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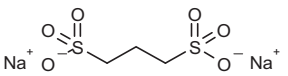
Eprodisate Sodium

Antiamyloidogenic Agent
Glycosaminoglycan Mimetic

Prop INNM; USAN

1,3-PDS
NC-503
Fibrillex™

1,3-Propanedisulfonate



$C_3H_6Na_2O_6S_2$
Mol wt: 248.1877

CAS: 036589-58-9

CAS: 021668-77-9 (as free acid)

EN: 296046

Abstract

Eprodisate sodium is a glycosaminoglycan (GAG) mimetic being developed for the treatment of amyloid A (AA) amyloidosis, a rare complication of chronic inflammatory disorders. In AA amyloidosis, GAG polymers interact with serum AA protein to cause structural rearrangement and deposition of the protein as insoluble plaques in visceral organs, blood vessels and skin, resulting in progressive organ failure and death. Eprodisate binds to the GAG binding site on serum AA to prevent its interaction with GAG and arrest amyloidosis. In a single phase II/III clinical trial, eprodisate delayed the onset of renal failure in AA amyloidosis patients with renal involvement.

Synthesis

Eprodisate sodium can be obtained by Strecker reaction of 1,3-dibromopropane (I) with sodium sulfite in hot aqueous solution. The inorganic salts (bromide, sulfite) present in the reaction mixture are removed by successive treatments with lead or barium salts, followed by silver oxide (1-3). In an improved procedure that does not generate inorganic byproducts, the title disulfonate is prepared by ring opening of 1,3-propanesultone (II) with sodium sulfite (4). Eprodisate sodium can also be obtained by the addition of sulfite to sodium allylsulfonate (III). Reaction of (III) with sodium bisulfite in the presence of a catalytic amount of ammonium peroxodisulfate affords trisodium 1,3-disulfonato-2-sulfinatopropane (IV) at lower reaction pH values, whereas at pH 5, a mixture of (IV) and eprodisate sodium is obtained. Similarly, addition of sodium bisulfite to (III) in the presence of one equivalent of sodium peroxodisulfate gives trisodium 1,2,3-propanetrisulfonate (V) at lower pH values, whereas at pH values > 7, the target 1,3-propanedisulfonate is selectively obtained (5). Scheme 1.

Background

Amyloid A (AA) amyloidosis is characterized by the deposition of insoluble misfolded serum AA protein as extracellular plaques in organs such as the spleen, kidneys (the two primary sites of deposition), heart, blood vessel walls, skin and intestine, among others. The disease is progressive and, although a rare condition, it is serious and usually fatal if left untreated (6, 7).

Serum AA is an acute-phase reactant produced by the liver in response to inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α. Under normal circumstances, infection or injury induces serum AA levels to rise from a baseline of 1-5 μg/ml to 1 mg/ml or higher during the inflammatory stages of a wound/infection response, which return to baseline within a week of the inflammatory stimulus. However, in chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and familial Mediterranean fever, or in chronic infections such as tuberculosis, serum AA levels remain high. For unknown reasons, up to 10% of patients with chronically elevated serum AA develop AA amyloidosis. Under disease conditions, the glycosaminoglycan (GAG) heparan sulfate induces partial denaturation of globular serum AA, which then refolds in a more stable form with an increased β-sheet content, and the refolded AA peptides cross-polymerize and stack together as insoluble fibrils. The disease progresses when the rate of fibril deposition exceeds that of removal (7, 8).

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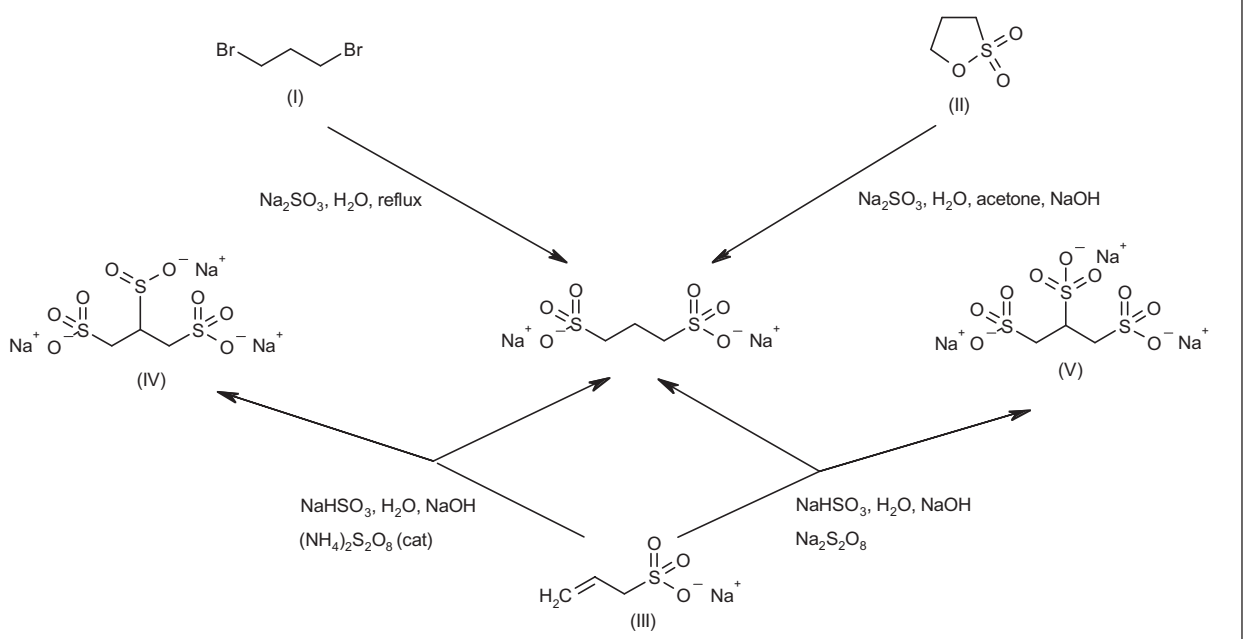
Scheme 1: Synthesis of Eprodisate Sodium



Currently, there is no FDA-approved therapy for AA amyloidosis, and management is focused on treating the underlying inflammation, and organ transplantation where necessary. However, progression of renal disease (the most frequent cause of death in AA amyloidosis patients, especially in those with a late diagnosis) remains a serious problem. Eprodisate sodium (1,3-propanedisulfonate, NC-503, Fibrillex™) has been shown to prevent heparan sulfate-mediated serum AA misfolding and aggregation *in vitro*, and significantly reduced AA plaque deposition in a mouse model of AA amyloidosis. The drug is currently being reviewed by the FDA for the treatment of AA amyloidosis with a renal component (7, 9).

Clinical Studies

In a 2-year multicenter, double-blind, parallel-design phase II/III clinical trial (FAST: Fibrillex AA amyloidosiS Trial) (10-15), 183 patients with AA amyloidosis and renal involvement were randomized to either eprodisate or placebo for 24 months. The primary outcome was a composite measurement of renal function and death. Cox proportional hazards regression analysis of the intent-to-treat population showed that patients in the eprodisate treatment group had a 42% reduction in the risk of worsening of renal function or death compared to placebo. Eprodisate reduced the rate of decline in mean creatinine clearance rate from –15.6 ml/min/1.73 m^2/year on placebo to –10.9 ml/min/1.73 m^2/year, and it delayed the mean time to a 50% reduction in creatinine clearance and progression to dialysis by 4.4 months (p = 0.029) and 5.3 months (p = 0.18), respectively. The Cochran-Mantel-Haenszel row mean scores test (which compares the number of events at the end of the study in the treatment and control groups) showed that 13.4% fewer patients on eprodisate had disease worsening than patients in the control group. Eprodisate was well tolerated, and the incidence and severity of adverse events were comparable to placebo.

In a substudy of the above clinical trial, fat aspirates were collected at baseline and AA protein levels were quantified by Congo red staining (n=156). This method showed 92% sensitivity and may be an easier and safer method than conventional renal biopsy for the diagnosis of AA amyloidosis (15).

In December 2004, 80% of patients entered an open-label extension of the above study, which is ongoing. At the end of 1 year, those who had been on active treatment for 3 years had a 41% reduced risk of renal decline or mortality compared to those who had been on placebo for 2 years and were then switched to eprodisate for 1 year (p = 0.011). This indicates an advantage to early treatment of AA amyloidosis, although those on placebo for 2 years and then switched to eprodisate for 1 year also demonstrated improvement (14).

An NDA for eprodisate was filed with the FDA in April 2006 and granted priority review, with a decision expected in August 2006 (14).

Sources

Neurochem, Inc. (CA); licensed for distribution in most countries to Centocor, Inc. (a subsidiary of Johnson & Johnson; US).

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