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A Review on Pyridazinone Compounds ABT-963 as Selective Cyclooxygenase Inhibitor

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Abstract

Vicinally disubstituted pyridazinones act as potent and selective COX-2 inhibitors. Compound, ABT-963, (2-(3,4-difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methanesulfonyl-phenyl)-2*H*-pyridazin-3-one) has an excellent selectivity (ratio of 276, COX-2/COX-1), improved aqueous solubility compared with celecoxib and rofecoxib, high oral anti-inflammatory potency and gastric safety in the animals. After oral administration, ABT-963 reduced prostaglandin (PG) E2 production and reduced the edema. ABT-963 dose dependently reduced nociception. ABT-963 significantly reduced bone loss and soft tissue destruction. ABT-963 is a highly selective COX-2 inhibitor that may be used in the treatment of the pain and inflammation associated with arthritis.

Keywords: Cyclooxygenase; Thromboxane; Prostaglandin; ABT-963

Introduction

Nonsteriodal anti-inflammatory drugs (NSAIDs) are efficacious for the treatment of pain associated with inflammatory disease. Selective cyclooxygenase-2 (COX-2) inhibitors (such as celecoxib, rofecoxib, and valdecoxib) have used in the treatment of inflammatory pain with an improved gastrointestinal tract (g.i.t) safety profile relative to conventional NSAIDs. These COX-2 inhibitors contain a core heterocyclic ring with two appropriately substituted phenyl rings appended to adjacent atoms. The NSAIDs constitute an important class of drugs with therapeutic applications and used in the treatment of inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) starting from the classic drug aspirin to the recent rise and fall of selective COX-2 inhibitors. The study their mechanism of action at the molecular level such as cyclooxygenase (COX) inhibition, development of selective COX-2 inhibitors, their adverse cardiovascular effects. The recent developments targeted to the design of effective anti-inflammatory drugs with reduced side effects. The structural basis for COX-1 and COX-2 inhibition is described along with methods used to evaluate COX-1/COX-2 inhibition. Some of the recent advances toward developing effective anti-inflammatory agents such as nitric oxide donor NO-NSAIDs, dual COX/LOX inhibitors and anti-TNF therapy. A great deal of progress has been made toward developing novel anti-inflammatory agents. The design and development of a safe, effective and economical therapy for treating inflammatory conditions still presents a major challenge [1,2].

Prostaglandins (PG) play a significant role in the maintenance of homeostasis and in the body's response to the environment. Two isozymes of cyclooxygenase (COX) are responsible for the biosynthesis of these mediators commonly called COX-1 and COX-2. Xie et al. [3,4] and Smith [5] have proposed that COX-2-generated PGs are mediators of inflammation, cellular proliferation, and pain, whereas COX-1-generated PG are involved in homeostasis in the stomach, kidney, and blood coagulation [6-8]. Prostaglandins (PG) modulated the pain and edema observed in a variety of inflammatory disorders. These compounds also play a role in protection of the gastric lining, hemodynamic functions such as platelet aggregation, as well as having a role in normal renal function. The first enzyme in the PG pathway is PG-H synthase, and this enzyme catalyzes two activities, COX and hydroperoxidase. Usually, both activities are termed COX. There are two isozymes of COX, termed COX-1 and COX-2. A wealth of work indicates that COX-1 is constitutively expressed in most tissues, whereas COX-2 is not normally expressed but is induced by cytokines, hormones, and growth factors [9,5]. Until recently, most clinically used inhibitors of PG formation inhibit both isozymes of COX. The result of inhibiting both isozymes of the enzyme is clinically significant inhibition of pain and inflammation accompanied by a significant incidence of GIT distress and renal complications. The GIT distress seen in the clinic can be modeled in rats or dogs by giving high doses of conventional NSAIDs.

The studies have demonstrated that COX-2 expression is somewhat limited in that it is found in cells involved in the inflammatory process and in tissues that are undergoing accelerated proliferation such as those in cancer growth. The COX-1 is more widely expressed and is primarily involved in homeostasis [10]. Recent clinical and pharmacological studies demonstrate the benefit of selectively inhibiting COX-2 while leaving COX-1 active [7,11]. The search for selective COX-2 inhibitors has been a challenging one. The catalytic sites of the two enzymes are very similar [12] and thus it has been difficult to find selective compounds. Thus far, various agents have the tricyclic general structure first described for DuP-697 [13]. The marketed compounds share many of the structural characteristics of DuP-697. Therefore, a new distinct chemical series may offer the opportunity for improved selectivity *in vitro*, pharmacological superiority and enhanced safety. Structurally distinct chemical series of COX-2 inhibitors that have high selectivity and potency. These compounds, containing a central pyridazinone ring, in general show improved potency and selectivity compared with previously published compounds. The lead compound in the series, ABT-963 has improved selectivity in human whole blood, enhanced aqueous solubility compared with the currently marketed compounds, and high oral potency *in vivo* and gastric safety in animals [14]. The mechanism of action of anti-inflammatory and analgesic agents such

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as aspirin and indomethacin. The mechanism of action of aspirin and other NSAIDs thereby increasing our ability to develop novel anti-inflammatory therapies [15]. The success of NSAIDs in treating various inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA) validated inhibition of the enzyme prostaglandin H synthase (PGHS) or cyclooxygenase (COX) as a highly suitable target in anti-inflammatory therapies [16,17]. However, the g.i.t toxicities associated with widespread NSAIDs use proved to be a major drawback during long term therapy [18]. The presence of an inducible isoform of the enzyme COX later identified as COX-2 [9,19-22]. This discovery led to the hypothesis that anti-inflammatory prostaglandins (PGs) were produced through constitutive expression of COX-1, whereas the proinflammatory PGs were produced via induction of the COX-2 isoform [23-26]. The traditional NSAIDs were known to inhibit both isoforms of COX and their adverse GIT toxicities were attributed to the inhibition of gastro protective PGs produced via the COX-1 pathway. Thereafter, scientist's efforts on the design of selective COX-2 inhibitors in order to develop superior anti-inflammatory and analgesic agents with reduced adverse effects compared to traditional NSAIDs. In 1999, the first selective COX-2 inhibitor celecoxib. This was followed by the selective COX-2 inhibitor rofecoxib. In a short period of time both celecoxib and rofecoxib reached smash hit status achieving sales [27-34]. In spite of this initial success after the launch of selective COX-2 inhibitors, concerns were raised regarding their adverse cardiovascular events [35]. Further studies, demonstrated that selective COX-2 inhibitors may tip the natural balance between prothrombotic thromboxane A2 (TxA2) and antithrombotic prostacyclin (PGI2) potentially increasing the possibility of a thrombotic cardiovascular event [36-38]. In 2004 rofecoxib was withdrawn from the world-wide market. In 2005, the coxibs increase the risk of cardiovascular events and recommended the suspension of valdecoxib. Celecoxib was allowed to remain in the market place, but with a black box warning indicating a risk of adverse cardiovascular events [39,30]. Furthermore, commonly used NSAIDs to make labeling changes to their products suggesting that adverse cardiovascular events could be a general effect for this class of compounds. The traditional NSAIDs based on their benefit to risk ratio [40-42]. Recently, to the use of NSAIDs, withdraw selective COX-2 inhibitor lumiracoxib due to concern regarding its liver toxicity [43]. In this review is to discuss the COX pathway, enzyme functions, selective COX-2 inhibitors and their COX-1/COX-2 selectivities. The underlying basis for adverse cardiovascular effects and progress made in the development of novel anti-inflammatory agents having reduced g.i.t and cardiovascular adverse effects will be the focused [44-46].

Pyridazinone Inhibitors

The discovery of selective COX-2 inhibitors was facilitated by the description of the crystal structure of human COX-1 and mouse COX-2 structures [47,48] as well as early clues from known inhibitors. These data indicated the possibility of replacing some moieties of known inhibitors with other components. In particular, the replacement of the 5-membered central rings contained in DuP-697 and celecoxib with a six-membered pyridazinone ring yielded potent inhibitors of COX-2. Early members of this series gave potent inhibition of recombinant COX-2 and good selectivity as assessed by cellular COX assays. A number of substituents were examined at C-2. A-241611 (2,4-Bis-(4-fluoro-phenyl)-5-(4-methanesulfonyl-phenyl)-2H-pyridazin-3-one) represented an early lead from this series and quite selective for the inhibition of COX-2 as measured by cellular assays. The selectivity, as assessed in these assays, was superior to celecoxib and similar to rofecoxib. The compound exhibited dose dependent activity in both inhibiting PG production and inflammation. Given the activity of A-241611 *in vivo* in acute models, compound in a more chronic established adjuvant arthritis model [49]. At an oral dose of 1 mg/kg given over a 2-week period, A-241611 produced a 73% inhibition of paw edema and was comparable with celecoxib. In addition, A-241611 reduced both paw tissue damage and bone destruction. Although the initial anti-inflammatory activity of A-241611 was very encouraging in both acute and chronic models in the rat.

Characterization of ABT-963

A 4-butoxy substituted compound, A-282904 (4-[1-(3,4-Difluoro-phenyl)-5-isobutoxy-6-oxo-1,6-dihydro-pyridazin-4-yl]-benzenesulfonamide) was found to have excellent anti-inflammatory and analgesic properties. This compound was more potent for COX-2 inhibition than A-241611. However, this compound still suffered from poor solubility. The addition of a tertiary alcohol to the terminal carbon of the alkoxy chain yielded ABT-963 (2-(3,4-Difluoro-phenyl)-4-(3-hydroxy-3-methyl-butoxy)-5-(4-methane-sulfonyl-phenyl)-2H-pyridazin-3-one), a potent and selective COX-2 inhibitor that had significantly increased solubility as compared to the earlier compounds as well as celecoxib and rofecoxib Further, ABT-963 demonstrated improved selectivity in whole blood assays and an improved pharmacokinetic profile. The COX-2 was assessed using LPS challenged blood for 24 hours. ABT-963 was very selective in these assays with an IC_{50} of 17 nM for COX-2 and 4.7 μM for COX-1. A selectivity ratio (COX-2/COX-1) of 276 was calculated from this data. The ABT-963 was also found to be a potent inhibitor of PGE2 formation with an IC_{50} of 130 nM. Platelet eicosanoid production was also inhibited at μM concentrations. The potency of ABT-963 against isolated enzymes was also assessed in partially purified preparations of human COX-2 and COX-1 expressed in baculo virus. The enzymatic reaction was initiated with the substrate AA and the production of PGE2 assessed by enzyme immunoassay. Inhibition of COX-2 by several classes of selective inhibitors has been shown to be time-dependent while COX-1 inhibition is not [50]. This was also seen with the early pyridazinone inhibitors such as A-282904. The COX-2 inhibitory potencies have been shown to be assay condition dependent [51]. In this system, ABT-963 yielded an IC_{50} of 2 μM with no inhibition of COX-1 at 300 μM. Thus the compound gave a selectivity ratio of >150 in this assay. In comparison, celecoxib gave an IC_{50} 12 nM against COX-2 and 4 μM against COX-1 with a resulting selectivity ratio of 333. Rofecoxib gave an IC_{50} of 190 nM against COX-2 with no significant inhibition at 100 μM of COX-1. Although this type of assay has not been predictive of selectivity *in vivo,* it does indicate that ABT-963 is a direct inhibitor of human COX-2 (Figure 1).

Discussion

Compounds with greater selectivity for COX-2 versus COX-1 have markedly attenuated g.i.t damage in rodents. The recent approval of COX-2-selective agents for use in human disease has been accompanied by initial safety results indicating a clear advantage for selective agents versus mixed inhibitors [11]. This and other evidence indicates that of the two known isozymes, COX-1 is responsible for gastric protection and hemodynamic balance, whereas COX-2 produces PGs in inflammation and cytokine/growth factor induced processes. The discovery of agents that selectively inhibit COX-2 and not COX-1 has proven challenging. This difficulty is derived from three sources. First, the active sites of the two proteins are very similar. There are few amino acid changes in the surface amino acids that form the active site pocket. This change may open a pocket that allows for some flexibility of binding. Other differences in the second layer of amino acids allows for

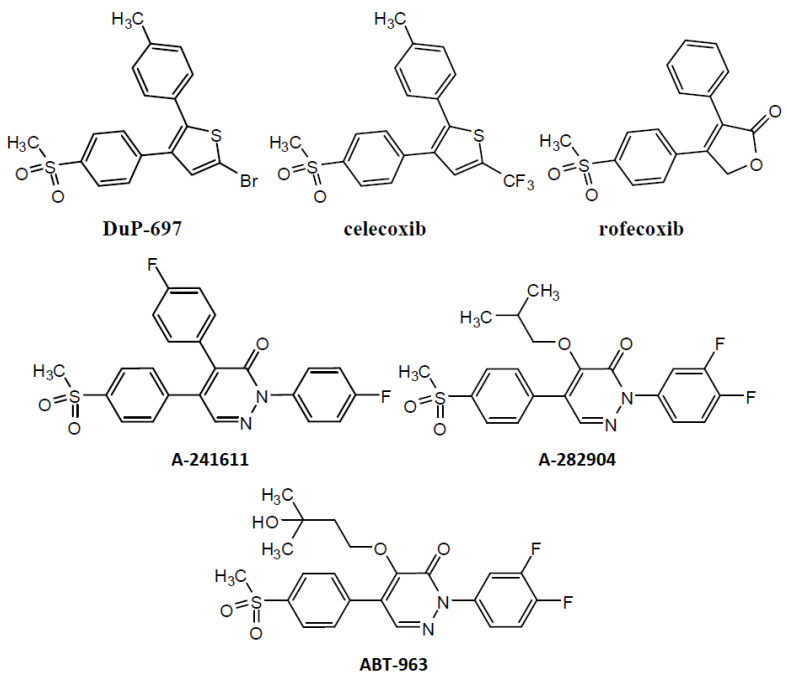

Figure 1: Structures of the inhibitors used in this study.

some increase in size of the right-hand side of the active site. The active site also is very hydrophobic, which allows very little hydrophilicity to be incorporated in the inhibitors [12]. The second source of difficulty in providing selective agents is providing agents that do not inhibit PG formation by inhibiting the release of AA. The AA is a substrate for both COX-1 and COX-2 and therefore agents that inhibit AA are nonselective. The third difficulty is accessing the compound's selectivity. Several methods had been published using different cells and stimuli with standard inhibitors. Approaches to assess *in vitro* selectivity for COX-2 versus COX-1 evolved over the course of discovering ABT-963. Initially, the early series selectivity values were determined in cell assays using the WISH cell line, which upon IL-1 stimulation, COX-2 is dramatically induced and large amounts of PGE2 are formed [52]. The COX-1 activity was determined in platelets, which only express COX-1 [53]. The later alkoxy and hydroxy alkoxy series were discovered using two whole blood assays performed essentially as described [54]. The clotting COX-1 assay and the ionophore whole blood assay for COX-1 gave similar results for compounds that inhibit COX-1. Various studies examining COX-2 expression in LPS-stimulated whole blood and product formation profiles indicated that a 24-h assay was required to selectively measure COX-2 inhibition in this assay. *In vitro*, ABT-963 selectively inhibits recombinant human COX-2 enzyme as well as COX-2-driven cellular production of PGs while leaving platelet COX-1 thromboxane production intact at concentrations where COX-2 is completely inhibited. In whole blood assays, ABT-963 is particularly potent and selective. Compared with other COX-2 inhibitors such as rofecoxib and celecoxib, ABT-963 was 11-fold more potent against COX-2 than celecoxib, whereas rofecoxib was 30-fold weaker against COX-2. ABT-963, celecoxib, and rofecoxib were all equally active at inhibiting COX-1. Thus, the selectivity ratios in blood were 157 for ABT-963, six for rofecoxib, and 14 for celecoxib [55]. This compound has potencies that are in the same range as ABT-963; however, it seems to be more potent in the rat assays. ABT-963 seems to be comparable with this agent.

The ABT-963 is an effective anti-inflammatory agent by vivo inhibition of both leukotrienes and PGs [56,57]. A significant level of induced COX-2 enzyme and implied that the majority of the PGE2 formed was from COX-2 [58]. This model gave good reproducibility and selective agents gave nearly complete inhibition of PGE2. This potency was similar to that seen with both rofecoxib and celecoxib. The compound also inhibited PG-driven inflammation and pain in acute rat models. ABT-963 was effective at reducing the edema caused by the release of PGs with an ED_{50} of 1.9 mg/kg. The selective agents that COX-2- derived PGs are involved in the inflammatory reaction [59,32]. ABT-963 was examined in an established adjuvant arthritis model in the rat. The established model exhibits pronounced soft tissue and synovial inflammation between day 16 and 30 and is accompanied by a marked progression of periosteal reactions, pannus formation, internal bone inflammation, fibrosis in the joints, and end-stage ankylosis [60-62]. Daily oral doses of ABT-963 from days 14 to 28 gave significant inhibition of paw swelling. In addition, COX-2 inhibition arrested the progression of the disease at the time of initial dosing. Similar results were also seen for indomethacin, suggesting that, in the rat, PGs play a significant role in the progression of bone loss. ABT-963 was examined in a dog model of cardiovascular safety and the data from these experiments suggest that ABT-963 may not have cardiovascular effects in humans. Only a minor affect was seen at the highest plasma level, which was 30- to 124-fold over the efficacious levels in the models of inflammation. Most importantly, ABT-963 dosed daily in dogs for 4 days at doses 20-fold above effective anti-inflammatory doses gave no GIT damage. Although preliminary, indicate that ABT-963 has the potential to have increased gastric safety. The higher level of exposure of the animals to the drug coupled with the increased selectivity further suggest that ABT-963 will have improved gastric safety in humans.

Conclusions

NSAIDs represent an important class of compounds. The rapid discovery of selective COX-2 inhibitors can be attributed to the

rational drug design approach. However, the cardiovascular side effects associated with selective COX-2 inhibitors highlights the pitfalls that may be encountered in the drug discovery paradigm. NO-NSAIDs, dual COX/LOX inhibitors and anti-TNF therapy represent novel approaches directed toward the development of effective anti-inflammatory therapy. ABT-963 has a preclinical anti-inflammatory and safety profile that suggests that this compound may be safe and effective in humans. Continued clinical evaluation of ABT-963 will determine the human safety and efficacy profile of this compound. In spite of the unprecedented advances in drug discovery, developing a safe, effective and economical therapy for treating inflammatory conditions still presents a major challenge.

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