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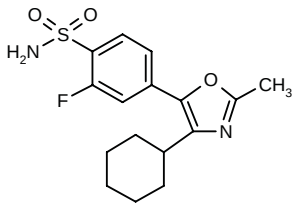
CCC: 0377-8282/98

JTE-522

Antiinflammatory
Cyclooxygenase-2 Inhibitor

4-(4-Cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide



$C_{16}H_{19}FN_2O_3S$ Mol wt: 338.40

CAS: 180200-68-4

EN: 239031

Synthesis

The condensation of cyclohexanecarbonyl chloride (I) with 3-fluorobenzyl bromide (II) by means of tetrakis-(triphenylphosphine)palladium and Zn in dimethoxyethane gives the ethanone (III), which is treated with lead tetraacetate in acetic acid, yielding the α-acetoxyethanone (IV). The cyclization of (IV) with ammonium acetate in refluxing acetic acid affords the oxazole derivative (V), which is treated with chlorosulfonic acid at 100 °C, yielding the 4-chlorosulfonyl derivative (VI). Finally, this compound is amidated with ammonia in THF/water (1). Scheme 1.

Introduction

It has long been assumed that nonsteroidal antiinflammatory drugs (NSAIDs) exert most of their antiinflammatory, analgesic and antipyretic activities through the inhibition of prostaglandin H synthase or cyclooxygenase (COX) (2). COX is the first enzyme in the prostanoid biosynthetic pathway catalyzing the conversion of arachidonic acid to prostaglandin H_2 as the first step in the synthesis of prostaglandins, prostacyclins and thromboxanes, all of which act as important mediators of both physiological and inflammatory responses (3, 4). The discovery of a second inducible isoenzyme (5, 6) has enabled the identification of two major isoforms of COX: the constitutive COX isoform, termed COX-1, and the inducible isoform, or COX-2.

The constitutive isoform COX-1 can be found under physiological conditions in most tissues while COX-2 is inducible mainly under inflammatory conditions (4). Thus, different roles have been proposed for each of these isoenzymes. The differential inhibition of COX-1 and COX-2 by certain NSAIDs (7) and a comparison of antiinflammatory activities with gastric and renal safety has led to the theory that NSAIDs exert their antiinflammatory activity primarily via inhibition of the inducible COX-2, whereas inhibition of constitutive COX-1 is responsible for their gastric and renal side effects and for the inhibition of platelet activation, an effect that is usually observed with classical NSAIDs, which are nonspecific and equipotent COX inhibitors (4, 8, 9).

Thus, the good relationship found between preferential inhibition of COX-2 relative to COX-1 *in vitro* and the improved pharmacological profile *in vivo* for various NSAIDs (4) support the hypothesis that preferential inhibition of COX-2 may produce antiinflammatory activity with a lower incidence of gastric and renal side effects than that associated with classical NSAIDs; however, some role for COX-1 in the pathogenesis of inflammation cannot be completely ruled out. Therefore, it is now assumed that whereas constitutive COX-1 is mainly associated with homeostasis, inducible COX-2 would be the major isoenzyme responsible for the production of proinflammatory mediators (2, 4). Based on the above, the selective inhibition of COX-2 has emerged as an interesting therapeutic target for the design of new NSAIDs with antiinflammatory activity accompanied by an improved side effect profile and increased tolerability.

Approved COX-2 preferential inhibitors include nabumetone, meloxicam and nimesulide. Specific COX-2 inhibitors in development include celecoxib (Searle/Pfizer/Yamanouchi), MK-966 (Vioxx™, Merck & Co.), GR-253035 (Glaxo-Wellcome) and JTE-522 (Japan Tobacco). Recent patents on COX-2 inhibitors are presented in Table I. There are at least 18 pharmaceutical companies with interest in developing COX-2 inhibitors.

Pharmacological Actions

JTE-522 is a new, potent and selective inhibitor of COX-2. It inhibits both sheep and human recombinant

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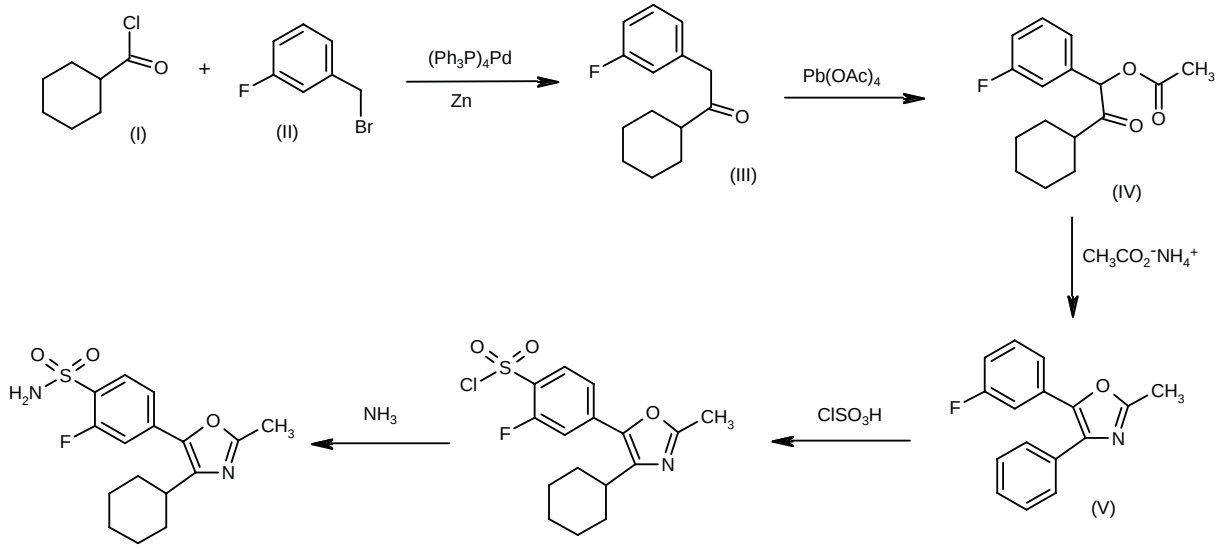
Scheme 1: Synthesis of JTE-522



COX-2 with IC_{50}s of 0.64 and 0.085 μM, respectively, without inhibiting either sheep or human platelet COX-1 at concentrations up to 100 mcM (10, 11). The resulting COX-1/COX-2 selectivity ratio of > 1176 for human isoenzyme indicates that JTE-522 is one of the most specific COX-2 inhibitors described to date (Table II).

The antiinflammatory activity of JTE-522 has been assessed in both *in vitro* and *in vivo* inflammation models. Studies in vitro have demonstrated that JTE-522, similar to NS-398 (another selective COX-2 inhibitor), markedly inhibited COX-2-dependent prostaglandin E_2 (PGE_2) production in rat peritoneal macrophage preparations, giving an IC_{50} value of 0.0022 μM compared to 0.0048 and 0.022 μM, respectively, for NS-398 and indomethacin (a nonselective COX inhibitor). In contrast, the compound only weakly inhibited COX-1-dependent PGE_2 production; corresponding IC_{50}s were 3.3, 4.5 and 0.19 μM for JTE-522, NS-398 and indomethacin, respectively (12).

In addition, *in vivo* studies showed that JTE-522 exhibited good oral antiinflammatory activity in a range of animal models (10-14) and, in contrast to nonspecific COX inhibitors such as indomethacin, did not induce severe gastric lesions in rats at doses up to 300 mg/kg p.o. (10, 11, 13, 14).

In rats with yeast-induced hyperthermia and hyperalgesia, title compound dose-dependently reversed the pyretic response (ED_{50} = 3.9 mg/kg p.o. *vs.* 1.4 mg/kg p.o. for indomethacin) as well as the nociceptive response (ED_{50} = 4.4 and 3.1 mg/kg p.o. for JTE-522 and indomethacin, respectively). JTE-522 also inhibited acute inflammation in the carrageenan-induced rat paw edema model (ED_{30} = 4.7 mg/kg p.o. *vs.* 1.6 mg/kg p.o. for indomethacin) and chronic inflammation in the rat adjuvant arthritis model following daily oral treatment with 0.3-3 mg/kg of the drug (10, 11).

Table I: Recent patents on COX-2 inhibitors.

Abbott	WO 9716435
US 5681842	WO 9728120
US 5750558	WO 9728121
WO 9741100	WO 9736863
ADIR	WO 9740012
EP 728755	WO 9803484
Almirall Prodesfarma	Roche
WO 9734882	EP 714895
American Home Prod.	EP 810218
WO 9804527	WO 9746524
Boehringer Ingelheim	Searle
WO 9746532	US 5616601
Chem. Pharm. Forsch.-Gesellschaft	WO 9603387
WO 9713767	WO 9603392
Chugai	WO 9616934
WO 9730030	WO 9624584
Fujisawa	WO 9624585
WO 9713755	WO 9625405
Glaxo Wellcome	WO 9638418
WO 9631509	WO 9638442
Hafslund Nycomed	WO 9738986
WO 9703953	SmithKline Beecham
Merck Frosst	WO 9640143
US 5510368	Toyama
WO 9606840	WO 9626921
WO 9613483	UPSA
WO 9619469	US 5686460
WO 9621667	US 5723485
WO 9623786	WO 9737984
WO 9637469	
WO 9714691	

Source: Prous Science Ensemble Database, where the chemical structures and further information can be found.

Table II: COX-1 and COX-2 inhibitory activity (IC_{50} μM) and selectivity (COX-1/COX-2) of COX inhibitors against ovine COX-1 (sheep seminal vesicle) and COX-2 (sheep placenta) isoenzymes.

Compound	COX-1	COX-2	COX-1/COX-2	References
Diclofenac	0.09	0.06	1.50	16
Flufenamic acid	4.9	19	0.26	16
Ibuprofen	97	407	0.24	16
	43	68	0.63	10
Indomethacin	0.27	12	0.022	10
	0.09	0.44	0.20	16
JTE-522	>100	0.64	>156	10
Mefenamic acid	17	>100	< 0.17	10
Naproxen	24	209	0.11	16
NS-398	>100	1.8	>55	10
Piroxicam	104	>850	< 0.12	16
Tenidap	2.1	5.2	0.40	16

Source: Prous Science MFLine® database. All data refer to sheep enzymes for comparison with title compound. Data referring to other sources and assays for assessing COX inhibitory activities are also available from the Prous Science MFLine® database for a wide range of compounds.

JTE-522 suppressed paw swelling in rats with adjuvant-induced arthritis (ED_{50} = 1.8 and 0.13 mg/kg p.o. for JTE-522 and indomethacin, respectively) and also prevented bone mineral density reductions induced by adjuvant treatment in paw (ED_{50} = 1.0 mg/kg p.o. *vs.* 0.33 mg/kg p.o. for indomethacin) and in lumbar vertebrae (dose range of 0.3-3 and 0.1-0.3 mg/kg p.o. for JTE-522 and indomethacin, respectively). Radiographic assessment showed that both JTE-522 and indomethacin also reduced severe disorganization of the bone in distal tibia, tarsus and calcaneus. This study showed that JTE-522 at 1 and 3 mg/kg p.o., like indomethacin at 0.1 and 0.3 mg/kg, significantly reduced urinary deoxypyrinoline and pyridinium cross-link levels, which would reflect the degree of degeneration and resorption of bone in arthritis-related disorders (14).

The antiinflammatory activity of JTE-522 compared with that of NS-398 and indomethacin was also evaluated using a recurrence model of air pouch-type allergic inflammation in rats, in which COX-2-derived PGE2 plays an important role as inflammatory mediator. JTE-522 (30-100 μg/pouch) dose-dependently suppressed accumulation of pouch fluid, infiltration into pouch fluid of neutrophils (leukocytes) and contents of PGE_2 in the pouch fluid, similar to NS-398 and indomethacin (12). Moreover, JTE-522 (10 mg/kg p.o.) attenuated the ozone-induced airway responsiveness to histamine in guinea pigs 5 h after exposure, although not immediately postexposure, without affecting airway inflammation measures (*e.g.*, neutrophil influx in bronchoalveolar lavage fluid) (15).

The results of these experimental studies indicate that JTE-522 may be a good candidate for the oral treatment of inflammatory diseases, with a lower potential to cause side effects as compared to classical NSAIDs such as indomethacin.

Clinical Studies

JTE-522 is currently undergoing phase II clinical trials for the treatment of rheumatoid arthritis and osteoarthritis (17, 18).

Manufacturer

Japan Tobacco, Inc. (JP); licensed to R.W. Johnson (US).

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