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CCC: 0377-8282/98

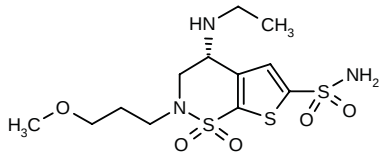
Brinzolamide

Prop INN; USAN

Antiglaucoma
Carbonic Anhydrase Inhibitor

Azopt®
AL-4862

4(*R*)-(Ethylamino)-2-(3-methoxypropyl)-3,4-dihydro-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide



$C_{12}H_{21}N_3O_5S_3$ Mol wt: 383.50

CAS: 138890-62-7

EN: 256930

Synthesis

Brinzolamide has been obtained by two different ways:

1) The reaction of 3-(2,5,5-trimethyl-1,3-dioxan-2-yl)thiophene (I) with butyl lithium, SO_2 and hydroxylamine-*O*-sulfonic acid in hexane/THF gives the corresponding sulfonamide (II), which is hydrolyzed with HCl yielding 3-acetylthiophene-2-sulfonamide (III). The cyclization of (III) with pyridinium bromide perbromide (IV) and $NaBH_4$ affords 4-hydroxy-3,4-dihydro-2*H*-thieno-[3,2-*e*][1,2]thiazine 1,1-dioxide (V), which is treated with 1,3-dibromopropane (VI) and NaH in DMF giving the corresponding 3-bromopropyl derivative (VII). The protection of the hydroxy group of (VII) with ethyl vinyl ether (VIII) in *p*-toluenesulfonic acid yields the ethoxyethyl ether (IX), which by reaction with sodium methoxide in refluxing methanol affords the 3-methoxypropyl derivative (X). The sulfonation of (X) with butyl lithium, SO_2 and hydroxylamine-*O*-sulfonic acid in hexane/THF gives the sulfonamide (XI), which is oxidized with CrO_3/H_2SO_4 to yield 2-(3-methoxypropyl)-4-oxo-3,4-dihydro-2*H*-thieno[3,2-*e*]-[1,2]thiazine-6-sulfonamide 1,1-dioxide (XII). The stereocontrolled reduction of (XII) with (+)-β-chlorodiisopinocamphenylborane [(+)-CDPB] in THF affords the 4(*S*)-hydroxy derivative (XIII), which is finally treated first with *p*-toluenesulfonyl chloride/triethylamine and then with ethylamine in THF (1, 2). Scheme 1.

2) The reaction of 3-acetyl-2,5-dichlorothiophene (XIV) with benzyl chloride and thiourea in ethanol/water gives 3-acetyl-2-(benzylsulfanyl)-5-chlorothiophene (XV), which is treated with Cl_2 gas in ethyl acetate yielding the expected sulfenyl chloride (XVI). The oxidation of (XVI) with H_2O_2/sodium tungstate and treatment with ammonia affords 3-acetyl-5-chlorothiophene-2-sulfonamide (XVII), which is brominated with pyridinium bromide perbromide (IV) giving the corresponding bromoacetyl derivative (XVIII). The reductive cyclization of (XVIII) with (+)-CDPB in THF affords the bicyclic 4(*S*)-hydroxy derivative (XIX), which is condensed with 3-methoxypropyl bromide (XX) by means of K_2CO_3 in DMSO giving 6-chloro-4(*S*)-hydroxy-2-(3-methoxypropyl)-3,4-dihydro-2*H*-thieno-[3,2-*e*][1,2]thiazine (XXI). The sulfonation of (XXI) with BuLi, SO_2 and hydroxylamine-*O*-sulfonic acid as before yields the sulfonamide (XIII), already obtained, which is finally treated with trimethyl ortoacetate and ethylamine in refluxing acetonitrile (3). Scheme 2.

Description

M.p. 125-7 °C, $[\alpha]_D^{312.6}$ –26.1° (c 1, citric acid buffer pH 3); hydrochloride salt, m.p. 175-7 °C, $[\alpha]_D$ +10.35° (c 1, H_2O).

Introduction

Glaucoma, the leading cause of irreversible blindness in the Western world, is characterized by a progressive damage of the optic nerve fiber associated with a loss of the visual field and/or abnormally high intraocular pressure (IOP). All forms of glaucoma result from interference with aqueous outflow. Primary open-angle (chronic simple) glaucoma is the most prevalent form. Compounds used to treat chronic glaucoma include β-blockers, cholinergic agonists and anticholinesterase miotics, epinephrine and its analogs, carbonic anhydrase inhibitors and α-adrenoreceptor agonists. IOP can presumably be reduced either transiently with osmotic agents, by increasing the outflow of aqueous humor with miotic agents and epinephrine, or by decreasing aqueous

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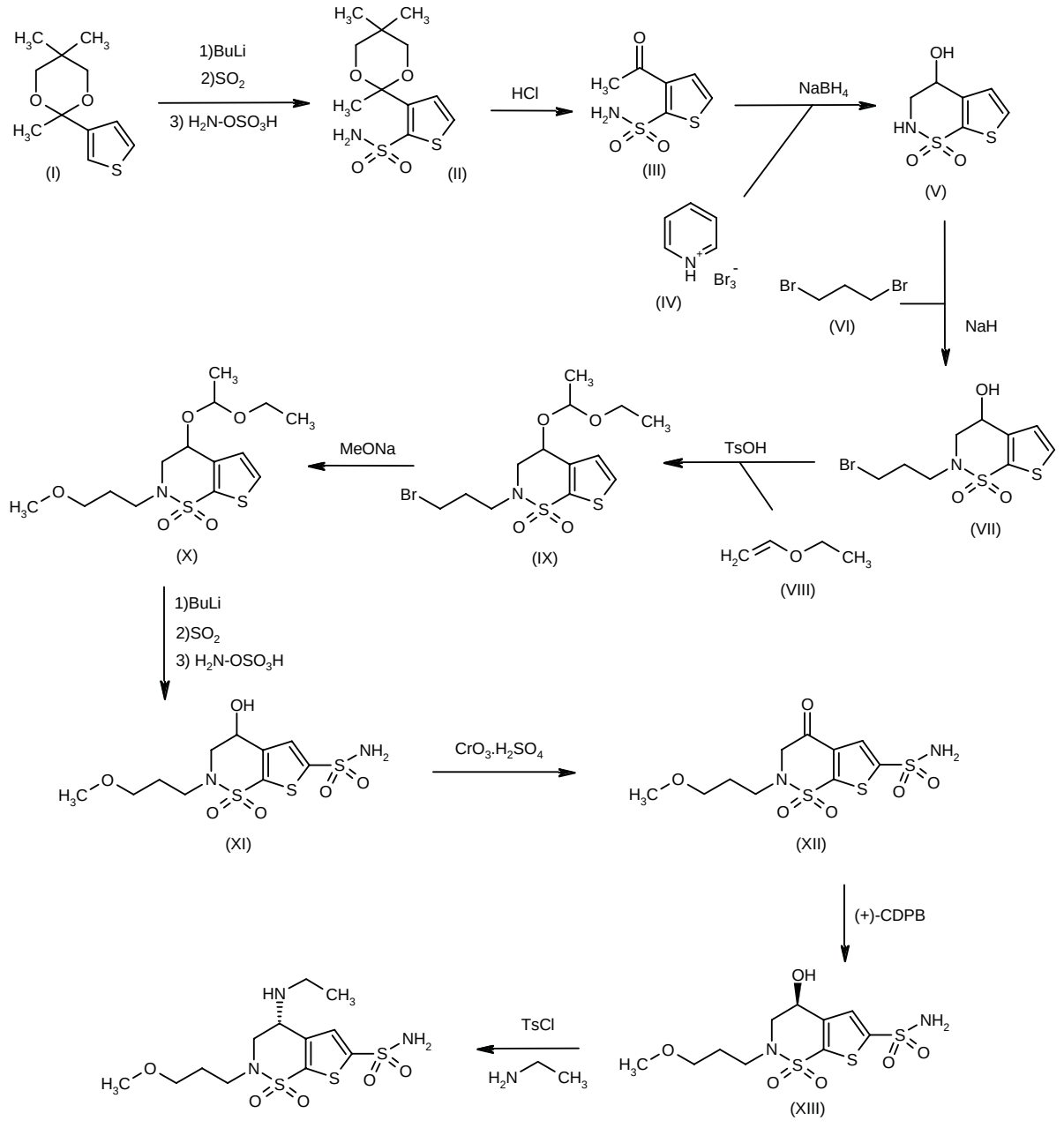
Scheme 1: Synthesis of Brinzolamide

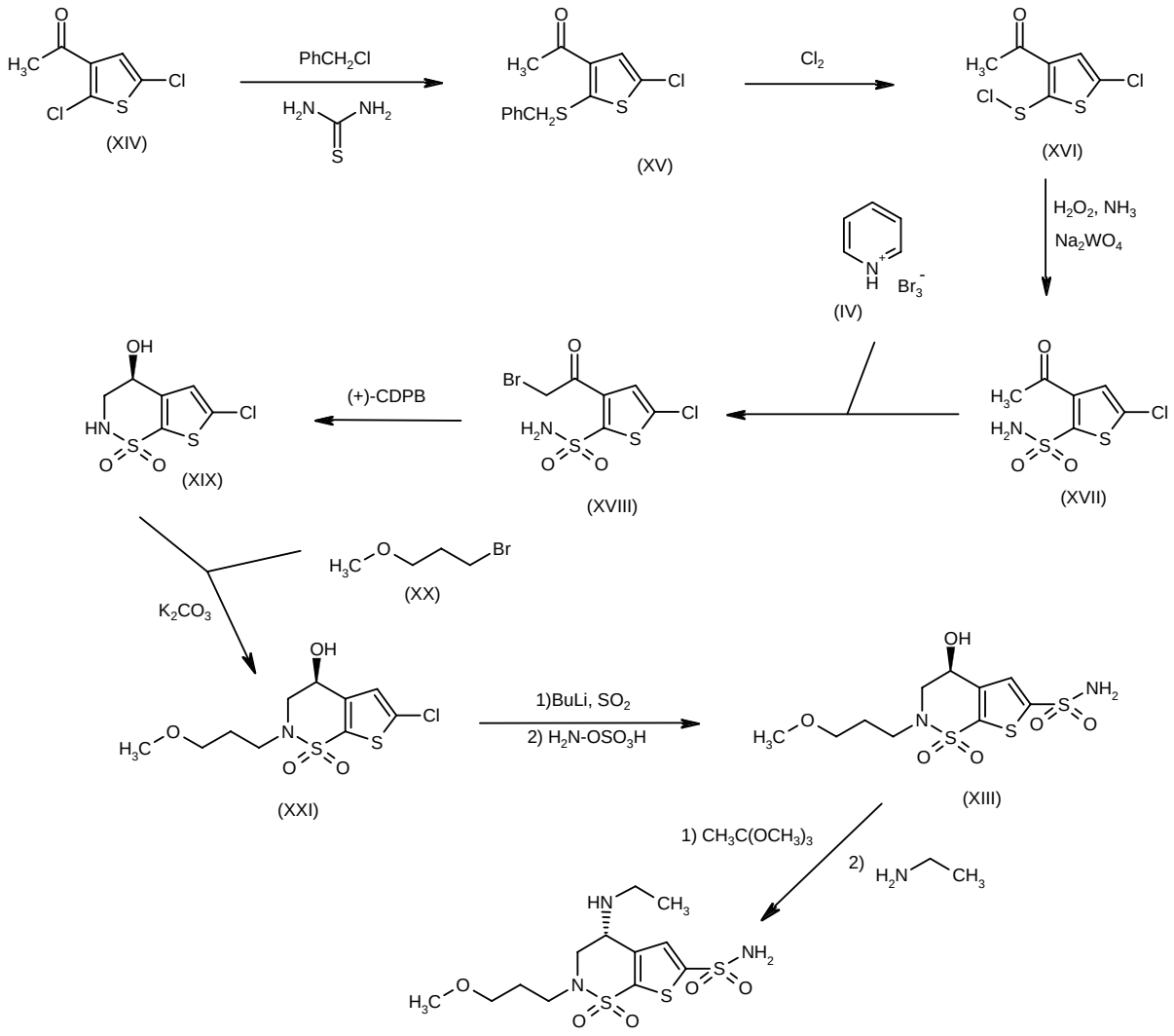


production with β-blockers, α-adrenergic agonists and carbonic anhydrase inhibitors. Drugs used for the treatment of glaucoma are listed in Table I.

Pharmacological Actions

Brinzolamide is a potent inhibitor of human carbonic anhydrase II (K_i = 0.13 ± 0.03 nM in a dansylamide assay, IC_{50} = 2.6 nM in a CO_2 hydration assay) with low aqueous solubility at pH 7.4 (0.038%). Topical administration of 600 µg (2%, 1 x 30 µl) and 1 mg (2%, 2 x 25 µl) brinzolamide in Dutch-belted rabbits reduced IOP by 18 and 22%, respectively, for at least 5 h postadministration. In the lasered monkey model, the compound at twice-daily doses of 300 and 600 µg lowered IOP by 27-30% within 3 h after the morning dose, while the effect on trough concentrations (8 a.m., 12 h after the evening dose) ranged from 15 to 22% (4).

Scheme 2: Synthesis of Brinzolamide



Clinical Studies

The safety and efficacy of brinzolamide were evaluated in a randomized, placebo-controlled trial in 108 patients with primary open-angle glaucoma or ocular hypertension. Study subjects were on a stable dosing regimen of timolol (0.5% b.i.d.) for at least 3 weeks and were randomized in a triple-masked manner to receive either brinzolamide (1.0% t.i.d.) and timolol (0.5% b.i.d.) or placebo and timolol for 3 months. Brinzolamide produced clinically and statistically significant reductions in IOP (13.2-16.6%) as compared to baseline values following monotherapy with timolol. The reductions induced with brinzolamide treatment were superior to those observed with placebo treatment. Brinzolamide was safe and well tolerated when administered together with timolol in this study group, and adverse effects were usually mild and resolved normally without treatment (5).

In a 1-week trial in 198 patients with primary open-angle glaucoma or ocular hypertension, brinzolamide 1% t.i.d. produced statistically less ocular discomfort than dorzolamide 2% t.i.d. and a greater percentage of patients reported no ocular discomfort. Frequency distribution of ocular discomfort revealed that a greater percentage of patients in the dorzolamide-treated group reported mild, moderate, severe and very severe discomfort as compared to the brinzolamide-treated group. Thus, the greater ocular comfort experienced in patients treated with brinzolamide may result in better dosing compliance as compared to patients treated with dorzolamide (6).

Table I: Recent and future therapeutic options for glaucoma.

Cholinergic agonists		
Pilocarpine (PilaSite)[1]	InSite Vision	Phase III
Pilocarpine[2]	LTS Lohmann	Clinical
Carbonic anhydrase inhibitors		
Dorzolamide HCl (Trusopt®)	Merck & Co.	Launched 1995
Brinzolamide (AL-4862)	Alcon	Launched 1998
Dorzolamide/Timolol (Cosopt®)	Merck & Co.	Registered 1998
AL-4623A	Alcon	Preclinical
Prostaglandins		
Latanoprost (Xalatan®)	Pharmacia & Upjohn	Launched 1996
Unoprostone isopropyl ester (Rescula®)	Ueno Fine Chemicals	Launched 1994
AGN-191151	Allergan	Preclinical
AGN-192024	Allergan	Preclinical
α_2-Adrenoceptor agonists		
Brimonidine tartrate (Alphagan®)	Pfizer; Allergan	Launched 1996
AGN-192836	Allergan	Preclinical
AGN-193080	Allergan	Preclinical
β-Adrenoceptor antagonists		
Levobunolol HCl (BetaSite)[3]	InSite Vision	Phase III
AM-140[4]	Amrad	Phase II
ISV-208	InSite Vision; Bausch & Lomb	Phase II
TIGR protein formation blocker		
ISV-205[5]	InSite Vision	Phase I
Cannabinoid CB2 receptor agonists		
US 5532237[6]	Merck Frosst	Biological testing
US 5605906[6]	Merck Frosst	Biological testing
Miscellaneous		
Collagenase	BioSpecifics Technologies; Bausch & Lomb	Preclinical

[1]Sustained-release eyedrop formulation. [2]Transdermal delivery system. [3]Sustained-release eyedrop formulation. [4]Discontinued 1996. [5]Formulation of diclofenac using DuraSite® drug delivery system. This new antiinflammatory agent blocks the formation of the TIGR protein encoded by the TIGR gene, which has been linked to a significant number of cases of glaucoma. [6]Recently described in patent literature. Source: Prous Science Ensemble database.

The safety and efficacy of brinzolamide (1% t.i.d. and b.i.d.) were compared to dorzolamide (2% t.i.d.) and timolol (0.5% b.i.d.) in 512 patients with primary open-angle glaucoma or ocular hypertension. Both dosing regimens of brinzolamide were clinically and statistically equivalent to dorzolamide t.i.d. at all measurements of IOP, and the reductions in IOP produced with brinzolamide treatment (15.4-21.4%) were considered to be clinically and statistically significant. However, the reductions in IOP after treatment with brinzolamide and dorzolamide were somewhat less than those observed with timolol treatment. Again, brinzolamide was shown to be safe and produced less ocular discomfort than dorzolamide (7).

Alcon recently launched the topical carbonic anhydrase inhibitor brinzolamide (Azopt™) in the U.S., its first market, for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It is supplied as an ophthalmic suspension, 1% (10 mg/ml) in DROP-TAINERS® dispensers containing 2.5, 5, 10 and 15 ml (8).

Manufacturer

Alcon Laboratories, Inc. (US).

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