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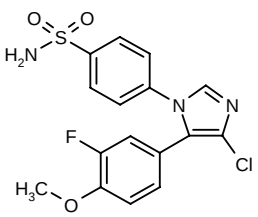
Cimicoxib

Prop INN

Antiarthritic
Analgesic
COX-2 Inhibitor

UR-8880

4-[4-Chloro-5-(3-fluoro-4-methoxyphenyl)-1*H*-imidazol-1-yl]benzenesulfonamide



$C_{16}H_{13}ClFN_3O_3S$
Mol wt: 381,8137
CAS: 265114-23-6
EN: 293295

Abstract

The discovery of an inducible form of cyclooxygenase (COX) stimulated the search for new, isoform-selective inhibitors that culminated in the introduction of an entirely new generation of antiinflammatory drugs with improved gastrointestinal tolerability. Cimicoxib (UR-8880), a new imidazole derivative, is a highly selective COX-2 inhibitor that exhibits promising antiinflammatory and analgesic activity. The compound showed good oral activity when tested in experimental models of acute and chronic inflammation and pain, comparable to celecoxib and rofecoxib. Cimicoxib exhibited a good pharmacokinetic profile in rats and dogs and a high safety margin as regards both the cardiorespiratory and central nervous systems. In humans, cimicoxib appeared to be safe and well tolerated at doses up to 600 mg. After repeated administration the compound was safe and well tolerated up to 100 mg and there was no significant accumulation after 12 doses. In subjects with moderate to severe postoperative dental pain, cimicoxib (50 and 100 mg) produced significant analgesia. A prodrug for parenteral use has recently been identified and is now in preclinical testing. Cimicoxib continues to undergo active clinical development as an antiinflammatory and analgesic agent.

Synthesis

Treatment of 4-(acetylamino)phenylsulfonyl chloride (I) with *tert*-butylamine yields sulfonamide (II), which on deprotection with potassium hydroxide gives amine (III). Reaction of compound (III) with 4-methoxy-3-fluorobenzaldehyde gives imine (IV), which is cyclized with tosylmethyl isocyanide to afford imidazole (V). Regioselective chlorination of compound (V) with *N*-chlorosuccinimide (NCS) to afford the chloroimidazole (VI) and then deprotection of the sulfonamide group of (VI) yields cimicoxib in 40% overall yield (1, 2). Scheme 1.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) have become the standard therapy for the management of inflammation and pain. Approximately 20 NSAIDs with diverse chemical structures have reached the market to date. Although NSAIDs do not reverse the course of systemic diseases such as arthritis, they have proved very useful in the symptomatic treatment of this condition because of their potent analgesic, antiinflammatory and antipyretic properties. The NSAIDs inhibit cyclooxygenase (COX), thereby preventing the synthesis and secretion of prostaglandins (PGs), endogenous lipid mediators of pain and inflammation. However, PGs also play a beneficial physiological role in protecting gastric mucosa and maintaining renal and platelet function. Thus, conventional NSAIDs can induce relevant unwanted adverse events such as gastric mucosal erosion and ulcer, nephrotoxicity, impaired hemostasis due to platelet inhibition and asthma. These adverse events can be serious and represent an important health concern. For example, in the U.S. alone, 16,500 patients die each year due to NSAID-induced gastrointestinal complications (3-5).

There are two COX isoforms – constitutive COX-1 and inducible COX-2 – which mediate the cytoprotective effects and inflammatory actions, respectively. Current

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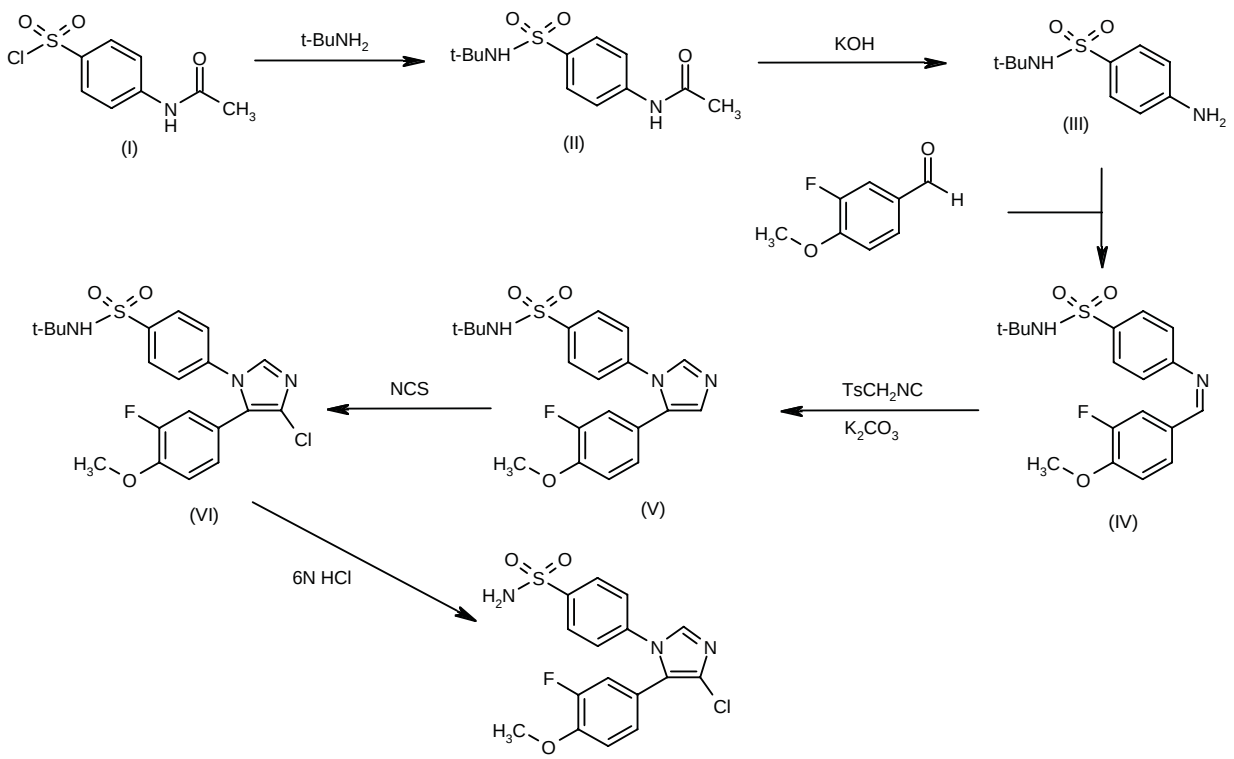
Scheme 1: Synthesis of Cimicoxib



research has therefore focused on searching for selective inhibitors of COX-2, which could provide beneficial antiinflammatory and analgesic effects without the gastrointestinal toxicity associated with conventional NSAIDs. The result of this research has been the launch of 4 selective COX-2 inhibitors in the U.S. and/or Europe: rofecoxib, celecoxib, valdecoxib and etoricoxib. This novel class of drugs is now widely used based on their potent antiinflammatory and analgesic efficacy and significantly reduced adverse events compared to conventional NSAIDs (6-9).

Unfortunately, selective COX-2 inhibitors have been suggested to have similar effects on edema, hypertension and nephrotoxicity as conventional NSAIDs. In addition, the potentially increased risk of thrombosis associated with selective COX-2 inhibitors still remains to be clarified (10). Thus, researchers continue to search for novel, safer selective COX-2 inhibitors. An emerging inhibitor is cimicoxib, a novel imidazole derivative which is a highly selective COX-2 inhibitor. Cimicoxib has been shown to be more potent *in vitro* than rofecoxib and celecoxib. The antiinflammatory and analgesic activity of the agent was comparable to that of celecoxib, rofecoxib and nonselective NSAIDS in preclinical models. However, cimicoxib exhibited good gastric tolerability even at high doses and was chosen for further development (11-13).

Pharmacological Actions

Cimicoxib is a very potent and highly selective COX-2 inhibitor. Using the gold standard model for *in vitro* testing of COX inhibitors (the human whole blood assay), cimicoxib showed a COX-2-inhibitory potency about 3 and 9 times greater than that of rofecoxib and celecoxib, respectively (IC_{50} = 69, 216 and 645 nM, respectively). Interestingly, a pharmacokinetic/pharmacodynamic (PK/PD) relationship was established in dogs between the plasma concentrations of cimicoxib and COX-2 inhibition using the *ex vivo* lipopolysaccharide (LPS)-induced PGE_2 assay. The IC_{50} value was 140 nM, which agrees with the IC_{50} values of cimicoxib in *in vitro* studies. For COX-1 activity it was not possible to establish any PK/PD relationship. Selectivity was also assessed using human U-937 and 143.98.2 cells expressing COX-1 and COX-2 enzyme activity, respectively. In this cell-based assay, cimicoxib showed 929-fold selectivity for COX-2. Under the same experimental conditions, selectivity ratios for celecoxib and rofecoxib were 74 and > 10,000, respectively. *In vivo* selectivity was evaluated by measuring the urinary excretion of the prostacyclin (PGI_2) metabolites 2,3-dinor-6-keto-$PGF_{1\alpha}$ (an index of systemic PGI_2) and 6-keto-$PGF_{1\alpha}$ (an index of renal PGI_2), as well as 11-dehydro-TxB_2 (an index of COX-1-dependent TxB_2

formation). As expected, 11-dehydro-TxB_2 was unaffected by cimicoxib 10 mg/kg/day for 28 days in rats, whereas 2,3-dinor-6-keto-$PGF_{1\alpha}$ was almost completely inhibited. The renal PGI_2 metabolite 6-keto-$PGF_{1\alpha}$ was not affected.

Cimicoxib had no significant binding affinity for 30 common receptor systems examined using radioligand binding studies, including adenosine, angiotensin, adrenergic, dopaminergic, cholinergic, histamine, 5-HT, opioid, benzodiazepine, CCK, GABA and NMDA receptors. In cellular functional assays, cimicoxib had no significant effects on phospholipase A_2 (PLA_2), endothelial nitric oxide synthase (eNOS), phosphodiesterase type 4 (PDE4), protein kinase A and C, ERK42, Na^+/K^+-ATPase, Na^+/H^+-antiport, $Na^+/K^+/Cl^-$ cotransport and O_2^- or H_2O_2 secretion.

The oral antiinflammatory and analgesic activity of cimicoxib has been demonstrated in several animal models of acute and chronic inflammation and hyperalgesia in rats (11). The compound exhibited marked analgesic activity in a model of carrageenan-induced inflammatory hyperalgesia (ED_{50} = 0.23 mg/kg). At a dose of 1 mg/kg, cimicoxib completely inhibited carrageenan-induced PGE_2 production in the air pouch model (ED_{50} = 0.20 mg/kg). In addition, the compound dose-dependently decreased acute inflammation in the carrageenan-induced edema assay (ED_{25} = 3.1 mg/kg). In all these models, cimicoxib showed similar efficacy to celecoxib and rofecoxib.

The antiinflammatory activity of cimicoxib (0.1-10 mg/kg/day p.o. for 28 days) was further demonstrated in the rat adjuvant-induced arthritis model. The compound significantly decreased secondary paw swelling by 96% at a dose of 1 mg/kg (ED_{50} = 0.18 mg/kg); celecoxib and indomethacin were also effective at 1 mg/kg, inhibiting swelling by 89% and 99%, respectively. Interestingly, treatment with cimicoxib significantly and dose-dependently reduced total radiographic scores of hind limbs by the end of treatment.

Additional activities, apart from COX-2 inhibition, are currently under evaluation. Effects on COX-2 mRNA expression and transcription factor DNA-binding activity, together with effects on cell proliferation and apoptosis induction, suggest that cimicoxib may have potential activity as a chemopreventive agent.

UR-14048 is a water-soluble prodrug of cimicoxib that has been selected as the best candidate for parenteral use. Intravenous administration of UR-14048 showed the same activity as ketorolac and parecoxib (3, 10 and 30 mg/kg i.v.) against acute inflammatory pain (thermal hyperalgesia) in the rat following intraplantar injection of carrageenan. The drug is now under preclinical evaluation for the treatment of acute pain.

Pharmacokinetics and Metabolism

In vitro studies showed that cimicoxib was metabolically more stable than celecoxib and similar to rofecoxib. In human liver microsomes, cimicoxib was metabolized to a lesser extent than celecoxib (25.6% and 51%, respectively). Rofecoxib was not metabolized due to the absence of cytosolic enzymes required for its metabolism. Experiments using human hepatocytes revealed that after 6 h of incubation, cimicoxib (40 μM) was metabolized more slowly than celecoxib (50.8% and 92%, respectively) and at a similar rate to rofecoxib (55%). *In vitro* metabolism of cimicoxib in primary hepatocytes was qualitatively similar in the species studied (humans, dogs, monkeys and rats). Cimicoxib undergoes phase I (demethylation) and subsequent phase II (conjugation) metabolic reactions. The glucuronoconjugate of demethylated cimicoxib was the main metabolite observed in human hepatocytes (48% at 6 h and 88% at 24 h of incubation at 5 μM), the demethylated and the sulfate conjugate being minor metabolites (< 10% of total radioactivity). The demethylated metabolite was inactive in both COX-1 and COX-2 activity assays. When compared to other selective COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib and etoricoxib (14-19), the metabolism of cimicoxib appears to be much less complex.

The pharmacokinetics of cimicoxib have been assessed in rats and dogs. Following single oral doses of [^{14}C]-cimicoxib to rats (1 mg/kg), the compound was rapidly absorbed and widely distributed throughout the body. Tissue radioactivity concentrations declined steadily after reaching maximum concentrations 3 h after administration. Radioactivity was mainly excreted in the feces (> 70%) by 168 h following both oral and i.v. administration; urinary excretion accounted for 20-30% of the dose. The main metabolites in urine were demethylated cimicoxib and the corresponding glucuronide and/or sulfate derivative. The similarities between the pattern of excretion following oral and i.v. administration indicate that oral doses are well absorbed in rats. Results after i.v. dosing in rats strongly suggest that biliary excretion was the major route of elimination.

The bioavailability in beagle dogs was approximately 75%. Following oral administration of [^{14}C]-cimicoxib (1 mg/kg, 15 μCi/kg) the compound was rapidly absorbed with a t_{max} of 2 h and a $t_{1/2}$ of about 7 h. In the dog, the drug was predominantly eliminated in the feces following i.v. administration (approximately 74% based on elimination of radioactivity). The remaining dose was eliminated in the urine (16% of excreted dose), indicating that biliary/intestinal excretion is the major route of elimination for cimicoxib in dogs. The demethylated compound was the only metabolite found in feces. This metabolite was also predominant in urine, but small quantities of the corresponding glucuronide and/or sulfate derivative were also found. Cimicoxib was extensively metabolized, as < 0.2% unchanged drug was detected in the feces and urine after i.v. administration.

Based on equilibrium dialysis studies, cimicoxib showed moderate binding to human plasma proteins (89-90%), similar to rofecoxib (90%) and less than celecoxib (99%).

The pharmacokinetics of cimicoxib have also been examined in humans in phase I studies. After single oral doses (3-600 mg) to healthy volunteers, cimicoxib was rapidly absorbed with a mean t_{max} of 1.3-1.7 h, indicating a rapid onset of action, and an elimination half life of 17-26 h at the expected therapeutic dose. The C_{max} and AUC increased in a dose-proportional manner over the expected therapeutic range (up to 75 mg). However, at higher doses (125-600 mg), the C_{max} and AUC were less than dose proportional, probably due to the low solubility of the drug, characteristic of several COX-2 inhibitors. Cimicoxib undergoes extensive hepatic metabolism. The major metabolite, the glucuronide conjugate of demethylated cimicoxib, accounted for nearly 50-60% of the excreted dose in urine at expected therapeutic doses. Little demethylated metabolite (< 1%) or unchanged drug (< 0.2%) was recovered in urine.

The pharmacokinetics of single and multiple 25- and 100-mg doses of cimicoxib have been evaluated. Single oral doses of cimicoxib were rapidly absorbed with a mean t_{max} value of 1.3 h and a mean t_{max} value of 1.0 h at steady state. Mean AUC values increased with dose after both single and multiple doses, but in a less-than-dose-proportional manner. The accumulation factor (R) during steady state showed a mean value of 1.27 for the 25-mg dose and 1.41 for the 100-mg dose, indicating that no significant accumulation occurred.

Toxicity

The LD_{50} for cimicoxib is > 2000 mg/kg when administered as a single oral dose to mice and rats. Toxicities observed in dogs following repeated dosing (5 weeks) were minimal. In rats, gastrointestinal ulceration was observed in highly exposed animals. Only these animals showed alterations considered secondary to gastrointestinal ulceration. Cimicoxib was not mutagenic in the reverse mutation Ames test, nor clastogenic in the micronucleus test using mouse bone marrow cells and in the chromosome aberration assay in human lymphocytes. Reproductive toxicology studies showed that the agent has no teratogenic effects in rat fetuses. However, cimicoxib, like other selective COX-2 inhibitors, produces fetal alterations in rabbits. These effects are expected from drugs producing prostaglandin inhibition.

Safety studies in dogs demonstrated that cimicoxib (1, 3, 10 and 30 mg/kg i.v.) has no effects on hemodynamic or respiratory parameters. No changes in the QTc interval were noted even at the highest dose. This was confirmed in *in vitro* experiments using isolated Purkinje fibers and HEK293 cells expressing the HERG current (I_{Kr}). Cimicoxib had no effect on action potential duration at 90% depolarization (APD_{90}) in Purkinje fibers, indicating that it is unlikely to prolong the QT interval.

Safety studies in rats and mice showed that cimicoxib has no effects on the central nervous system at doses up to 1000 mg/kg p.o. Single doses did not alter spontaneous motor activity in mice nor induce physiological or behavioral alterations in rats. Rat body temperature was not affected by administration of the compound. Moreover, cimicoxib at a rather high dose (100 mg/kg b.i.d. for 5 days) did not induce any gastrointestinal microbleeding, as assessed by fecal ^{51}Cr excretion. In contrast, nonselective NSAIDs, such as indomethacin (5 mg/kg) or diclofenac (10 mg/kg), as well as the preferential COX-2 inhibitor meloxicam (10 mg/kg), produced a significant increase in ^{51}Cr fecal excretion (7.5%, 15.8% and 12.2% of injected activity, respectively, compared to control animals) (10). Accordingly, no inhibition of PGE_2 in rat stomach was found after 21 days of treatment with cimicoxib 10 mg/kg/day. On the other hand, indomethacin at 1 mg/kg/day induced almost complete inhibition of gastric PGE_2. Gastrointestinal safety studies showed no effect on gastric acid secretion in rats or on intestinal transit in mice at up to 1000 mg/kg.

The potential prothrombotic activity of the selective COX-2 inhibitor was evaluated in rats and rabbits. Cimicoxib 10 mg/kg p.o. administered for 28 days did not affect any of the cardiovascular parameters studied (heart rate, blood pressure, experimental thrombosis) in either normotensive or hypertensive rats. In hypercholesterolemic rabbits, cimicoxib did not change either the platelet surface expression of CD62P (a marker of platelet activation) or the extent of atherosclerotic lesions in the aorta. Renal parameters (urinary volume, ion excretion, creatinine clearance) were assessed in the same animals. No alterations were observed in the cimicoxib treatment group. However, in hypertensive rats, rofecoxib produced a decrease in urine volume and Na^+ excretion.

Clinical Studies

An initial double-blind, randomized, placebo- and active treatment-controlled clinical study was conducted to assess the safety of single rising doses of cimicoxib in healthy volunteers, as well as to obtain preliminary data on the human pharmacokinetic and pharmacodynamic profile of the drug (20). Compound was administered orally at single doses of 3, 6, 12, 25, 50, 75, 125, 200, 325, 450 and 600 mg as a solution in comparison to a corresponding volume of a matching placebo or 25 mg rofecoxib. All doses of cimicoxib were safe and well tolerated. No relevant changes were observed in biochemical, hematological, vital signs or ECG parameters. No serious or severe adverse events were reported during the study. *Ex vivo* COX-2-inhibitory activity, as assessed by inhibition of whole-blood LPS-stimulated PGE_2 at 1.5 h postdosing, revealed that cimicoxib produces a dose-dependent inhibition of COX-2 activity, from 12.6% at 3 mg to 59.6% inhibition at 600 mg. Cimicoxib 25 mg and rofecoxib 25 mg produced similar inhibition of COX-2 activity.

A second, similarly designed phase I study was carried out in healthy volunteers to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of

cimicoxib at steady state. Single and multiple (12 administrations) doses of 25 and 100 mg cimicoxib as a solution, or a corresponding volume of a matching placebo or 25 mg rofecoxib suspension, were administered once daily. Cimicoxib was safe and well tolerated at both doses. No adverse events occurred during the course of the study, except for 1 episode of fatigue experienced by a subject on placebo. No clinically significant and/or consistent drug-related changes in vital signs, physical examination, ECG parameters and laboratory values were observed. *Ex vivo* measurements of whole blood LPS-induced PGE_2 production revealed that 12 doses of 25 mg cimicoxib inhibit COX-2 activity to a similar extent as 25 mg rofecoxib, whereas 100 mg cimicoxib produces a higher inhibition.

A population PK/PD analysis was conducted with pharmacokinetic and pharmacodynamic data from both phase I studies. Using a type I indirect response model, also known as a model for inhibition of response production, an IC_{50} of 187 nM was calculated.

A double-blind, randomized phase II study was performed in 251 patients experiencing moderate to severe postoperative pain following extraction of 1 or more impacted third molars. The aim of this study was to compare the analgesic efficacy and safety of cimicoxib at single oral doses of 50, 100 and 200 mg with 50 mg rofecoxib and placebo. Pain intensity (using standard categorical and visual analog scales) and pain relief were assessed at scheduled times over the 24-h postdosing period. Time to onset was measured using a standardized 2-stopwatch technique. Cimicoxib 50 and 100 mg showed analgesic efficacy greater than placebo in the primary efficacy variable (TOTPR-6). The median time until onset of analgesia was significantly shorter with cimicoxib 50 mg (0.4 h, CI95%: 0.3; 0.4) than rofecoxib 50 mg (0.5 h, CI95%: 0.3; 0.7) (Bonferroni's test). Cimicoxib 50 mg was comparable to rofecoxib 50 mg and superior to placebo in patient global evaluation. All treatments were safe and well tolerated.

Cimicoxib continues to undergo active clinical development. An open-label trial in 6 healthy volunteers is in progress to assess the absorption, distribution, metabolism and excretion of single oral doses of [^{14}C]-cimicoxib (75 mg, 75 μCi). An open-label trial is also under way in 24 healthy volunteers to assess the relative bioavailability of a tablet versus an oral solution of cimicoxib (50 mg) and the interaction with food.

Source

J. Uriach & Cia. SA (ES).

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