in endothelial cells [86–88]. Importantly, COX-1, but not COX-2, is expressed as the dominant, constitutive isoform in gastric epithelial cells and is the major source of cytoprotective PG formation. Inhibition of COX-1 at this site is thought to account largely for the gastric adverse events that complicate therapy with NSAIDs, thus providing the rationale for the development of NSAIDs specific for inhibition of COX-2. NSAIDs inhibit the COX enzymes and PG production; they do not inhibit the LOX pathways of AA metabolism and hence do not suppress LT formation. Glucocorticoids suppress the induced expression of COX-2 and thus COX-2-mediated PG production. They also inhibit the action of phospholipase A_2, which releases AA from the cell membrane. These effects contribute to the anti-inflammatory actions of glucocorticoids [57]. The vast majority of NSAIDs are act as reversible, competitive inhibitors of COX activity. Most NSAIDs inhibit both COX-1 and COX-2 with little selectivity. The hypothesis that the anti-inflammatory effects of NSAIDs would be accompanied by a lower ulcerogenic potential propelled efforts to design drugs with greater selectivity for COX-2 versus COX-1. These efforts led to the approval as selective COX-2 inhibitors. The hypothalamus regulates the set point at which body temperature is maintained. This set point is elevated in fever, and NSAIDs promote its return to normal. These drugs do not influence body temperature when it is elevated by factors such as exercise or in response to ambient temperature. Fever may reflect infection or result from tissue damage, inflammation, graft rejection, or malignancy. These conditions all enhance formation of cytokines such as IL-1, IL-6, interferons, and TNF-α. The cytokines increase synthesis of PGE_2 adjacent to the preoptic hypothalamic area; PGE_2, in turn, increases cyclic AMP and triggers the hypothalamus to elevate body temperature by promoting an increase in heat generation and a decrease in heat loss. NSAIDs suppress this response by inhibiting PGE_2 synthesis. PGs, especially PGE_2. As with pain, NSAIDs do not inhibit the fever caused by directly administered PGs; rather they inhibit fever caused by agents that enhance the synthesis of IL-1 and other cytokines, which presumably cause fever, by inducing the endogenous synthesis of PGs [72, 73].

8. Discussion

Interference with the synthesis of eicosanoids affects many therapeutic agents, including analgesics, anti-inflammatory drugs, and antithrombotic agents. In platelets, the major cyclooxygenase (COX) product is thromboxane A_2 (TXA_2), an inducer of platelet aggregation and a potent vasoconstrictor. NSAIDs block the production of TXA_2 and COX-1. The action of NASIDs (e.g., aspirin) on platelet COX is permanent. Moreover, they potentially are less efficacious because of inhibition of prostacyclin production. Higher doses also increase toxicity, especially bleeding, but thrombocytopenia and neutropenia can also occur. Those NSAIDs that are reversible inhibitors of COX-1 have not been shown to have antithrombotic efficacy. These NSAIDs are used to prevent the thrombotic stroke, angina, MI, and coronary artery diseases and in certain other high-risk patients. Currently used NSAIDs act by inhibiting the PGs-G/H synthase enzymes or COX-1 and COX-2. The inhibition of COX-2 mediates the antipyretic, analgesic, and anti-inflammatory actions, while the simultaneous inhibition of COX-1 largely but not exclusively accounts for unwanted adverse effects in the gastrointestinal tract. Mostly NSAIDs compete in a reversible manner with the arachidonic acid (AA) substrate at the active site of COX. Antipyretic and analgesic agents partly inhibited COXs but appear to have fewer g.i.t side effects than the NSAIDs. Histamine was one of the first identified mediators of the inflammatory process [89, 90]. Bradykinin, 5-hydroxytryptamine (serotonin, 5-HT), lipid autacoid, and platelet-activating factor (PAF) also may play a role in mediating inflammation. However, PAF inhibitor has been proven to be disappointing in the treatment of inflammation. The majority of currently known NSAIDs mainly act peripherally by blocking the production of PGs through inhibition of COX enzymes, COX-1 and COX-2, to varying extents. These drugs tend to produce side effects such as g.i.t ulceration and suppression of renal function due to inhibition of the constitutive COX-1, which is responsible for the production of PGs, responsible for gastroprotection and vascular homeostasis [91, 92]. 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. Thrombosis is the pathological extension of the normal haemostatic process that is required to prevent blood loss following damage to the vascular wall. Uncontrolled PA and platelet adhesion to the subendothelium of damaged blood vessels causes life-threatening diseases such as MI, transient ischemic attack, and unstable angina. Platelet activation is a complex phenomenon, which causes PA and plays an important role in occlusive thrombus formation at the site of adhesion and downstream after embolization. Both are

implicated as the early events in the genesis of angina, MI, and stroke. A general rule appears to be that a drug which causes an increase in intracellular cAMP inhibit platelet aggregation whereas agents resulting in a reduction in cAMP levels accelerate PA. This paper focused on inhibitors on platelet cAMP-PDE and those of TXA_2 synthase, with emphasis on newer, more potent compounds as potential antithrombotic agents [93–96].

9. Conclusion

Pyridazine and related compounds have shown diverse biological activities. They bind to physiological targets or receptors, producing many possible mechanisms of actions. Pyridazines are inexpensive and easily synthetically available and therefore have been examined as biologically active drugs. A slight variation in the substitution pattern on the pyridazine nucleus often causes a marked difference in activities and therefore pyridazines with various substituents are being synthesized and tested for varieties of pharmacological activities in search of better medicinal agents. Furthermore, some of these derivatives have been reported to exhibit significant biological activities and great interest has arisen in the design and synthesis of new pyridazines to explore their pharmacological activities. The pyridazine fused with other ring nucleus, which has a useful structure for further molecular exploration for the development of new derivatives with different biological activities, has received much attention in recent years.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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