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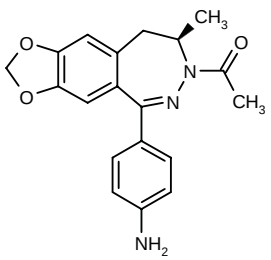
Talampanel

Prop INN

Antiepileptic
Neuroprotectant
Skeletal Muscle Relaxant

GYKI-53773
IDR-53773
LY-300164

7-Acetyl-5-(4-aminophenyl)-8(*R*)-methyl-8,9-dihydro-7*H*-1,3-dioxolo[4,5-*h*][2,3]benzodiazepine



$C_{19}H_{19}N_3O_3$ Mol wt: 337.3820

CAS: 161832-65-1

EN: 228517

Synthesis

1-(3,4-Methylenedioxyphenyl)-2-propanol is condensed with 4-nitrobenzaldehyde. The resulting compound is oxidized in DMF, followed by treatment with acetylhydrazine. Then, the chiral hydroxy group is mesylated and cyclized by means of NaOH. The last step is the reduction of the nitro group (1, 2). Scheme 1.

Description

White crystals from 50% ethanol, m.p. 198-200 °C, soluble in methanol, ethanol, acetonitrile and DMSO and insoluble in water.

Introduction

Continuing our work with 2,3-benzodiazepines, we synthesized a tricyclic analog of GYKI-52322 (3, 4). The linearly condensed dioxolane ring completely changed the biological profile of the molecule from a neuroleptic to an antiepileptic. The first such compound from this series was GYKI-52466. Later studies led to the discovery of GYKI-53773 (talampanel), which was selected for further development.

Pharmacological Actions

GYKI-53773 exhibited selective noncompetitive AMPA antagonism in in vitro functional tests. In fact, the compound inhibited AMPA currents in isolated cerebellar Purkinje cells (IC_{50} = 2.5 μM, in the whole-cell patch clamp assay) and inhibited AMPA-induced chicken retinal spreading depression with an IC_{50} value of 1.7 μM.

In vivo, GYKI-53773 displayed broad-spectrum anticonvulsant activity in mice by protecting against seizures induced by electroshock, pentylenetrazole, strychnine, bemegride, bicuculline, picrotoxin, nicotine, 3-mercaptopropionic acid and 4-aminopyridine (ED_{50} = 8.6, 16.8, 17.4, 23.9, 14.6, 7.2,. 22.7, 17.1 and 8.4 mg/kg, respectively).

The compound was also shown to inhibit tremors induced by oxotremorine, harmaline and GYKI-20039 in mice, with respective ED_{50} values of 5.6, 9.0 and 10.6 mg/kg p.o.

GYKI-53773 showed potent skeletal muscle relaxant effects in mice, with ED_{50} values of 13.4 mg/kg i.p. on the inclined screen and 2.3 mg/kg i.p. on the rotorod test (5).

In a model of transient cerebral ischemia in rats the compound protected against cell death induced by middle cerebral artery occlusion; a dose of 6 x 2 mg/kg i.v. decreased the infarcted area by 47%, compared to control animals.

Moreover, GYKI-53773 given at a dose of 2 x 30 mg/kg/d for 7 days reduced the symptoms of rat experimental autoimmune encephalomyelitis by 78%, as compared to control animals (6).

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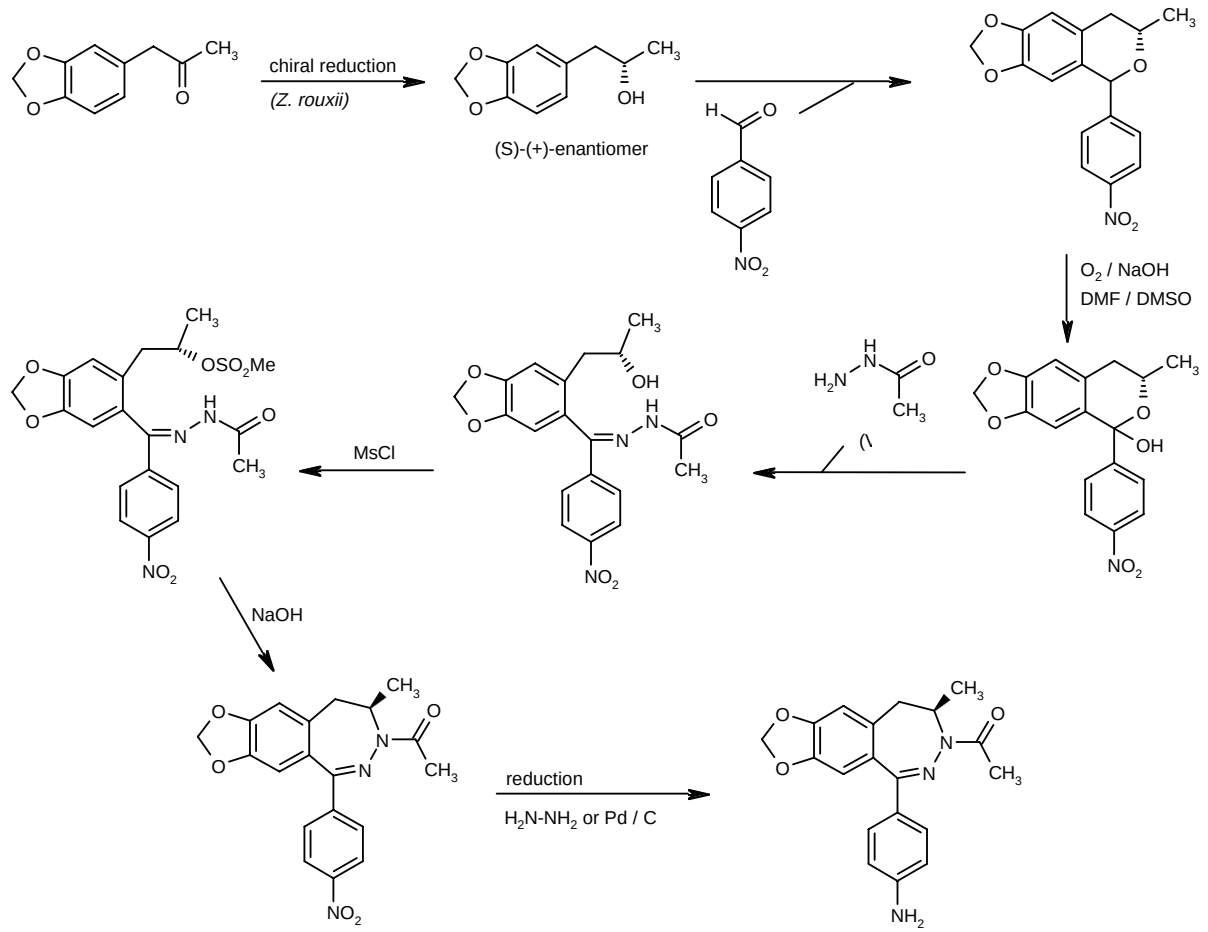
Scheme 1: Synthesis of Talampanel



GYKI-53773 was less toxic in rats than in mice, displaying acute oral LD_{50} values of 141 and 71 mg/kg, respectively.

Pharmacokinetics and Metabolism

The absorption, distribution and metabolism of talampanel were investigated in mice, rats, dogs, monkeys and men following oral and intravenous administration. After oral administration, the molecule was well absorbed by all species. In healthy volunteers after oral dosing (3, 6, 10, 20, 50, 70 and 100 mg) the C_{max} ranged from 71.1-838 μg/l and the t_{max} was 1.7-2.3 h with the 10 mg and 100 mg doses. The mean half-life increased from 3.7 to 6.8 h for the 10-100 mg dose range. The biotransformation of talampanel was different across species. A major route of metabolism was *N*-acetylation, which is extensive in monkeys, moderate in rats, poor in mice and men and negligible in dogs. In men, 6 metabolites were identified; the phase I pathways were deacetylation, *N*-oxidation and oxidation, followed by *O*-dealkylation to form a catechol. The phase II conjugation included *O*- and *N*-glucuronidation, *N*-acetylation, and catechol methylation. The protein binding was 67.3-87.9% among the different species (74.2% in men). The elimination in monkeys was 43.7% in the urine and 32.8% in the feces after a single oral dose.

Ivax has entered into an exclusive agreement with Lilly to develop and market talampanel on a worldwide basis. Phase II trials of the drug in patients with severe epilepsy not responsive to other drugs have shown efficacy, and phase III studies are planned to confirm and expand these results. Talampanel was initially discovered at the Institute for Drug Research in Hungary, now a wholly owned subsidiary of Ivax (7).

Manufacturer

IVAX Corp. (US); licensed to Eli Lilly and Company (US).

References

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