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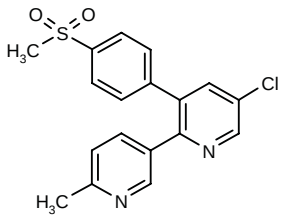
Etoricoxib

USAN

Analgesic Drug
Antiarthritic
Cyclooxygenase-2 Inhibitor

L-791456
MK-0663
MK-663

5-Chloro-3-[4-(methylsulfonyl)phenyl]-2-(6-methylpyridin-3-yl)pyridine
5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine



$C_{18}H_{15}ClN_2O_2S$ Mol wt: 358.8475

CAS: 202409-33-4
CAS: 202409-40-3 (as monohydrochloride)

EN: 261533

Synthesis

Etoricoxib can be prepared by a number of synthetic strategies involving several approaches to the synthesis of two key intermediates, dichloropyridine (VIII) and ketosulfone (XXIV):

1) Synthesis of etoricoxib via dichloropyridine (VIII):

a) The bromination of 5-chloro-2-hydroxypyridine (I) with Br_2 in acetic acid gives 3-bromo-5-chloro-2-hydroxypyridine (II), which is treated with benzyl bromide and Ag_2CO_3 in hot benzene to yield benzyl ether (III). Condensation of (III) with 4-(methylsulfanyl)phenylboronic acid (IV) by means of $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing ethanol/benzene affords 2-(benzyloxy)-5-chloro-3-[4-(methylsulfanyl)phenyl]pyridine (V), which is oxidized with OsO_4 and sodium sulfite to furnish sulfone (VI). Treatment of (VI) with TFA provides the 2-hydroxypyridine (VII), which is reacted with $POCl_3$ to yield 2,5-dichloro-3-[4-(methylsulfonyl)phenyl]pyridine (VIII) (1). Scheme 1.

b) Bromination of 2-amino-5-chloropyridine (IX) with Br_2 in acetic acid provides 2-amino-3-bromo-5-chloropyridine (X), which is condensed with 4-(methylsulfanyl)-phenylboronic acid (IV) by means of $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing ethanol/benzene to give 2-amino-5-chloro-3-[4-(methylsulfanyl)phenyl]pyridine (XI). Oxidation of compound (XI) with OsO_4 as before yields sulfone (XII), which is converted into compound (VIII) by treatment first with $NaNO_2$ and HCl and then chlorination with $POCl_3$ (1, 2). Scheme 1.

Finally, compound (VIII) is condensed with either trimethyl(6-methyl-3-pyridyl)tin (XIII) (1, 2) or the boronate ester lithium salt (XIV) (2) by means of $Pd(PPh_3)_4$ to afford etoricoxib (1, 2). Scheme 2.

The metalated pyridine (XIII) is obtained by esterification of 3-hydroxy-6-methylpyridine (XV) with triflic anhydride to give the corresponding triflate (XVI), which is treated with hexamethylditin to afford the target tin intermediate (XIII) (1). The boronate lithium salt (XIV) is prepared by treatment of 5-bromo-2-methylpyridine (XVII) with *n*-BuLi followed by addition of triisopropyl borate (2). Scheme 2.

2) Synthesis of etoricoxib via ketosulfone (XXIV):

a) The reaction of 6-methylpyridine-3-carboxylic acid methyl ester (XVIII) with *N*,*O*-dimethylhydroxylamine and isopropylmagnesium chloride in toluene gives the *N*-methoxyamide (XIX), which is reduced with DIBAL to afford 6-methylpyridine-3-carbaldehyde (XX). Reaction of aldehyde (XX) with aniline and diphenyl phosphite provides the diphenyl phosphonate (XXI), which is condensed with 4-(methylsulfonyl)benzaldehyde (XXII) by means of potassium *tert*-butoxide in HF to yield the enimine (XXIII). Finally, this compound is hydrolyzed with HCl to give ketosulfone (XXIV) (3). Scheme 3.

b) Condensation of *N*-methoxyamide (XIX) with 4-(methylsulfanyl)benzylmagnesium bromide (XXV) in toluene/THF gives 1-(6-methylpyridin-3-yl)-2-[4-(methylsulfanyl)phenyl]ethanone (XXVI), which is finally

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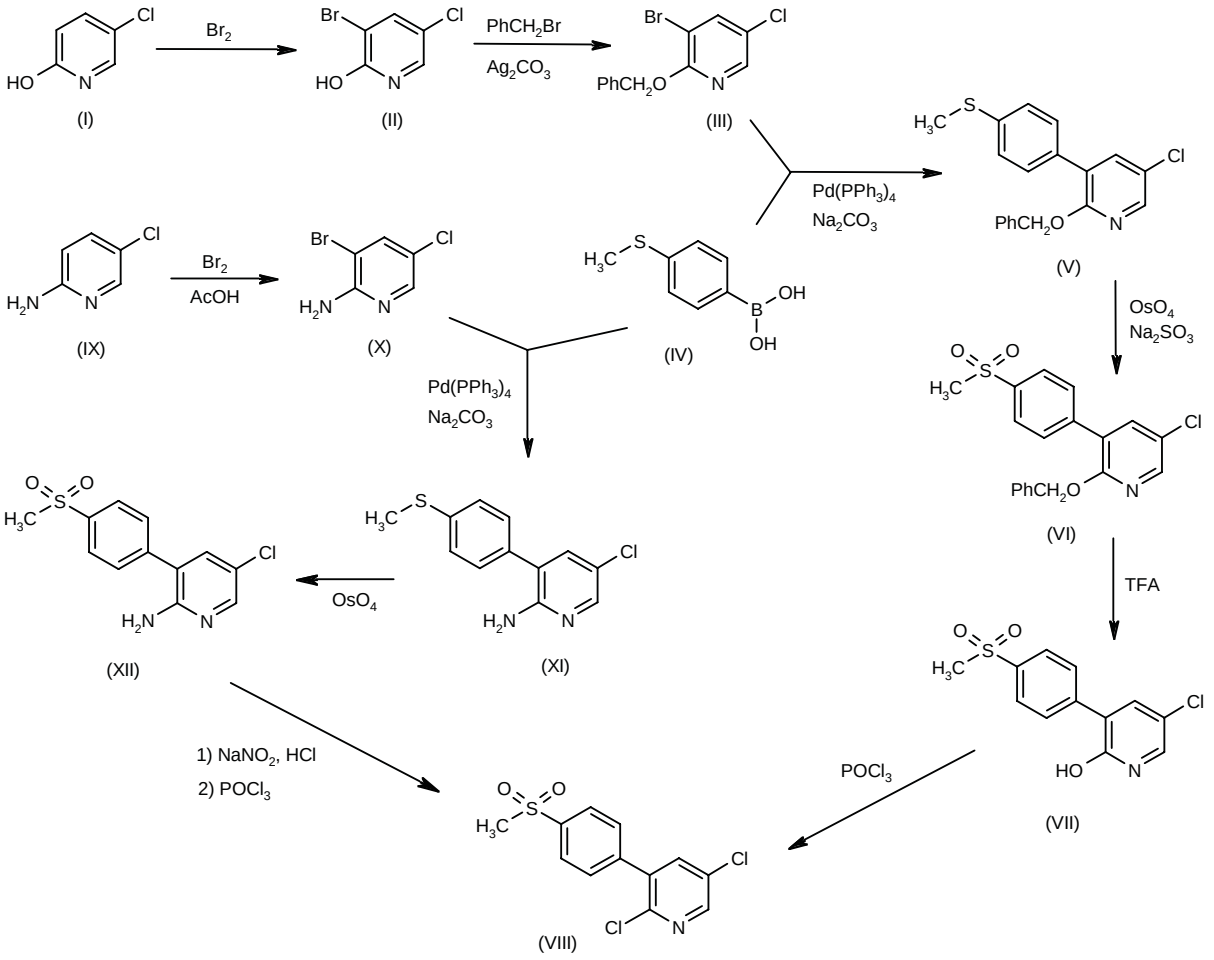
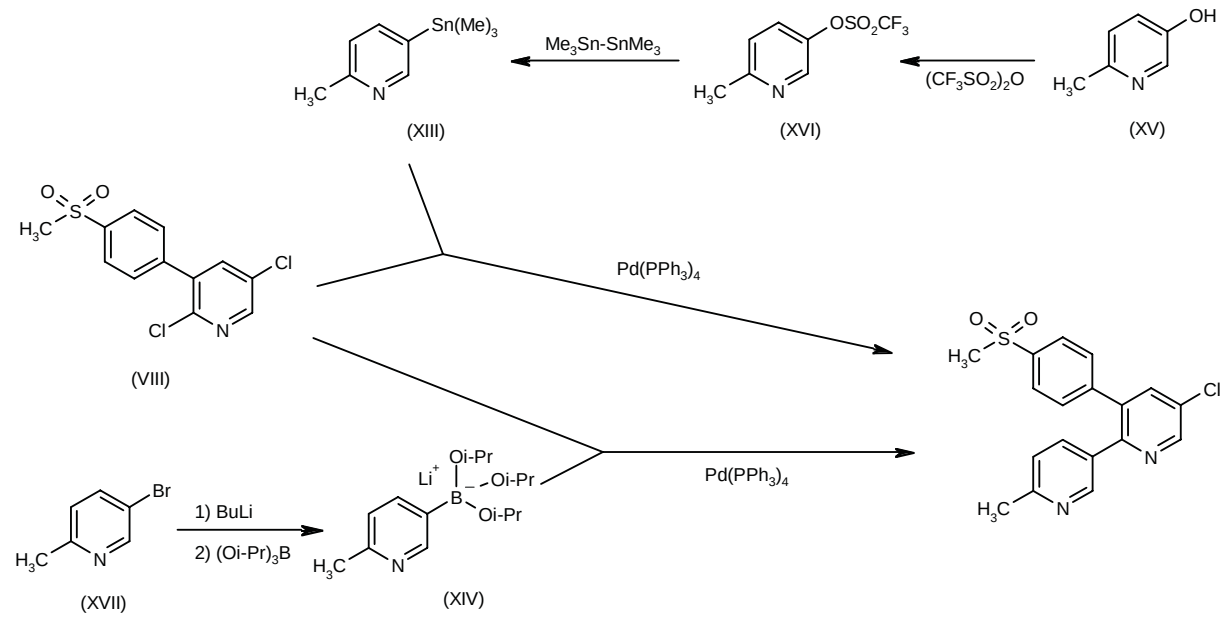
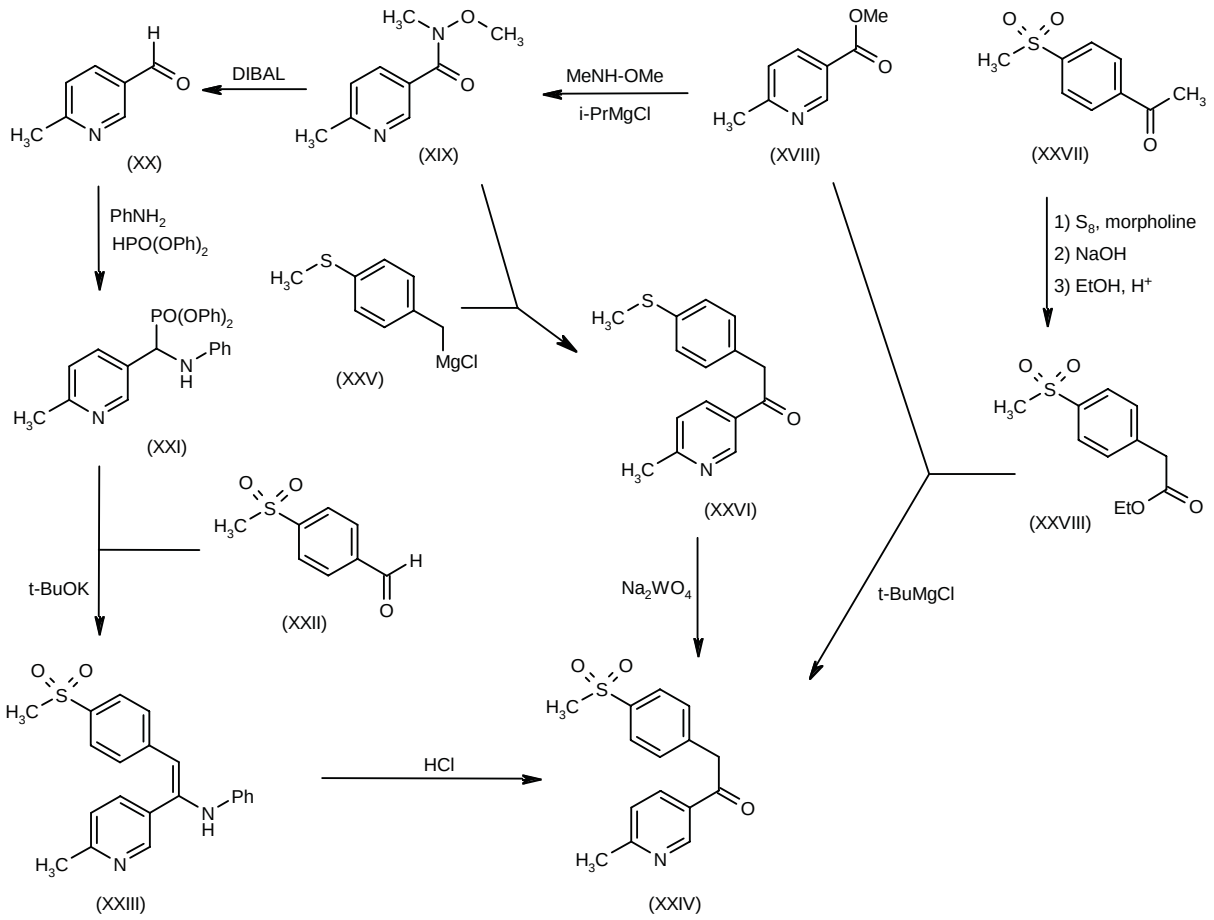
Scheme 1: Synthesis of Intermediate (VIII) of Etoricoxib



Scheme 2: Synthesis of Etoricoxib



Scheme 3: Synthesis of Intermediate (XXIV) of Etoricoxib



oxidized with Na_2WO_4 to yield ketosulfone (XXIV) (3, 4). Scheme 3.

c) Oxidation of 4'-(methylsulfonyl)acetophenone (XXVII) with S_8 and morpholine, followed by esterification with ethanol, affords 2-[4-(methylsulfonyl)phenyl]acetic acid ethyl ester (XXVIII); which is condensed with 6-methylpyridine-3-carboxylic acid methyl ester (XVIII) by means of *t*-BuMgCl in hot THF to furnish ketosulfone (XXIV) (3). Scheme 3.

Finally, etoricoxib is obtained by several related ways:

Cyclization of ketosulfone (XXIV) with 2-chloromalondialdehyde (XXIX) or the aniline derivative (XXX) and ammonium acetate in hot propionic acid (3). Scheme 4.

Cyclization of ketosulfone (XXIV) with aminoacrolein (XXXI) in the absence of ammonium acetate. Aminoacrolein (XXXI) is prepared by treatment of chloromalondialdehyde (XXIX) with isopropanol, yielding the ether (XXXII) and followed by reaction with ammoniun hydroxide (3). Scheme 4.

Cyclization of the lithium enolate of ketosulfone (XXIV) with 2,3-dichloroacrolein (XXXIII) – obtained by treatment of chloromalondialdehyde (XXIX) with oxalyl chloride and DMF in toluene – followed by reaction with ammonium acetate or anhydrous ammonia (3). Scheme 4.

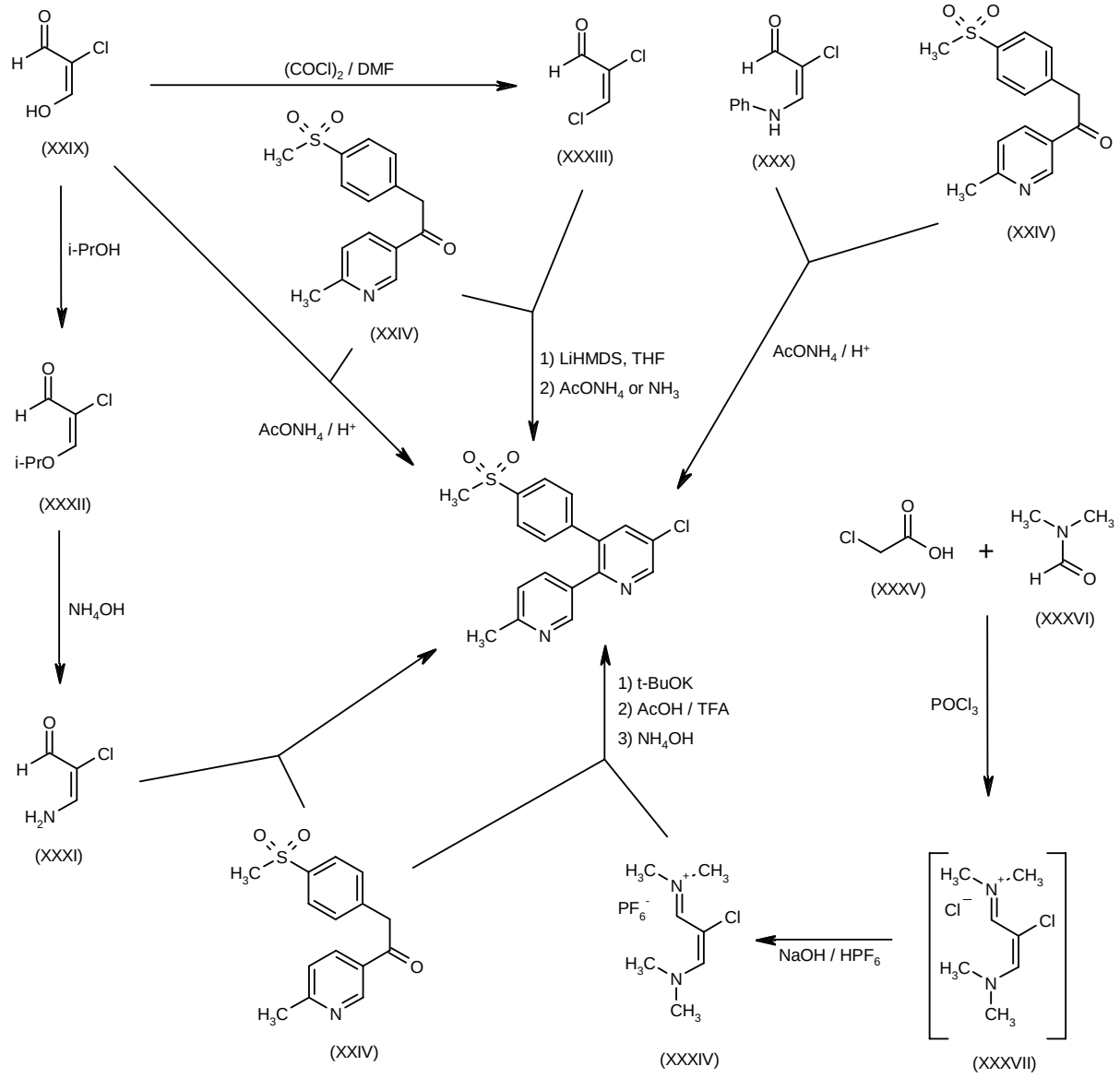
Reaction of ketosulfone (XXIV) with 2-chloro-1,3-bis(dimethylamino)trimethinium hexaflourophosphate salt (XXXIV) in the presence of an equimolar amount of *t*-BuOK followed by treatment with AcOH/TFA and then heating at reflux with an excess of ammonium hydroxide (3-5). Scheme 4.

2-Chloro-1,3-bis(dimethylamino)trimethinium hexaflourophosphate salt (XXXIV) is obtained by reaction of chloroacetic acid (XXXV) with hot dimethylformamide (XXXVI) and $POCl_3$, and then the reaction mixture is treated with 5N NaOH and hexafluorophosphoric acid in water (4, 6). Scheme 4.

Introduction

Although aspirin has been widely used as a treatment for pain and as an antipyretic since the synthesis of

Scheme 4: Synthesis of Etoricoxib



acetylsalicylic acid in 1897, gastrointestinal adverse events associated with its use has prompted the search for aspirin-like or nonsteroidal antiinflammatory drugs (NSAIDs) that are free of gastrotoxic effects. Approximately 20 NSAIDs have entered the market although none of them are free of adverse gastrointestinal effects and the incidence of hospital referrals for ulcer complications has actually increased since the mid-1960s (7).

NSAIDs target cyclooxygenases (COX) which catalyze the conversion of arachidonic acid to prostaglandin H_2, the precursor for prostaglandins, prostacyclins and thromboxanes. Two isoforms of COX have been identified and shown to possess the same catalytic properties although they are differentially expressed (8-10). Constitutive COX-1 is expressed in healthy tissue where it catalyzes the production of prostanoids involved in gastric cytoprotection, renal homeostasis and platelet aggregation. In contrast, the second isoform, inducible COX-2, is present only in basal levels in certain tissues and is upregulated in response to inflammatory or mitogenic stimuli. The discovery of this second isoform initiated the development of novel antiinflammatory agents with improved gastrointestinal tolerability (8-10). The search for specific COX-2 inhibitors has been extensive, eventually leading to the discovery of new generation NSAIDs such as celecoxib (11) and rofecoxib (12). These novel NSAIDs have shown efficacy in the treatment of symptoms of osteoarthritis and relief of acute pain. Moreover,

Table I: Inhibitory activity and selectivity for COX-2 vs. COX-1 of selected COX-2 inhibitors launched or under active clinical development (Prous Science MFLine database).

Compound	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Arthritis[c]	Edema[d]	Pain[e]
	IC_{50} (μM)		COX-1/COX-2		ED_{50} (mg/kg p.o.)	
ASA	1.7-4.5 (28, 29)	13.9->100 (28, 29)	≤ 0.22	175-185 (30, 31)	148 (30)	141 (32)
Celecoxib	1.2-6.7 (28, 33-35)	0.16-1.0 (28, 33-35)	6.9	0.37 (33)	3.2-8.4 (33, 35, 36)	7.9 (36)
Etodolac	9.0-19.6 (28, 29, 37)	2.2-3.7 (28, 29, 37)	4.8	0.5-4.0 (30, 31, 38)	23-36 (30, 38)	–
Etoricoxib	116 (18)	1.1 (2, 18)	105	0.70 (2)	0.6 (2)	0.3 (2)
Meloxicam	1.4-5.7 (28, 35, 36, 39)	0.25-2.1 (28, 35, 37, 39)	3.1	0.35 (39)	–	–
Nimesulide	4.1-10.0 (28, 29, 37)	0.18-1.9 (28, 29, 37)	9.1	–	7.0 (40)	–
Rofecoxib	18.8-63.0 (28, 34, 35)	0.50-0.84 (28, 34, 35)	54	–	1.5-1.7 (34, 35)	1.0 (35)
Valdecoxib	25.4 (33)	0.89 (33)	29	0.032 (33)	10.2 (33)	–

[a]Inhibition of COX-1 and COX-2 in human whole blood. [b]Selectivity for COX-2 *vs.* COX-1 calculated from mean values. [c]Inhibition of adjuvant-induced arthritis in rats. [d]Inhibition of carrageenan-induced edema in rats. [e]Inhibition of carrageenan-induced pain in the paw-pressure test in rats. References in parentheses.

treatment with these agents was associated with an improved safety profile (13-16). A table showing the chemical structures of COX-2 inhibitors launched or under development was recently published in this journal (17).

Preparation of a series of novel orally active 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridine COX-2 inhibitors led to the discovery of etoricoxib (MK-663). This agent emerged as one of the most potent and selective COX-2 inhibitors to date, with efficacy seen against inflammation, pyrexia, pain and arthritis in preclinical models, and was selected for further development (2).

Pharmacological Studies

The inhibitory activity of etoricoxib against COX-1 and COX-2 isozymes was examined *in vitro* using an arachidonic acid-stimulated CHO cell line expressing COX-2, human whole blood to assess inhibition of both COX-1 (*i.e.*, serum thromboxane B_2 generation after clotting) and COX-2 (*i.e.*, lipopolysaccharide [LPS]-induced prostaglandin E_2 [PGE_2] synthesis) activity and U937 cells incubated with a low concentration (0.1 μM) of arachidonic acid to measure intrinsic COX-1 activity. The IC_{50} values obtained for etoricoxib for inhibition of COX-2 from CHO cells and human whole blood were 0.079 ± 0.012 and 1.1 ± 0.1 μM, respectively, as compared to 12 ± 2.5 and 116 ± 18 μM, respectively, obtained for inhibition of COX-1 using microsomes from U937 cells and human whole blood, respectively. In comparison, the IC_{50} values for indomethacin against CHO COX-2, human whole blood COX-1 and U937 microsomal COX-1 were 0.027 ± 0.006, 0.19 ± 0.02 and 0.02 ± 0.001 μM, respectively. The IC_{50} values obtained for rofecoxib, valdecoxib and celecoxib for inhibition of COX-1 using the U937 microsomes stimulated with low concentrations of arachidonic acid were 2 ± 0.5, 0.25 ± 0.02 and 0.052 ± 0.09 μM, respectively. Etoricoxib did not inhibit platelet or human recombinant COX-1 (IC_{50} = > 100 μM). The COX-1/COX-2 ratio of IC_{50} values for etoricoxib in the human whole blood assay was 106 as compared to 35, 30, 7.6, 7.3, 2.4 and 2 for rofecoxib, valdecoxib, celecoxib, nimesulide, etodolac and meloxicam, respectively (2, 18, 19). The inhibitory activity and selectivity for COX-2 *versus* COX-1 of these COX-2 inhibitors is given in Table I.

The potency of etoricoxib was also demonstrated in studies using in vivo rat models of carrageenan-induced paw edema, carrageenan-induced paw hyperalgesia, LPS-induced pyresis and adjuvant-induced arthritis. Treatment with etoricoxib at doses of 0.1-30 mg/kg resulted in dose-dependent inhibition in all models. The ID_{50} values for etoricoxib reported for these models were 0.64 ± 0.07, 0.34 ± 0.09, 0.88 ± 0.16 and 0.6 ± 0.1 mg/kg, respectively. In contrast, the ID_{50} values for indomethacin were 2.0 ± 0.2, 1.5 ± 0.4, 1.1 ± 0.2 and 0.4 mg/kg, respectively, and 1.5 ± 0.1, 1.0 ± 0.2, 0.24 ± 0.07 and 0.7 ± 0.1 mg/kg, respectively, for rofecoxib. Etoricoxib had no effects on gastrointestinal permeability at doses up to 200 mg/kg/day for 10 days (2, 18, 19).

In *in vivo* experiments using squirrel monkeys, treatment with etoricoxib (3 mg/kg) was shown to reverse LPS-induced pyresis by 81 ± 3% within 2 h of dosing; the same dose of rofecoxib or diclofenac decreased endotoxin-induced pyresis by 72 ± 6 and 96 ± 3%, respectively. Moreover, the agent displayed a favorable profile in stringent models of ulcerogenicity. A dose of 100 mg/kg b.i.d. in rats given for 10 days did not significantly affect urinary [^{51}Cr] excretion as compared to single-dose indomethacin or diclofenac (10 mg/kg), which caused leakge of [^{51}Cr] into urine that was 20-50 times more than that observed for controls. In addition, 100 mg/kg/day etoricoxib for 5 days had no effect on [^{51}Cr]-EDTA fecal excretion in a squirrel monkey model of gastropathy as compared to lower doses (3 mg/kg) of diclofenac or naproxen, which significantly increased fecal [^{51}Cr] excretion (2, 19).

Pharmacokinetics

A placebo-controlled study conducted in 24 healthy subjects examined the pharmacokinetics of single doses (5-500 mg) and multiple doses (25, 50, 100 or 150 mg

once daily for 9 days) of oral etoricoxib. The mean C_{max} values after single dosing ranged from 0.2-21.8 μM. At steady state following multiple dosing, the mean C_{max} values ranged from 1.5-8.2 μM for all dose groups. The median t_{max} was 12 h and the AUC_{0-24} geometric means for doses of 25, 50, 100 and 150 mg were 3.8, 6.6, 12 and 22.4 μg/h/ml, respectively, after the first dose and 6.5, 9.8, 19.2 and 36.8 μg/h/ml, respectively, on day 9. The mean AUC_{0-24} accumulation ratio was 14.4 h (20).

Another pharmacokinetic study conducted in 12 healthy subjects showed that antacids (10 ml calcium carbonate [2500 mg] or 20 ml Maalox®) did not affect the pharmacokinetics of single-dose etoricoxib (120 mg). The mean AUC_{∞} values for etoricoxib alone and in combination with calcium carbonate and Maalox® were 33.10, 32.57 and 35.61 μg·h/ml, respectively. The mean C_{max} values were 2396, 1850 and 2027 ng/ml, respectively, and the mean t_{max} values were 1.58, 1.58 and 1.79 h, respectively. It was concluded that antacids had no clinically significant effects on the absorption of etoricoxib (21).

Results from a placebo-controlled, 2-period crossover study in 12 healthy subjects showed that etoricoxib (120 mg/day for 14 days) did not alter the pharmacokinetics of either prednisolone (30 mg i.v. on day 10) or prednisone (30 mg p.o. on days 14). No significant differences were observed in the steroid C_{max}, $t_{1/2}$ or t_{max} values and mean transcortin and albumin concentrations were unchanged with combination treatment, indicating that there were probably no alterations in protein binding of the steroids (22).

Clinical Studies

A single-dose (5, 10, 25, 50, 125, 250 and 500 mg) and multiple-dose (25, 50, 100 or 150 mg once daily for 9 days), placebo-controlled study conducted in 24 healthy subjects demonstrated the efficacy of oral etoricoxib in inhibiting LPS-induced PGE_2 production in *ex vivo* assays. Etoricoxib was well tolerated. The maximum mean inhibitory (I_{max}) values obtained for LPS-induced PGE_2 production following the respective single doses were 20.3, 37, 39.5, 71.6, 85.4, 94.6 and 92.1% as compared to 12.6% with placebo; PGE_2 was significantly inhibited for 24 h postdosing. The I_{max} values on day 9 following multiple doses with 25, 50, 100 and 150 mg were 75.3, 62.1, 81.6 and 93.3%, respectively, as compared to 13.1% obtained with the placebo. No significant alterations in serum thromboxane B_2, bleeding time or arachidonic acid-induced platelet aggregation were observed (23).

A randomized, double-blind, placebo- and comparator (400 mg ibuprofen)-controlled trial conducted in 398 patients experiencing moderate to severe pain after removal of at least 2 third molars, showed the efficacy of single-dose etoricoxib (60, 120, 180, 240 mg) for acute dental pain. Etoricoxib was well tolerated at all doses tested. Both etoricoxib- and ibuprofen-treated patients reported significantly greater total pain relief as compared to placebo. The overall analgesic effects as measured using TOPAR8 (total pain relief over 8 h) were 16, 22, 23.5, 20.7 and 18.6 for 60, 120, 180 and 240 mg etoricoxib and ibuprofen, respectively, as compared to 5.2 for placebo; SPID8 (sum of pain intensity difference over 8 h) values and patient's global evaluation (0-4 scale where 0 = poor and 4 = excellent) indicated similar efficacy for etoricoxib and ibuprofen over placebo. Patient's global scores were 2.1, 2.6, 2.9, 2.7 and 2.6 for the respective doses of etoricoxib and ibuprofen, as compared to 0.5 for placebo. Of the patients treated with 60, 120, 180 and 240 mg etoricoxib, 64, 83, 89 and 84%, respectively, rated the agent as good, very good or excellent; only 78 and 19% of the ibuprofen- and placebo-treated patients, respectively, indicated the same ratings for their treatments (24) (Box 1).

The efficacy of single-dose etoricoxib (120 mg) as a treatment for acute dental pain was further demonstrated in a randomized, double-blind, placebo-controlled trial conducted in 200 patients experiencing moderate to severe pain after removal of at least 2 third molars. In this study, comparator groups included naproxen sodium (550 mg) and acetaminophen/codeine (600/60 mg). Etoricoxib was well tolerated. The least squares means for TOPAR8 were 20.1, 20.6, 10.7 and 4.6 for etoricoxib, naproxen, acetaminophen/codeine and placebo, respectively. All 3 test agents displayed a similar rapid onset of action (~30 min). Etoricoxib exhibited the longest duration of a action which was > 24 h followed by naproxen (~22 h), acetaminophen/codeine (~5.2 h) and placebo (2 h). From these results, it was concluded that etoricoxib had analgesic efficacy similar to naproxen but significantly greater than acetaminophen/codeine (25).

The efficacy and tolerability of etoricoxib (5, 10, 30, 60 and 90 mg once daily for 6 weeks) as a treatment for osteoarthritis of the knees was shown in a multicenter, randomized, triple-blind, placebo-controlled trial involving 617 patients. This 6-week part of the study was followed by an 8-week double-blind extension study in which 550 patients participated; those patients previously given 5 or 10 mg etoricoxib were switched to 30 mg etoricoxib or 150 mg diclofenac. Etoricoxib-treated patients showed significantly greater efficacy as compared to placebo according to the WOMAC VA 3.0 pain subscale, patient's global assessment of response to therapy and investigator global assessment of disease status. Mean changes over weeks 2-6 in the WOMAC pain subscale as compared to placebo were –7.6, –9.5, –13.9, –22.3 and –19.2 mm (VAS) for the 5, 10, 30, 60 and 90 mg doses of etoricoxib, respectively. Etoricoxib was well tolerated for all 14 weeks of treatment. No significant differences were observed in the first part of the study in terms of patient discontinuations due to adverse events. Moreover, no clinically significant dose-related trends for adverse events, serious adverse events or drug-related adverse events were observed. Similar tolerability results were observed in the 8-week extension study (26).

Box 1: The effects of etoricoxib in the treatment of acute dental pain (24) [Prous Science CSline database].

Design	Comparative, randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with moderate or severe pain after removal of at least 2 third molars (n = 398)
Treatments	Etoricoxib, 60 mg (n = 75) Etoricoxib, 120 mg (n = 76) Etoricoxib, 180 mg (n = 74) Etoricoxib, 240 mg (n = 76) Ibuprofen, 400 mg (n = 48) Placebo (n = 49)
Results	Total pain relief score @ 8 h: E180 (23.5) ≥ E120 (22.0) ≥ E240 (20.7) ≥ I (18.6) ≥ E60 (16.0) > P (5.2) [$p < 0.05$] Sum of pain intensity on the patient's global evaluation (0-4 scale), change @ 8 h: E180 (2.9) ≥ E240 (2.7) ≥ E120 (2.6) ≥ I (2.3) ≥ E60 (2.1) > P (0.5) Rate of patients who assessed the treatment as good/very good/excellent (%): E180 (89) ≥ E240 (84) ≥ E120 (83) ≥ I (78) ≥ E60 (64) > P (19)
Conclusions	Etoricoxib was well tolerated and effective in moderate or severe dental pain. The minimum recommended dose was 120 mg

Phase III trials involving etoricoxib as a treatment for osteoarthritis, rheumatoid arthritis and pain are currently being completed (27).

Manufacturer

Merck & Co., Inc. (US).

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