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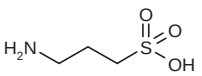
Tramiprosate

Prop INN; USAN

Antiamyloidogenic Agent
Treatment of Alzheimer's Disease
Treatment of Hemorrhagic Stroke

3-APS
NC-531
NC-758
Alzhemed™
Cerebril™
3-Aminopropane-1-sulfonic acid



$C_3H_9NO_3S$
Mol wt: 139.1745

CAS: 003687-18-1
EN: 277136

Abstract

Current treatments for Alzheimer's disease (AD) provide relief of symptoms but there is a need for treatments that protect neurons from further degeneration. Tramiprosate interacts with soluble β-amyloid (Aβ) peptides in the brain of transgenic mice to promote their clearance and reduce the accumulation of neurotoxic amyloid fibrils. Initial clinical evaluation has shown tramiprosate to reduce Aβ in the brains of patients with mild to moderate AD, and to stabilize cognitive function over 3 years in an extension trial. These same actions are predicted to benefit patients with hemorrhagic stroke. Tramiprosate is in phase III clinical trials for the treatment of mild to moderate AD and has completed phase II trials for the treatment of hemorrhagic stroke due to cerebral amyloid angiopathy (CAA).

Synthesis

Tramiprosate can be synthesized in several different ways:

1) Reaction of a molar excess of 1,3-dibromopropane (I) with sodium sulfite in aqueous ethanol gives sodium 3-bromo-1-propanesulfonate (II), which is subsequently treated with concentrated ammonium hydroxide to produce the target aminosulfonic acid (1, 2). Scheme 1.

2) In an alternative procedure, 3-chloropropylamine hydrochloride (III) is displaced with aqueous sodium sulfite to afford the corresponding sulfonic acid (3). Scheme 1.

3) Tramiprosate can also be obtained by ring opening of 1,3-propane sultone (IV) with either gaseous ammonia or aqueous ammonium hydroxide in acetone. A related 2-step procedure consists of the reaction of sultone (IV) with benzylamine to afford *N*-benzyltramiprosate (V), which is subsequently debenzylated to produce the title compound. Similarly, reaction of (IV) with sodium azide in aqueous tetrahydrofuran gives the azidosulfonic acid (VI), which is reduced to the corresponding amine by either catalytic hydrogenation or by the Staudinger reaction (4). Scheme 1.

4) Tramiprosate can also be obtained by oxidation of its sulfinic acid (XII) and thiosulfonic acid (XIII) analogues, which can be prepared as follows:

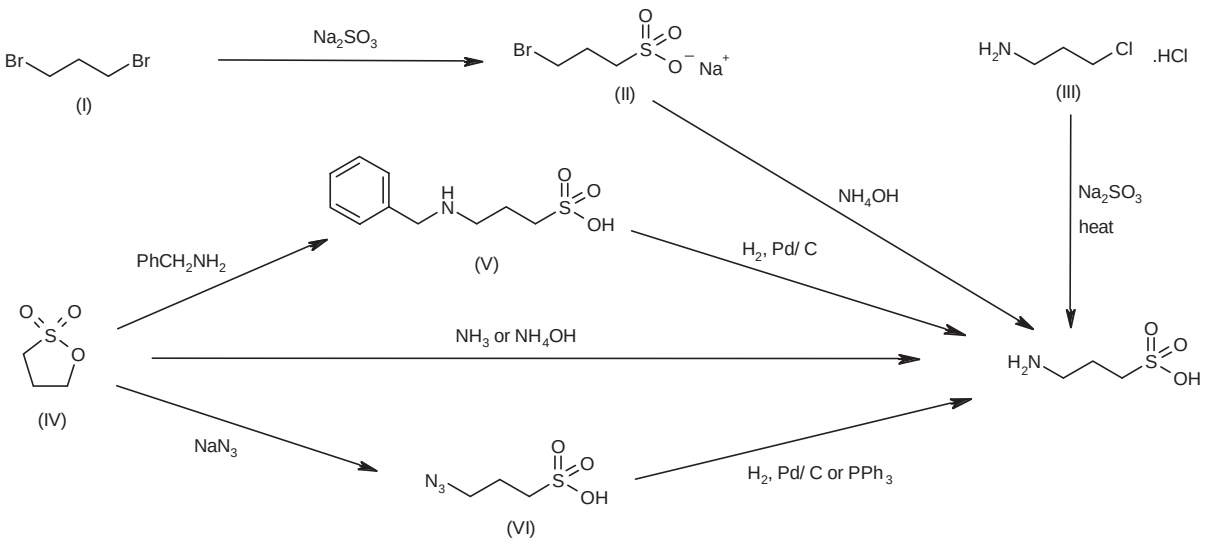
Treatment of 3-bromopropylphthalimide (VII) with KSH generated *in situ* gives the thiol (VIII), which is dimerized to the corresponding disulfide (IX) by oxidation with iodine. Subsequent hydrolysis of the bisphthalimide (IX) with hydrobromic acid provides homocystamine dihydrobromide (X). Oxidation of disulfide (X) by means of H_2O_2 in the presence of KI, followed by dismutation of the intermediate *S,S*-dioxide (XI) under alkaline conditions, generates a mixture of disulfide (X) and the sulfinic acid homohypotaurine (XII). Optionally, the sulfinic acid (XII) can be converted to homothiotaurine (XIII) by treatment with sulfur and NaOH. Finally, the oxidation of either (XII) or (XIII) with hydrogen peroxide in the presence of traces of ammonium molybdate gives the corresponding sulfonic cid (5). Scheme 2.

Background

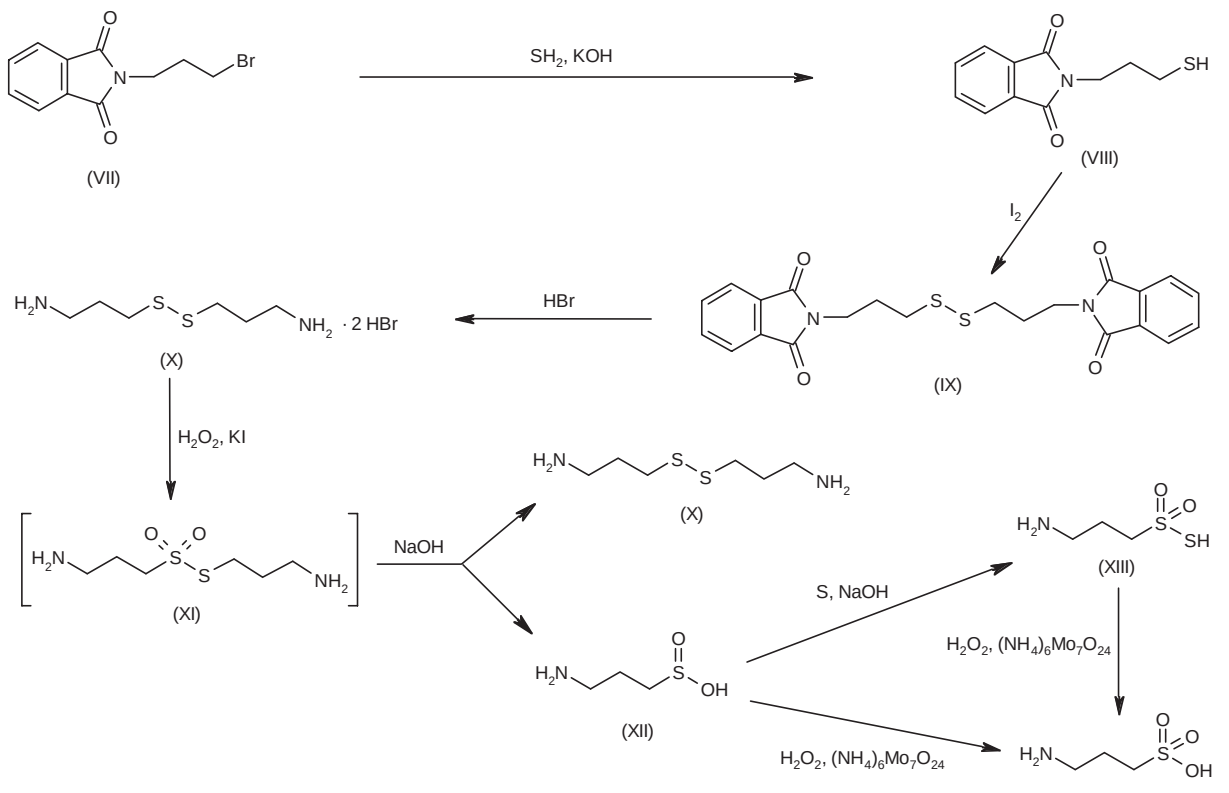
Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the death of nerve cells in the brain, in turn leading to loss of mental functions such as memory and learning. Current treatments for AD consist of drugs such as cholinesterase inhibitors that compensate for the loss of neurotransmitters and

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

Scheme 1: Synthesis of Tramiprosate



Scheme 2: Synthesis of Tramiprosate



provide relief of symptoms but do not alter the progression of the disease. There is an unmet medical need for therapies that target the cause of AD and slow down or stop the pathology of the disease, as well as the decline in mental functions (6, 7).

The pathological hallmarks of AD are deposits of amyloid peptides (plaques) around the neurons in the brain, and bundles of hyperphosphorylated tau protein (neurofibrillary tangles) within the neurons. The amyloid hypothesis postulates that accumulation of amyloid pep-

tides is primarily responsible for the pathology of AD, in which case therapies that modulate the accumulation of amyloid peptide might be expected to slow or halt the progression of AD. The principal components of the amyloid plaques are peptide fragments (amino acids 1-40 and 1-42) of amyloid precursor protein (APP), known as β-amyloid (Aβ) 40 and 42. It is the imbalance between Aβ production and Aβ clearance that leads to accumulation of the peptides in AD patients. Glycosaminoglycans (GAGs) bind to the soluble Aβ peptides and promote the formation of neurotoxic insoluble fibrils, which are the components of plaques. Tramiprosate mimics the anionic properties of GAGs, binds to the soluble Aβ peptides, and maintains the peptides in their soluble form. Tramiprosate may also promote their clearance from the brain. If current clinical trials are successful, tramiprosate (Alzhemed™) may become the first in a new class of drug aimed at stopping the progression of AD (6, 8).

Tramiprosate (Cerebril™) is also being developed for the treatment of patients with amyloid-associated stroke; 7% of strokes are caused by amyloid deposits in the vascular tissue of the brain (cerebral amyloid angiopathy, or CAA). As with AD, the disease is progressive and the condition of patients with CAA often deteriorates through a series of strokes. Treatment with tramiprosate aims to prevent further buildup of amyloid deposits and halt the progression of the disease (9).

Preclinical Pharmacology

Tramiprosate was selected from among several GAG mimetics due to its ability to bind to soluble Aβ and reduce fibrillogenesis *in vitro* (10). Transgenic mice expressing human APP accumulate soluble and fibrillar Aβ and form plaques. Treatment of the AD TgCRND8 mice with tramiprosate at 100 mg/kg/day (s.c.) for 8 weeks led to a 30% reduction in the number and size of parenchymal plaques, a 30% reduction in cerebral vascular amyloid deposits and a 60% reduction in plasma levels of $A\beta_{40/42}$. Mice treated with 500 mg/kg/day (s.c.) for 8 weeks showed 35% and 20% reductions, respectively, in the brain levels of $A\beta_{40}$ and $A\beta_{42}$ (8, 11).

In vitro studies have recently shown that tramiprosate decreases $A\beta_{42}$-induced cell death in rat neuronal cell cultures (100 μM) and SH-S5Y5 neuroblastoma cells (200 μM) by 38% and 51%, respectively (8).

Safety

Preclinical studies in rats and dogs showed that tramiprosate is safe, with no clinically significant adverse effects observed at 350 mg/kg/day for up to 39 weeks. The main adverse effects were diarrhea and emesis. The drug did not exhibit mutagenic or clastogenic effects in several assays (8).

A double-blind, randomized, placebo-controlled phase I study found that tramiprosate was safe and well tolerated in healthy young subjects receiving single oral doses of 100, 200, 300 and 400 mg (n=9/group). A group of 6 elderly subjects (> 55 years) received a single oral dose of 200 mg, and again the drug was well tolerated. The most common side effects were nausea and vomiting. These effects were dose-related and transient, and the maximum tolerated dose was established at 200 mg (12).

A 3-month double-blind, randomized, placebo-controlled phase II study in patients with mild to moderate AD found tramiprosate to be safe at all dose levels up to the maximum dose tested (150 mg b.i.d. p.o.). Three of 58 patients withdrew from the study due to adverse effects, the most frequent being nausea and vomiting, which were dose-related and transient (13).

Clinical Studies

At the end of the 3-month phase II study described above, levels of $A\beta_{42}$ in the cerebrospinal fluid (CSF) were reduced by up to 70% at the two higher doses tested (100 and 150 mg b.i.d. p.o.) (13, 14). At 3 months, 42 of the original 58 patients opted to enter an open-label extension of the phase II study to receive 150 mg tramiprosate b.i.d. This study has now been running for 3 years and the data from a range of cognitive function tests suggest that the drug helps to stabilize cognitive function, particularly in the group with mild AD. At study entry, patients had Mini Mental State Examination (MMSE) scores between 13 and 25, with a subgroup being classified as having mild AD (MMSE 19-25). The mean changes in MMSE scores after 1 year were –1.7 ± 4.6 overall and –0.7 ± 4.6 for patients with mild AD. The mean changes in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores after 1 year were 4.3 ± 7.2 for all patients in the study (n=30) and 1.4 ± 6.1 in the subgroup of patients with mild AD (n=18) (13-16). At 20 months the scores were 7.2 ± 1.2 for all patients (n=24) and 2.6 ± 1.9 for the mild AD subgroup (n=13) (15, 17). The mean changes in the Clinical Dementia Rating-sum of the boxes score (CDR-SB) after 1 year were 1.9 ± 2.8 overall and 2.2 ± 3.0 for patients with mild AD. The best response was seen in patients with mild AD given the dose of 150 mg, showing minimal changes in all scores (16). At 3 years, tramiprosate was reported to continue to have a beneficial effect on cognitive performance measures, and 4 of 9 patients with mild AD had shown no change from baseline (15, 17).

Neurochem is currently conducting an 18-month randomized, double-blind, placebo-controlled, parallel phase III clinical trial of tramiprosate in patients with mild to moderate AD in the U.S. and Canada. The trial is scheduled to be completed by January 2007 and includes an open-label extension phase (18, 19). A second 18-month phase III clinical trial of tramiprosate is being conducted in Europe. The trial was initiated in September 2005 and is expected to enroll 930 patients with mild to moderate AD. Enrollment is expected to be completed in the fall of 2006 (20).

A phase II study of tramiprosate (Cerebril™) in patients with lobar hemorrhage related to CAA demonstrated that the drug was safe at all doses tested (100,

200 and 300 mg once daily for 12 weeks) and well tolerated up to 200 mg/day. Adverse effects were as described for tramiprosate in AD patients, with 5 of 20 patients withdrawing from the study due to adverse effects (9, 21, 22).

Source

Neurochem, Inc. (CA).

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