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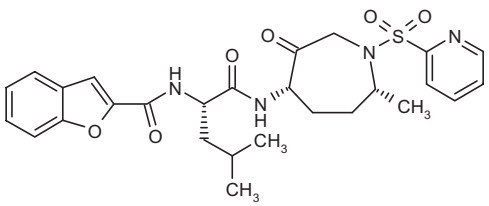
Relacatib

Prop INN; USAN

Prevention and Treatment of Bone Metastases
Treatment of Osteoarthritis
Treatment of Osteoporosis
Cathepsin K inhibitor

GSK-462795
SB-462795

N^2-(1-Benzofuran-2-ylcarbonyl)-N^1-[7(*R*)-methyl-3-oxo-1-(2-pyridinylsulfonyl)perhydroazepin-4(*S*)-yl]-L-leucinamide



$C_{27}H_{32}N_4O_6S$
Mol wt: 540.6323

CAS: 362505-84-8

CAS: 362507-64-0 (as enantiomer)

EN: 310712

Abstract

Cathepsin K is a cysteine protease synthesized by osteoclasts and one of the major effectors of osteoclastic bone resorption. As such, it is an attractive target for therapeutic intervention in the treatment of osteoporosis and other bone disorders causing bone degradation. Relacatib (SB-462795) is a high-potency inhibitor of cathepsin K with demonstrated antiresorptive activity in normal and ovariectomized monkeys. Studies in ovariectomized monkeys also demonstrated a greater stimulatory effect on cortical bone compared to alendronate, with significant improvements in bone mineral density and bone mineral content compared with vehicle-treated controls. Studies in monkeys indicate site-specific differences between alendronate and relacatib which may translate into differential efficacy. Relacatib is scheduled to enter phase II development for the prevention and treatment of bone metastases in 2006.

Synthesis

Several synthetic methods have been described for relacatib:

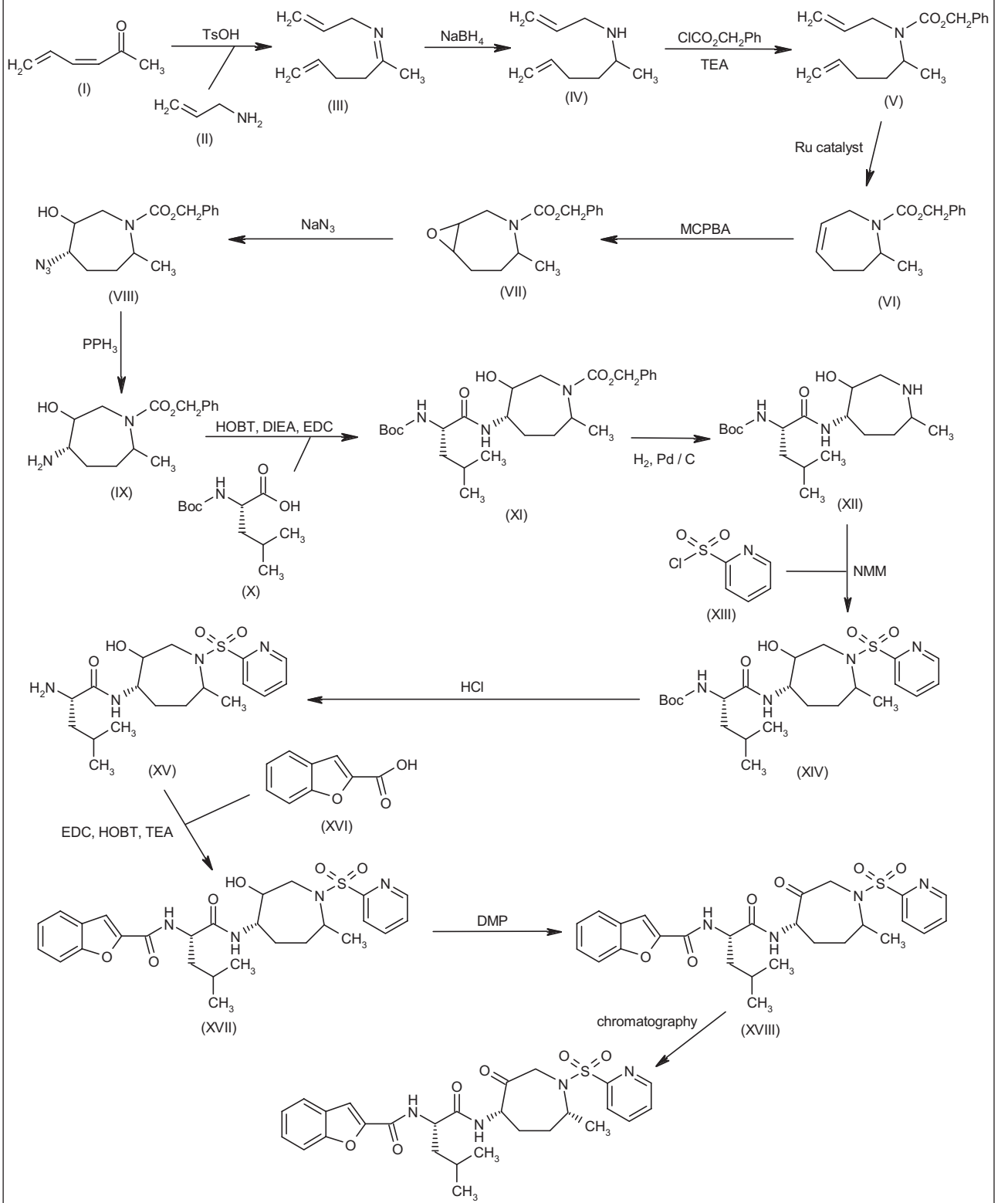
1) The reaction of 3,5-dihexen-2-one (I) with allylamine (II) by means of TsOH in dichloromethane gives *N*-allyl-1-methyl-4-penten-1-ylideneimine (III), which is reduced with $NaBH_4$ in methanol to yield *N*-allyl-*N*-(1-methyl-4-penten-1-yl)amine (IV). The reaction of amine (IV) with benzyl chloroformate by means of TEA in dichloromethane affords the carbamate (V), which is submitted to cyclization by means of an Ru catalyst (Grubbs' catalyst) in dichloromethane to provide 2-methyl-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylic acid benzyl ester (VI). The reaction of (VI) with MCPBA in dichloromethane gives the epoxide (VII), which is treated with NaN_3 in aqueous ethanol to yield 5-azido-6-hydroxy-2-methylazepine-1-carboxylic acid benzyl ester (VIII). The reduction of the azido group of (VIII) by means of PPh_3 in THF/water affords the corresponding amino derivative (IX), which is condensed with *N*-Boc-L-leucine (X) by means of HOBt, EDC and DIEA in DMF to provide the leucinamide derivative (XI). The elimination of the benzyl ester group of (XI) by hydrogenation with H_2 over Pd/C in EtOAc/MeOH gives the azepine (XII), which is acylated by means of pyridine-2-sulfonyl chloride (XIII) and NMM in dichloromethane to yield the sulfonamide (XIV). The deprotection of the amino group of (XIV) by means of HCl in dioxane affords compound (XV) with a free amino group, which is condensed with benzofuran-2-carbonyl chloride (XVI) by means of EDC, HOBt and TEA in DMF to provide the carboxamide (XVII). Finally, the secondary OH group of (XVII) is oxidized by means of DMP in dichloromethane to give the azepinone (XVIII) as a diastereomeric mixture, which is separated by column chromatography to obtain relacatib (1, 2). Scheme 1.

2) The preparation of the synthetic precursor (XXIX) is performed as follows:

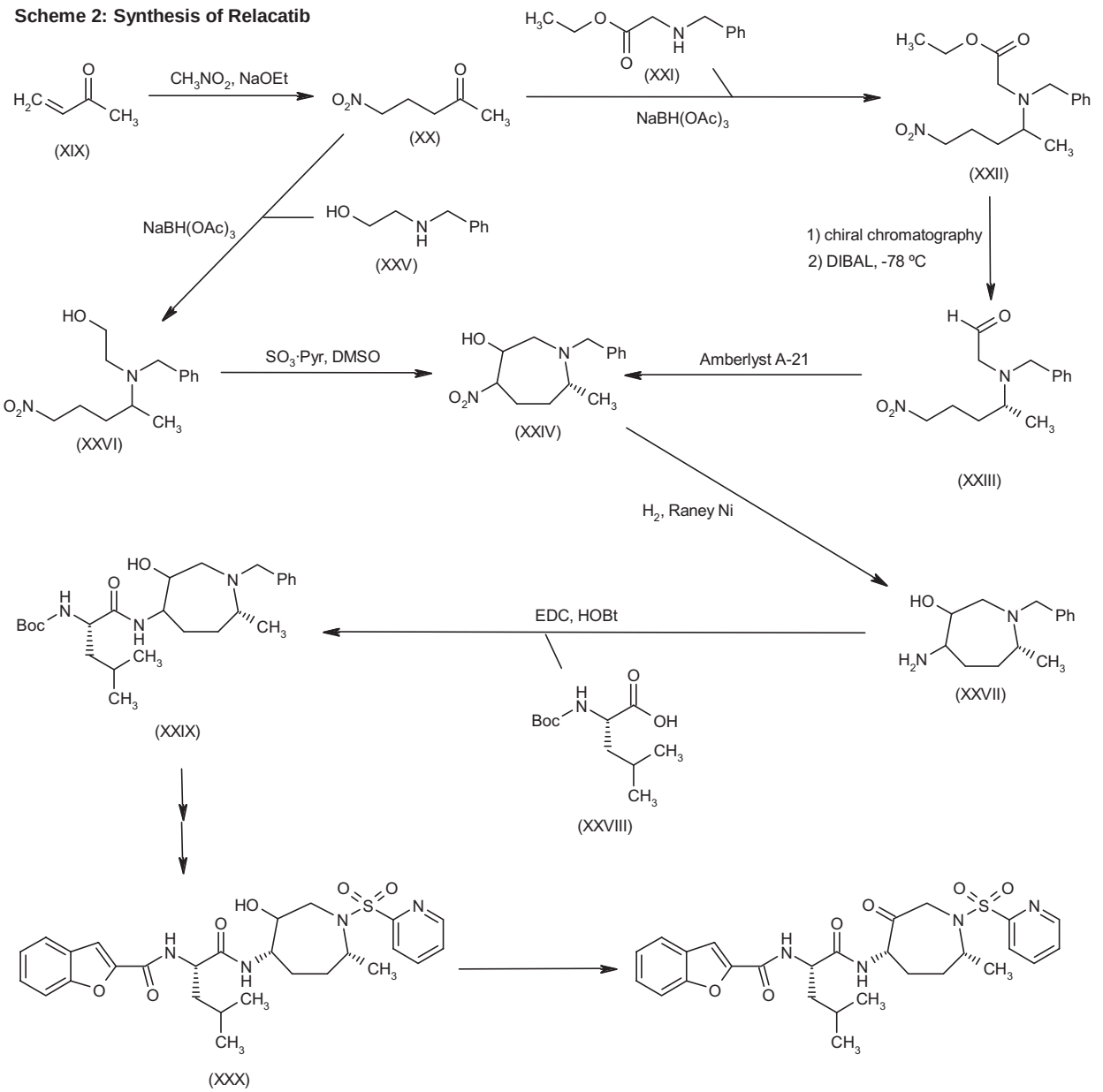
The conjugate addition of nitromethane to methyl vinyl ketone (XIX) affords the nitro ketone (XX), which is reductively aminated with *N*-benzylglycine ethyl ester (XXI) to produce the racemic amino ester (XXII). After resolution of (XXII) by chiral HPLC, the desired (*R*)-enantiomer is

J.A. McIntyre, N. Serradell, J. Bolós. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Relacatib



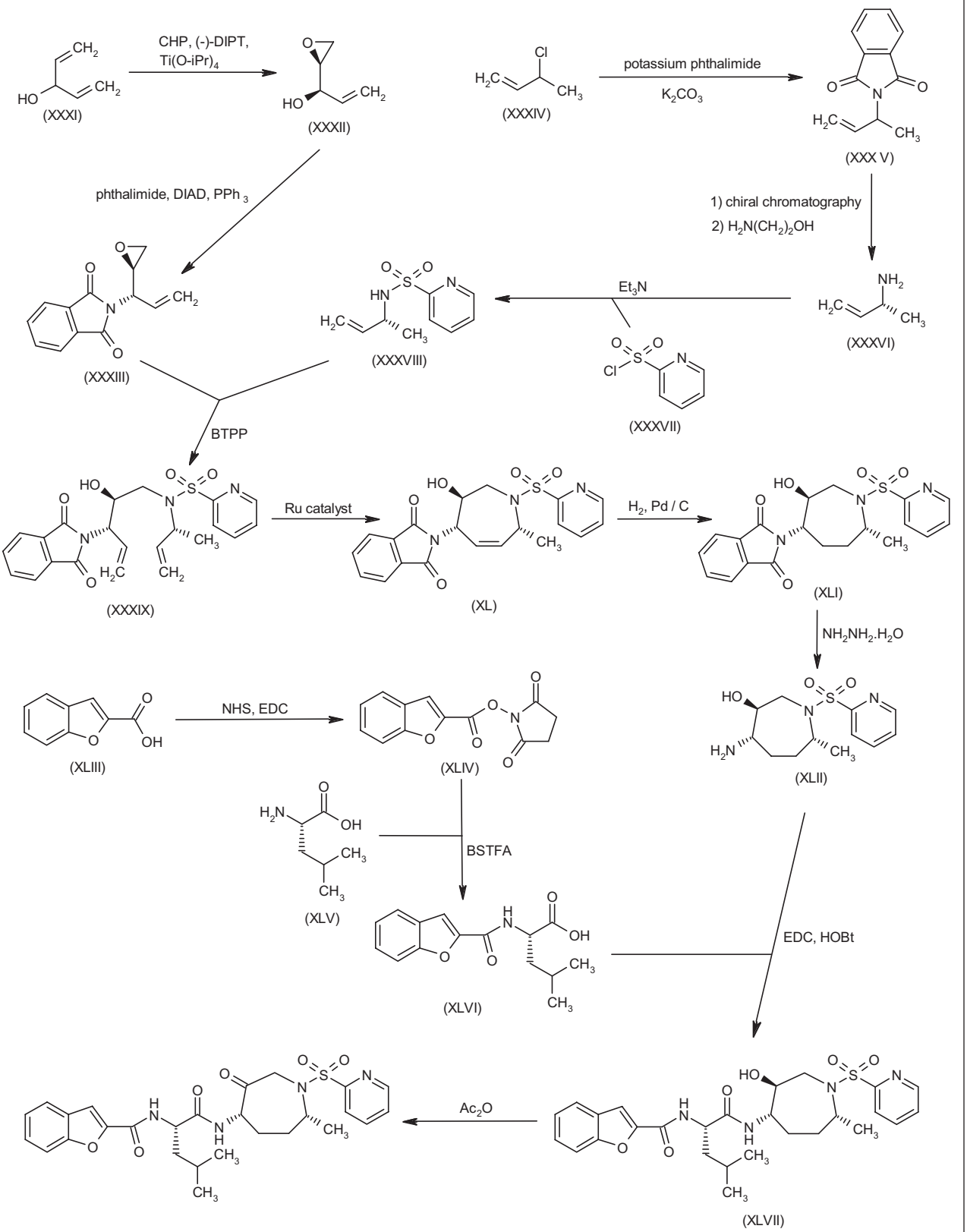
Scheme 2: Synthesis of Relacatib



reduced to the aldehyde (XXIII) using DIBAL in cold dichloromethane. Subsequent cyclization of the nitro aldehyde (XXIII) in the presence of the basic ion-exchange resin Amberlyst A-21 gives the azepinol (XXIV). Alternatively, reductive amination of the nitro ketone (XX) with *N*-benzylethanolamine (XXV) gives the amino alcohol (XXVI), which, upon Swern oxidation with sulfur trioxide-pyridine complex in DMSO, gives the cyclized azepinol (XXIV). Nitro group reduction in (XXIV) by hydrogenation over Raney nickel provides the aminoazepine (XXVII), which is then coupled with *N*-Boc-L-leucine (XXVIII) by means of EDC and HOBt to give the *N*-azepinyl leucinamide (XXIX). Conversion of intermediate (XXIX) to relacatib is performed via derivatization to the azepinol precursor (XXX), which can be finally oxidized to the target azepinone (3). Scheme 2.

3) Asymmetric epoxidation of the pentadienol (XXXI) in the presence of cumene hydroperoxide (CHP) and (–)-diisopropyl tartrate (DIPT) affords the epoxy alcohol (XXXII), which is subjected to Mitsunobu coupling with phthalimide to produce the phthalimido epoxide (XXXIII). Condensation of 3-chloro-1-butene (XXXIV) with potassium phthalimide yields the racemic 1-methylallyl phthalimide (XXXV), which is resolved into the enantiomers

Scheme 3: Synthesis of Relacatib



employing chiral chromatography. Deprotection of the desired (*R*)-phthalimide with ethanolamine, followed by acylation of the resulting chiral amine (XXXVI) with pyridine-2-sulfonyl chloride (XXXVII), gives the sulfonamide (XXXVIII). This is then coupled with epoxide (XXXIII) in the presence of *tert*-butylimino tri(pyrrolidino)phosphorane (BTPP) to furnish the open-chain diene (XXXIX), which undergoes ring-closing metathesis to the tetrahydroazepine (XL) in the presence of a Ru catalyst. Subsequent hydrogenation of (XL), followed by phthaloyl group hydrazinolysis in the resulting hexahydroazepine (XLI), provides the amino azepine derivative (XLII) (4). After activation of benzofuran-2-carboxylic acid (XLIII) as the succinimidyl ester (XLIV) using *N*-hydroxysuccinimide and EDC, coupling with L-leucine (XLV) in the presence of bis(trimethylsilyl)trifluoroacetamide (BSTFA) gives the corresponding *N*-acyl leucine (XLVI). This is then coupled with the intermediate aminoazepine (XLII) to furnish (XLVII), which is finally oxidized to relacatib by means of Ac_2O in DMSO (4). Scheme 3.

Background

Osteoporosis is a metabolic bone disease characterized by low bone mass and structural deterioration of bone tissue. Throughout the normal human lifetime there is a continuous process of bone erosion and bone formation by osteoclasts and osteoblasts, respectively. Until the time of peak bone mass in the mid-20s, the process of modeling takes place when new bone is formed more quickly than old bone is resorbed, while in the first years of the menopause bone loss in women is accelerated. Cathepsin K is a cysteine protease of the papain family that is synthesized by osteoclasts and is one of the major effectors of bone degradation during the process of bone resorption. As such, cathepsin K has been implicated in osteoporosis and other bone disorders causing bone degradation (5, 6).

Relacatib (SB-462795) is a potent inhibitor of cathepsin K with favorable pharmacokinetic characteristics in rats and monkeys (2). It is expected to move into phase II development for the prevention and treatment of bone metastases during 2006 and is also in development for the treatment of osteoporosis and osteoarthritis (7, 8).

Preclinical Pharmacology

Relacatib demonstrated potent inhibition (K_i = 0.041 nM) of human cathepsin K and inhibited osteoclast resorption in an *in vitro* assay with an IC_{50} value of 22 nM (2).

The antiresorptive activity of relacatib was evaluated in normal and ovariectomized monkeys. A single s.c. dose of 12 mg/kg resulted in 70% and 78% inhibition, respectively, of serum *C*-terminal telopeptide of type I collagen (CTx) at 1.5 and 72 h. Oral relacatib doses of 10 and 30 mg/kg resulted in an approximately 50% reduction in urinary *N*-terminal telopeptide of type I collagen (NTx) in the first 24 h. The maximal effect was observed in normal female monkeys following a single oral dose of 10 mg/kg. This resulted in a 38% reduction in urinary NTx over 48 h. Repeated oral administration (3 mg/kg) for 5 days resulted in progressive inhibition that was maximal (57%) on day 5. Relacatib had no significant impact on serum levels of osteocalcin, a biomarker of bone formation (9).

The pharmacological and toxicological effects of relacatib were evaluated in male monkeys. Doses of 3, 30 or 1000 mg/kg were administered by daily gavage for 52 weeks. The higher doses significantly reduced cartilage and bone resorption biomarkers at week 52, as demonstrated by 79% and 74% reductions, respectively, in the urinary type II collagen/creatinine ratio in the two higher dose groups. Furthermore, there were 35% and 43% decreases, respectively, in the bone formation marker bone-specific alkaline phosphatase, but no significant changes in serum osteocalcin levels. Significant increases in bone mineral density were also seen. In the mid-femur, there was a dose-dependent decrease in medullary cavity area, consistent with stimulation of bone formation on the periosteal surface. Biomechanical testing in lumbar vertebrae also demonstrated increases in maximum load of 42% and 49%, respectively, for doses of 30 and 1000 mg/kg. Histomorphometric data showed significantly decreased activation on all endosteal surfaces, consistent with a reduction in bone turnover. Relacatib was well tolerated, with no evidence of toxicity even at the highest dose (10).

The cortical bone-forming effect of relacatib was evaluated in aged ovariectomized monkeys treated with 1, 3 or 10 mg/kg/day by gavage for 9 months. There were significant, dose-dependent reductions in urinary NTx. Serum osteocalcin was significantly increased from 3 to 9 months (1 mg/kg/day) and at 9 months (3 mg/kg/day). Histomorphometric data demonstrated a dose-dependent reduction in both bone resorption and formation parameters at cancellous sites, but there was a significant stimulatory effect on femur periosteal bone at the lowest dose and a significant increase in endosteal turnover, which was inversely related to dose level. The results demonstrated a novel stimulatory effect on cortical bone for relacatib (11).

The effect of relacatib on the loss of bone mass was also investigated in aged ovariectomized monkeys treated with 1, 3 or 10 mg/kg/day by gavage for 9 months. There was a significant, dose-dependent improvement in bone mineral density at the lumbar spine and proximal and distal femur after 9 months compared with vehicle-treated animals. At the distal femur and the lumbar spine, relacatib prevented the loss of 73% and 42%, respectively, of bone mineral density compared with control animals. Total bone mineral content and cortical bone mineral content were significantly improved by relacatib (40% and 56%, respectively). In comparison with alendronate (0.05 mg/kg i.v. every other week), relacatib was more effective at the cortical bone site, indicating site-specific differences between bisphosphonates and cathepsin inhibitors (12).

Pharmacokinetics and Metabolism

In pharmacokinetic studies in rats, relacatib had a half-life of approximately 109 min and an oral bioavailability of 89% (2).

Clinical Studies

Results from a phase I clinical study in healthy volunteers receiving once-daily oral treatment with relacatib (10-80 mg) demonstrated a significant, dose-dependent increase in serum levels of pyridinoline crosslinked CTx (ICTP) after 14 days (13). Phase II trials are scheduled to begin this year for the prevention of bone metastases (7, 8).

Sources

GlaxoSmithKline (US); developed in collaboration with Human Genome Sciences, Inc. (US).

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