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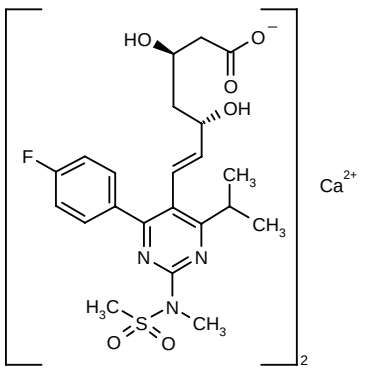
CCC: 0377-8282/99

ZD-4522

Hypolipidemic
HMG-CoA Reductase Inhibitor

S-4522

(+)-(3*R*,5*S*)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylamino)pyrimidin-5-yl]-3,5-dihydroxy-6(*E*)-heptenoic acid calcium salt (2:1)



$2C_{22}H_{27}FN_3O_6S.Ca$ Mol wt: 1001.1470

CAS: 147098-20-2
CAS: 147098-18-8 (as monosodium salt)

EN: 243619
EN: 192585 (as sodium salt)

Synthesis

The condensation of 4-fluorobenzaldehyde (I) with 4-methyl-3-oxopentanoic acid ethyl ester (II) by means of piperidine/AcOH in refluxing benzene gives the corresponding benzylidene derivative (III), which is cyclized with *S*-methylisothiourea (IV) and oxidized with DDQ, affording the pyrimidine derivative (V). The oxidation of (V) with *m*-chloroperbenzoic acid (*m*-CPBA) gives the expected methanesulfonyl derivative (VI), which is treated first with methylamine and then with methanesulfonyl chloride to provide the *N*-methylmethanesulfonamide (VII). The reduction of the ester group of (VII) with DIBAL in toluene, followed by selective oxidation of the resulting alcohol with TPAP, affords the aldehyde (VIII), which is submitted to a Wittig condensation with the phosphorane (IX) in acetonitrile to give the protected heptenoate (X). The deprotection of (X) with FH and the controlled reduction of the resulting keto alcohol with Et_2BOMe and $NaBH_4$ affords the chiral dihydroxyheptenoate (XI), which is hydrolyzed with NaOH in ethanol, yielding the corresponding sodium salt (XII). Finally, this compound is treated with calcium chloride (1, 2). Scheme 1.

Description

$[\alpha]_D^{24}$ +14.8° (c 1.012, 50% MeOH) (1); starts to melt at 155 °C, but the definitive m.p. is ambiguous (2), $[\alpha]_D^{25}$ +6.3° (c 2.011, MeOH) (2).

Introduction

The enzymatic biosynthesis of cholesterol is a complex process requiring more than 25 reaction steps. The four principal steps of the pathway include conversion of acetic acid to mevalonic acid, conversion of mevalonic acid into squalene, conversion of squalene into lanosterol and conversion of lanosterol into cholesterol. Inhibiting the synthesis of cholesterol has been established as one of the most effective approaches to lowering serum cholesterol. Several enzymes have been selected as targets for hypocholesterolemic drug design. Among these enzymes, HMG-CoA reductase [EC 1.1.1.34], the rate-limiting enzyme in cholesterol biosynthesis, catalyzes the reduction of HMG-CoA into mevalonic acid. Inhibition of this enzyme has proven to be an effective means for lowering serum triglycerides and LDL levels in humans. The present status of HMG-CoA reductase inhibitors in development and the biological activity of these compounds were reported extensively in a recent monograph in this journal (3).

In an effort to identify more potent HMG-CoA reductase inhibitors, scientists at Shionogi synthesized a series of methanesulfonamide pyrimidine- and *N*-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates and identified S-4522 (ZD-4522) as a candidate for further evaluation (1).

Pharmacological Actions

In early *in vitro* studies, ZD-4522 was shown to be approximately 4.42 times more potent than lovastatin in inhibiting the HMG-CoA reductase enzyme in isolated rat

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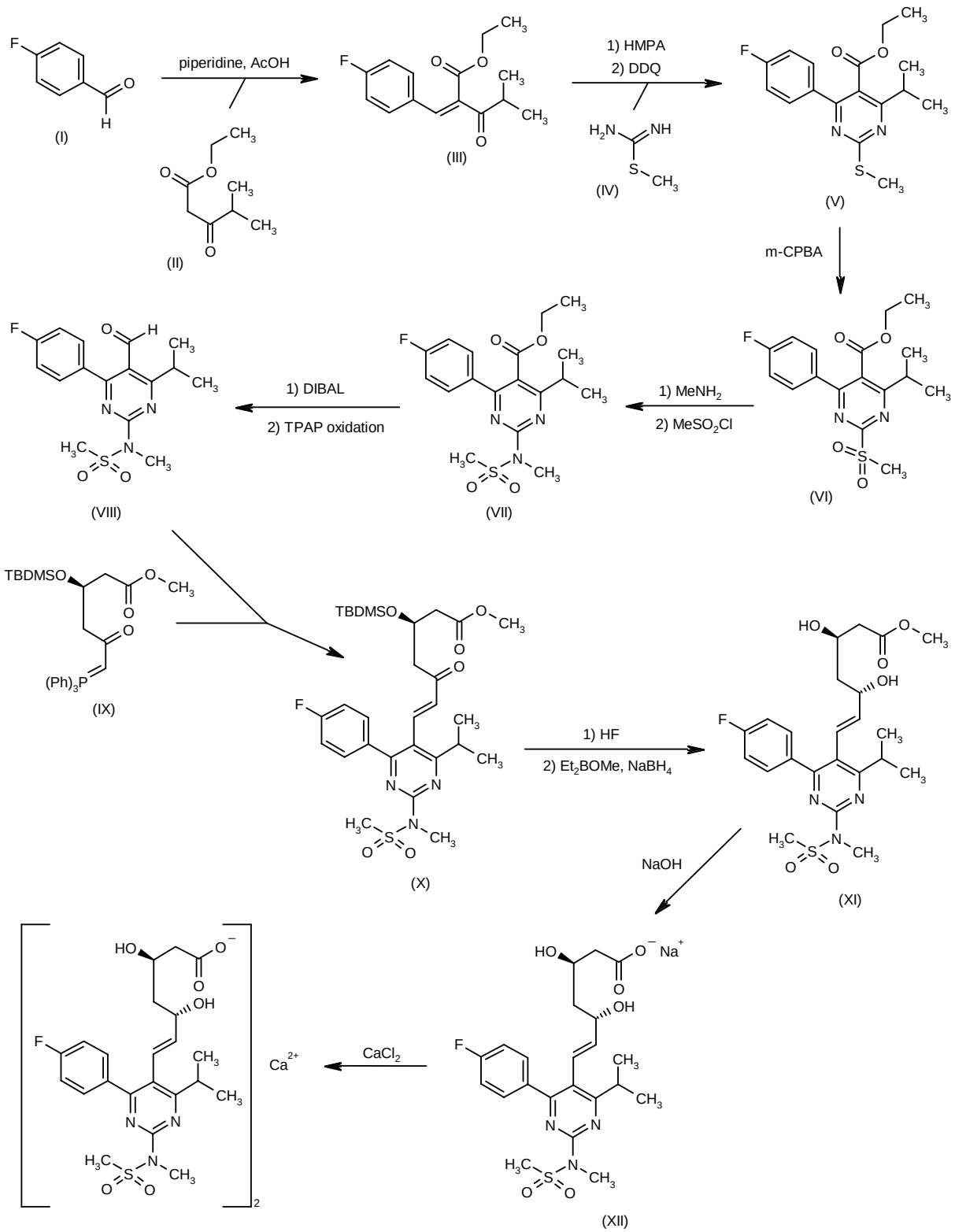
Scheme 1: Synthesis of ZD-4522



liver hepatocytes (IC_{50} = 11 nM for title compound *vs.* IC_{50} = 27 for lovastatin). ZD-4522 also inhibited cholesterol biosynthesis in isolated rat liver hepatocytes with an IC_{50} of 1.12 nM, being approximately 100-fold more potent than pravastatin (IC_{50} = 198 nM) in this model. In cultured human hepatoma (Hep-G2) cells, the title compound increased the mRNA of LDL receptors by approximately 10 times more than pravastatin, indicating an increased potential to lower serum cholesterol (1).

The inhibitory activity of ZD-4522 on sterol synthesis was compared *in vivo* in various rat tissues. The compound showed significantly more potent activity in the liver than in peripheral tissues, indicating that it will be associated with a reduced incidence of side effects (2, 3). Furthermore, the selectivity of ZD-4522 for hepatic tissues was superior to that of pravastatin and simvastatin (4).

In vivo in normolipemic male beagle dogs, oral administration of ZD-4522 (3 mg/kg/day x 14 days) was associated with a 26% decrease in plasma cholesterol levels, as compared to a decrease of only 18% with pravastatin. In cynomolgus monkeys, the study compound (12.5 mg/kg) reduced plasma cholesterol levels by 22%, while pravastatin lowered serum cholesterol levels by 19% at a much higher dosage (50 mg/kg) (1).

Clinical Studies

Based on the promising findings obtained in animal studies, ZD-4522 was advanced to clinical testing. The compound is considered a “superstatin” due to its ability, at well-tolerated doses, to lower LDL cholesterol and triglycerides to a much greater extent than first-generation statins (5). As-yet-unpublished phase II trial results confirm that ZD-4522 is at least as effective as atorvastatin and has excellent tolerability. Phase I, phase IIa and phase IIb trials of ZD-4522 have been completed and an accelerated phase III development program has been initiated (6, 7).

Manufacturer

Shionogi & Co., Ltd. (JP); licensed to AstraZeneca plc (GB).

References

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