CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-816

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA # 20-816 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-550 Trade (generic) name/dosage form: Azopt (brinzolamide ophthalmic suspension), 1.0% Action: (AP) AE NA

Applicant Alcon Laboratories Therapeutic Class 1S

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Reduction of IOP

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

PM — 2/5/98

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig (NDA)/PLA # 20-816
HFD-550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

ITEM 15. DEBARMENT STATEMENT

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Alcon Laboratories, Inc. certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity in connection with this application the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

EXCLUSIVITY SUMMARY for NDA # 20-816 **SUPPL #** _____

Trade Name Azopt **Generic Name** brinzolamide ophthalmic Susp. 1.0%

Applicant Name Alcon Laboratories, Inc. **HFD-** 550

Approval Date, if known _____

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5yrs

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 2/5/98

Signature Date

Title: Regulatory Health Project Manager

/S/ 4/1/98

Signature of Division Director Date

Death

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PART 13 PATENT AND EXCLUSIVITY INFORMATION

A. Patent Information

Below are listed all patents known to the applicant that claim the drug or a method of using the drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, sale, or use of the drug.

1.	U.S. Patent No.:	5,240,923
	Issue Date:	August 31, 1993
	Expiration Date:	August 31, 2010
	Patent Owner:	Alcon Laboratories, Inc.
	Claims For:	Compound, Formulations and Methods of Use - Controlling Intraocular Pressure
2.	U.S. Patent No.:	5,378,703
	Issue Date:	January 3, 1995
	Expiration Date:	August 31, 2010
	Patent Owner:	Alcon Laboratories, Inc.
	Claims For:	Compound, Formulation and Methods for Use - Controlling Intraocular Pressure
3.	U.S. Patent No.:	5,461,081
	Issue Date:	October 24, 1995
	Expiration Date:	October 24, 2012
	Patent Owner:	Alcon Laboratories, Inc.
	Claims For:	Formulation and Method for Delivery

US005240923A

United States Patent [19]

Dean et al.

[11] Patent Number: 5,240,923

[45] Date of Patent: Aug. 31, 1993

[54] SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS

[75] Inventors: Thomas R. Dean, Weatherford; Hwang-Hsing Chen; Jesse A. May, both of Fort Worth, all of Tex.

[73] Assignee: Alcon Laboratories, Inc., Fort Worth, Tex.

[21] Appl. No.: 775,313

[22] Filed: Oct. 9, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 618,765, Nov. 27, 1990, Pat. No. 5,153,192, which is a continuation-in-part of Ser. No. 506,780, Apr. 9, 1990, abandoned.

[51] Int. Cl.[5] C07D 513/04; A61K 31/54

[52] U.S. Cl. 514/226.5; 544/48; 540/552; 548/207; 548/209; 548/212; 514/373; 514/211

[58] Field of Search 544/48; 548/207, 209, 548/212; 540/552; 514/226.5, 373, 211

[56] References Cited

U.S. PATENT DOCUMENTS

4,731,368	3/1988	Hoffman, Jr. et al.	514/301
4,746,745	5/1988	Maren	548/139
4,797,413	1/1989	Baldwin et al	514/432
4,847,289	7/1989	Baldwin et al	514/445

FOREIGN PATENT DOCUMENTS

1096916 1/1961 Fed. Rep. of Germany .
1516024 6/1978 United Kingdom .

OTHER PUBLICATIONS

"The Reactions of Some Thiophene Sulfonyl Derivatives," Cremyln et al., *Phosphorus and Sulfur*, vol. 10, pp. 111-119, 1981.

"Studien in der Thiophenreihe. XXIV.[2] Uber Nitrothiophene and Thiophensulfochloride," Steinkopf et al., *Justus Liebigs Analen Der Chemie*, vol. 501, pp. 174-186, 1933.

"Heterocyclic Disulphonamides and Their Diuretic Properties," deStevens et al., *Journal of Medicinal and Pharmaceutical Chemistry*, vol. 1(6), pp. 565-576, 1959.

Primary Examiner—John M. Ford
Attorney, Agent, or Firm—James A. Arno; Sally S. Yeager

[57] ABSTRACT

Sulfonamides and pharmaceutical compositions containing the compounds useful in controlling intraocular pressure are disclosed. Methods for controlling intraocular pressure through administration of the compositions are also disclosed.

14 Claims, No Drawings

13-0002

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated, is substituted optionally with H or C_{1-6} alkyl or in which said carbon is substituted optionally with C_{1-6} alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl, Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkyl C_{3-5}-cycloalkyl; $C(=O)R_7$ or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, thiazolidine 1,1-dioxide, or tetrahydrooxazine, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ oron nitrogen with C_{1-4} alkoxy, $C(=O)R_7$, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on sulfur by $(=O)_m$, wherein m is 0-2.

R_7 is C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_9$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or a heteroaromatic group either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)n$ NR_5R_6, $S(=O)mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0-2.

R_8 is C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$.

R_9 C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino and

G is C(=O) or SO_2.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where i and j are numbers from 1 to 8 for example. This C_{i-j} definition includes both the straight and branched chain isomers. For example, C_{1-4} alkyl would designate methyl through the butyl isomers; and C_{1-4} alkoxy would designate methoxy through the butoxy isomers.

The term "halogen," either alone or in compound words such as "haloalkyl," means fluorine, chlorine, bromine or iodine. Further, when used in compound words such as "haloalkyl," said alkyl may be partially or fully substituted with halogen atoms, which may be the same or different.

The term heteroaromatic means a monocyclic ring system of 5 or 6 atoms comprised of C, N, O and or S such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine.

Structure [I] includes isomers, wherein R_3 and GNR_1R_2 are attached to the 4 and 5 position respectively or R_3 is attached to the 5 position and GNR_1R_2 is attached to the 4 position. Many of the novel compounds of Structure [I] possess one or more chiral centers and this invention includes all enantiomers, diastereomers and mixtures thereof.

SYNTHESIS

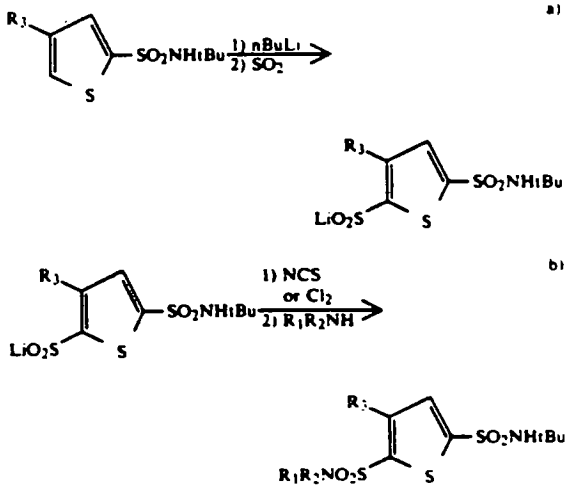
Compounds of the present invention can be prepared using a variety of procedures, a number of which are described below in equations 1 through 7.

Many of the novel compounds of Structure [I] can be prepared from N-t-Bu thiophene-2-sulfonamides with R_3 substituents according to the scheme shown in equation 1.

In general, N-t-Bu thiophene-2-sulfonamides can be metallated in the 5-position at low temperatures using a strong organometallic base such as n-butyllithium and condensed with sulfur dioxide gas to produce intermediate sulfinate salts (equation 1a). These intermediates can be readily oxidized to the corresponding sulfonyl chloride which in turn can be aminated with primary or secondary amines, bearing the requisite R_1 and R_2 substituents, to furnish the novel compounds of Structure [I] (equation 1b).

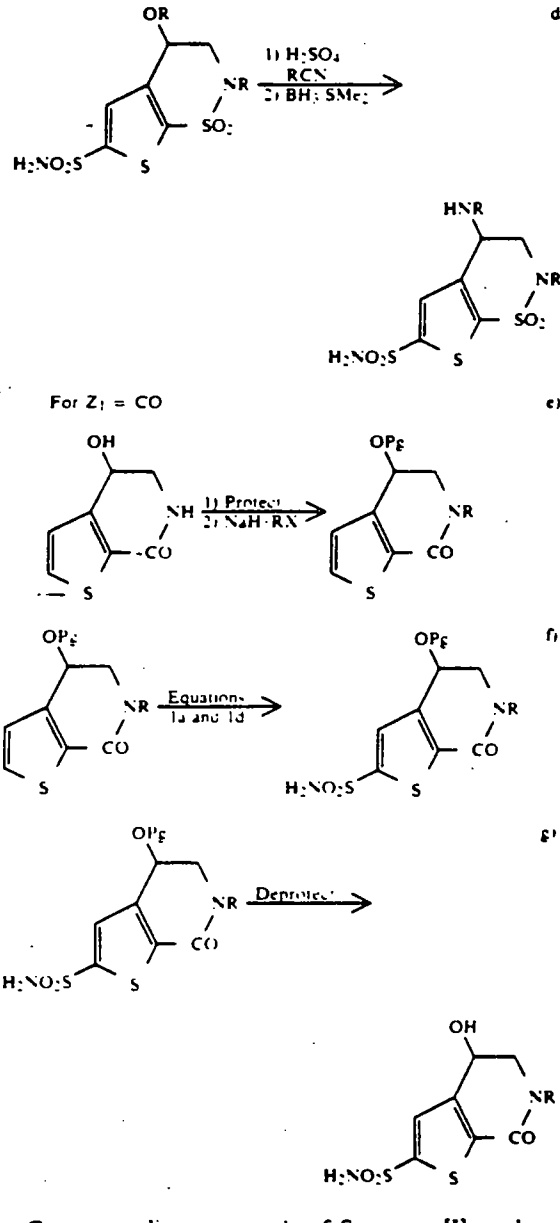
In many cases it is more advantageous to prepare initially simplified primary or secondary sulfonamides via the above sequence and then append the more complex R_1 and/or R_2 substituents using standard alkylation reactions (equation 1c). This sequence can furnish directly the novel compounds of Structure [1] or the R_1, R_2 and R_3 substituents can be modified to furnish the cyclic and/or acyclic novel compounds of Structure [1] using methods known to one skilled in the art. Primary sulfonamides can be prepared from the corresponding sulfonyl chloride by amination with ammonia or directly from sulfinate salts using hydroxylamine-O-sulfonic acid (equation 1d).

Equation 1

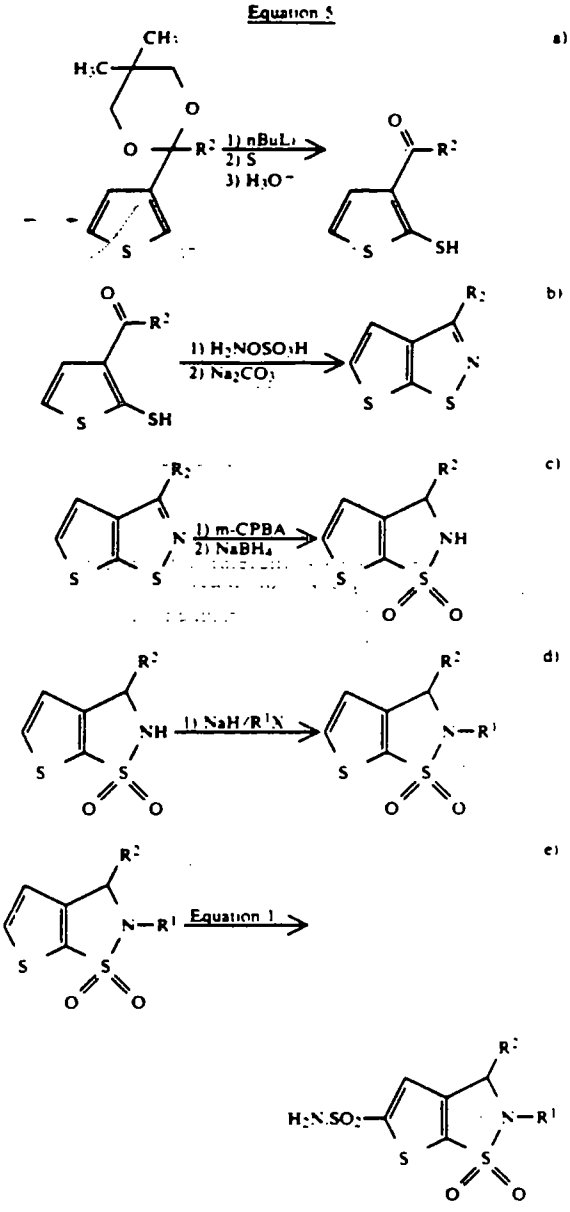


-continued

Equation 4



Equation 5



Certain cyclic compounds of Structure [I], such as the 2,3-dihydrothienoisothiazoles, can be obtained through the modification of an existing cyclic compound (equation 5). The metallated ketals of equation 3 can be readily converted to the desired intermediate mercaptoketones as shown in equation 5a, and the oxime O-esters of such compounds can be cyclized according to equation 5b. Oxidation and subsequent reduction of the thienoisothiazole by procedures well known in the art provides the intermediate cyclic sulfonamides shown in equation 5c. These cyclic sulfonamides can be substituted on nitrogen utilizing standard alkylation conditions such as demonstrated by equation 5d. Incorporation of the primary sulfonamide into position five of these examples of Structure [I] can be accomplished under the basic conditions demonstrated by equations 1a-d.

Yet other cyclic compounds of Structure [I], such as tetrahydrothienothiazepines, can be prepared from substituted thiophenesulfonamides according to equation 6. Thiophene acetals can be metallated in the two position with strong metallic bases in a manner similar to that described in equation 3a for thiophene ketals. These intermediates can be further converted to the thiophene-2-sulfonamides desired for equation 6a in a manner similar to that described for thiophene ketals by equations 3a and 1d. Thiophene acetals can be readily converted to the corresponding aldehydes by acid hydrolysis, and reaction of these aldehydes with an olefinic Grignard reagent can provide the olefin intermediates of equation 6a. The allylic alcohols from equation 6a can be oxidized to intermediate ketones by a variety of procedures well known to the art, and these ketones can be cyclized upon treatment under basic conditions, such as sodium carbonate, to the cyclic sulfonamides

N-[2-(4-morpholinyl)ethyl]-2,5-thiophenedisulfonamide hydrochloride

Step A: N-(1,1-Dimethylethyl)-2-thiophenesulfonamide

To a solution of t-butylamine (8.35 g, 0.114 mol) in dry tetrahydrofuran (THF) (20 mL) cooled to 0° C. was added dropwise 2-thiophenesulfonyl chloride (5.0 g, 27.4 mmol). After the addition was completed, the reaction mixture was warmed to ambient temperature and stirred overnight. The mixture was extracted with ethyl acetate (3×80 mL) and the combined extracts were washed with water, dried over molecular sieves and concentrated. The residue was chromatographed on (silica, eluting with 25% ethyl acetate-hexane) to yield 5.62 g (94%) of solid: mp 80°-82° C.

Step B:
N-(1,1-Dimethylethyl)-2,5-thiophenedisulfonamide

To a solution of the product from Step A (1.5 g, 6.85 mmol) in THF (10 mL) cooled to −60° C. was added n-butyllithiumin hexane (2.5 M, 6.0 mL, 15.1 mmol). The mixture was stirred for 15 min at −60° C. and for 30 min at −10° C. Sulfur dioxide gas was passed through the surface of the mixture for 10 min. The cooling bath was removed and the mixture was stirred for an additional 1 h.

The volatiles were evaporated and the residue was dissolved in water (30 mL) and sodium acetate trihydrate (5.59 g, 41.1 mmol) was added. The mixture was cooled in an ice-water bath and hydroxylamine-O-sulfonic acid (2.71 g, 23.9 mmol) was added. The cooling bath was removed and the mixture was stirred for 2 h. The suspension was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were washed with 5% sodium bicarbonate solution, brine and dried over molecular sieves. The solvent was evaporated and the residue was chromatographed on (silica, eluting with 40% ethyl acetate-hexane) to yield 1.25 g (61%) of a liquid which solidified on standing: mp 116°-120° C.

Step C:
N-(1,1-Dimethylethyl)-N'-[2-(4-morpholinyl)ethyl]-2,5-thiophenedisulfonamide

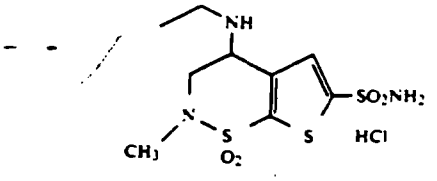
A solution of the product from Step B (1.05 g, 3.52 mmol), sodium hydride (60% dispersion in mineral oil, 310 mg, 7.75 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (0.721 g, 3.88 mmol) in anhydrous dimethylformamide (DMF) (20 mL) was heated at 110° C. for 2.5 h and then stirred at ambient temperature overnight. The reaction mixture was extracted with ethyl acetate (3×100 mL), washed with brine, dried over molecular sieves and concentrated. The residue was chromatographed (silica, elution with 50% ethyl acetate-hexane) to yield 0.32 g (22%) of the desired product:

Step D:
N-[2-(4-Morpholinyl)ethyl]-2,5-thiophenedisulfonamide hydrochloride

A solution of the product from Step C (0.31 g, 0.75 mmol) in trifluoroacetic acid (7 mL) was stirred at ambient temperature for 4 h. The trifluoroacetic acid was evaporated and the residue was chromatographed (silica, eluting with methylene chloride-methanol-ammonium hydroxide (10/1/0.1)) to give 230 mg (86%) of a viscous liquid. The liquid was dissolved in ethanol and treated with ethanolic HCl. Evaporation gave a white solid which was recrystallized from ethanol-water to afford colorless crystals (145 mg): mp 219°-220° C.

Analysis calculated for $C_{10}H_{18}ClN_3O_5S_3$: C, 30.65; H, 4.63; N, 10.72 Found: C, 30.54; H, 4.67; N, 10.64.

Example 2



4-Ethylamino-3,4-Dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:
3-(2,5,5-Trimethyl-1,3-dioxane-2-yl)-2-thiophenesulfonamide

To a solution of 3-(2,5,5-Trimethyl-1,3-dioxane-2-yl)thiophene (2.5 g, 11.7 mmol) in hexane (30 mL) cooled to 0° C. was added via syringe n-butyllithium in hexane (2.5 M, 10.3 mL, 25.7 mmol) over 5 min. The mixture was stirred at 0° C. for 20 min, the ice bath was removed and the stirring was continued for 30 min. At this time a white precipitate formed. The mixture was cooled to −60° C. and THF (20 mL) was added. Sulfur dioxide was then passed through the surface of the mixture for 30 min. The mixture was warmed to ambient temperature and stirred for an additional 15 min. The volatiles were evaporated and to the residue was added water (50 mL) and sodium acetate trihydrate (9.55 g, 70.2 mmol). The solution was cooled on an ice bath and hydroxylamine-O-sulfonic acid (4.62 g, 40.9 mmol) was added. The mixture was stirred at ambient temperature for 1 h, extracted with ethyl acetate (3×100 mL) and the combined extracts were washed with a sodium bicarbonate solution, brine and dried over molecular sieves. Evaporation to dryness gave a viscous liquid (4.93 g), which was chromatographed (silica, eluting with 33% ethyl acetate-hexane) to give a solid (2.47 g, 72%): mp 200°-202° C.

Step B: 3-Acetyl-2-thiophenesulfonamide

A mixture of the compound from Step A (9.45 g, 32.5 mmol) and 1N HCl (100 mL) in THF (100 mL) was heated at reflux for 1 h. The THF was evaporated and the aqueous solution was made basic by the addition of sodium bicarbonate. The mixture was cooled using an ice bath and the precipatiate was filtered, washed with cold water and dried in vacuo to give 5.83 g (88%) of a solid: mp 193°-196° C.

Step C:
3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

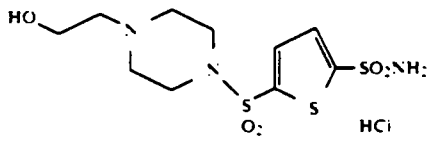
The product from Step B (5.73 g, 28.0 mmol) was dissolved in hot THF (200 mL). The solution was cooled to 10.C. and pyridinium bromide perbromide (10.73 g, 33.5 mmol) was added. The mixture was allowed to stir at ambient temperature for 1 h. The volatiles were evaporated and the residue was mixed with water. The precipitate was filtered, washed with cold water and dried in vacuo overnight to give 7.77 g of a solid. A portion of this solid (3.49 g, 12.3 mmol) was

trihydrate (3.03 g, 22.2 mmol) was added. The mixture was cooled to 0° C. and hydroxylamine-O-sulfonic acid (1.51 g, 13.3 mmol) was added. The mixture was stirred overnight, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (3×80 mL). The combined extracts were washed, dried and evaporated in a manner analogous to Step A to furnish a viscous liquid (2.17 g). This was chromatographed (silica, methylene chloride—methanol—ethyl acetate, 20/1/10)) to give some recovered starting material (1.15 g, 53%) and the desired product (0.82 g, 30%). This product was treated with ethanolic HCl and crystallized from ethanol to furnish white crystals: mp 172°-173° C.

Analysis calculated for $C_{11}H_{20}ClN_3O_5S_3$: C, 32.55; H, 4.97; N, 10.35. Found: C, 32.67; H, 4.92; N, 10.28.

This method can be used to prepary many of the novel compounds of Structure [1] wherein the R_1 and R_2 substituents are joined to form a ring of 5 to 6 atoms. In many cases the simplified heterocyclic rings used to couple with sulfonyl chlorides, such as that in Step A or those described in equations 1 and 2, are available commercially. Other examples can be prepared using methods known to one skilled in the art. A useful series of references pertinent to this method are "Comprehensive Heterocyclic Chemistry," A. R. Katritzky et al. Volumes 2-6, and references cited therein.

EXAMPLE 4

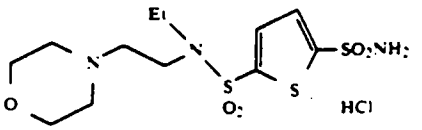


5-[[4-12-Hydroxyethyl)piperazinyl]sulfonyl]-2-thiophenesulfonamide hydrochloride

To a solution of 2-[[4-(2-hydroxyethyl)piperazinyl]-sulfonyl]thiophene (2.5 g, 9.0 g mmol) in THF (15 mL) cooled to −78° C. was added slowly over 5 min n-butyllithium (2.5M, 8.5 mL, 20.8 mmol). The mixture was allowed to stir for 40 min at −65° C. and 20 min at −40° C. when a stream of sulfur dioxide was passed through the surface for 30 min. The mixture was warmed to ambient temperature, stirred for 1.5 h then evaporated to dryness. The residue was dissolved in water (30 mL) and sodium acetate trihydrate (6.16 g, 45.3 mmol) was added. The mixture was cooled to 0° C. and hydroxylamine-O-sulfonic acid (3.59 g, 31.7 mmol) was added. The mixture was stirred overnight, neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (3×80 mL). The combined extracts were washed, dried and evaporated to furnish a viscous liquid (3.15 9). This was chromatographed (silica, methylene chloride—methanol 70/1) to give some recovered starting material (1.24 g, 50%) and the desired product as a liquid (0.8 g, 25%). The liquid was dissolved in ethanol, filtered and treated with ethanolic HCl. The mixture was filtered and the solid dried to give the desired product (0.54 g): mp 206°-207° C.

Analysis calculated for $C_{10}H_{18}ClN_3O_5S3$: C.30.65; H. 4.65; N, 10.72 Found: C.30.62; H. 4.64; N, 10.68.

EXAMPLE 5



N-Ethyl-N-[2-(4-morpholinyl)ethyl]-2,5-thiophenedisulfonamide hydrochloride

Step A:
N-Ethyl-N-[2-(4-morpholinyl)ethyl]-2-thiophenesulfonamide

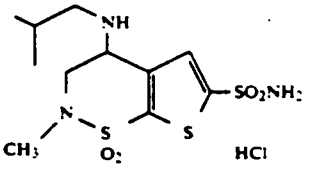
To a mixture of sodium hydride (60% dispersion in mineral oil, 0.606 g, 15.1 mmol) in N,N-dimethyl formamide (DMF) (60 mL) cooled to 0° C. was added N-[2-(4-morpholinyl)ethyl]-2-thiophenesulfonamide (3.8 g, 13.8 mmol). The mixture was stirred for 1 h and then allowed to warm to ambient temperature overnight. The mixture was poured onto water, extracted with ethyl acetate, dried and concentrated to furnish a viscous oil (3.81 g). The liquid was dissolved in ethyl acetate and washed with 1 H NaOH, brine, dried and concentrated. This liquid was chromatographed (silica, ethyl acetate) to give the desired product as a liquid (2.95 g, 70%).

Step B:
N-Ethyl-N-[2-(4-morpholinyl)ethyl]-2,5-thiophenedisulfonamide hydrochloride

The product from Step A (2.2 g, 7.24 mmol) was treated sequentially with n-butyllithium, sulfurdioxide, hydroxylamine-O-sulfonic acid and ethanolic HCl in much the same way as described in Example 4 to furnish the desired product as a hygroscopic white solid: mp 80°-85° C.

Analysis calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.32; H, 5.28; N, 10.01 Found: C, 34.06; H, 5.20; N, 9.66.

EXAMPLE 6



3,4-Dihydro-2-methyl-4-(2-methyl)propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:
3,4-Dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-4-ol-1,1-dioxide

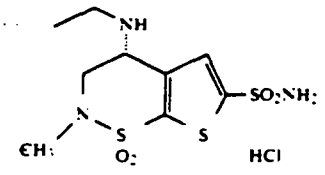
To a mixture of sodium hydride (60% dispersion in mineral oil, 1.352 g, 33.8 mmol) in DMF (60 mL) was added 2,3-dihydro-4-hydroxy-2H-thieno [2,3-e]-1,2-thiazine 1,1-dioxide (6.30 g, 30.7 mmol), prepared using the procedure described in Example 2. The mixture was cooled (dry ice-acetone bath) and methyl iodide (4.8 9, 33.8 mmol) was added over 5 min. After the addition was complete, the mixture was allowed to warm to

4-Bromo-5-[[4-(2-hydroxyethyl)-piperazinyl]sulfonyl]-2-thiophenesulfonamide hydrochloride

A sample of 4-bromo-5-chlorosulfonyl-thiophene-2-sulfonamide (5.2 g, 15.2 mmol) was treated sequentially with 1-(2-hydroxyethyl)-piperazine (4.97 g, 38.0 mmol) and ethanolic HCl in much the same way as described in Example 8, Step B, to furnish the desired hydrochloride salt. This material was recrystallized from methanol to give a white solid: mp 212° C.

Analysis calculated for $C_{10}H_{17}BrClN_3O_5S_3$—0.25 H_2O: C, 25.27; H, 3.71; N, 8.84 Found: C, 25.47; H, 3.51; N, 8.46

EXAMPLE 10

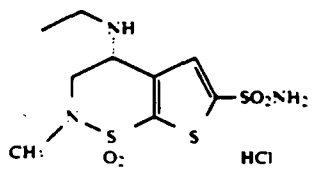


R-(+)-4-Ethylamino-3,4-dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

A hot solution (about 80° C.) of the free base corresponding to Example 2 (10.88 g, 33.5 mmol) in n-propanol (250 mL) was mixed with a hot solution of di-p-toluoyl-D-tartaric acid (3.27 g, 8.47 mmol) in n-proponol (250 mL). Activated carbon (2.0 g) was added and the mixture was kept at greater than 50° C. for 30 min and filtered through a pad of celite. The filtrate was concentrated to about 200 mL and was placed in the freezer overnight. The solid was filtered, washed with cold n-propanol and dried to give the tartrate salt (6.95 g), which was recrystallized four times from hot n-propanol (250, 200, 160 and 160 mL respectively) to afford the tartrate (4.30 g). The salt was mixed with a saturated sodium bicarbonate solution (300 mL) and the resulting suspension was allowed to stir for 1 h and was extracted with ethyl acetate (3 × 300 mL). The extracts were dried, filtered and evaporated to dryness to afford the free base (2.71 g), which was treated with 2N HCl to give 2.71 g of the salt, $[\alpha]_D$ +14.7° C. (c=0.55, H_2O); mp 261°-263° C.

Analysis calculated for $C_9H_{16}ClN_3O_4S_3$—0.5 H_2O: C, 29.87; H, 4.46; N, 11.61 Found: C, 29.85; H, 4.28; N, 11.36

EXAMPLE 11



Alternative preparation of:

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

Step A: 3-(2,5,5-Trimethyl-1,3-dioxan-2-yl)thiophene

Hydrogen chloride gas was bubbled briefly into a mixture of 3-acetylthiophene (100 g, 0.794 mol) and 2,2-dimethyl-1,3-propanediol (1.5 eq, 1.19 mol, 123 g) in toluene (650 mL) and the mixture was refluxed for 18 h with water removal using a Dean-Starck trap. Since only about half of the theoretical amount of water had been removed after this time, a few drops of concentrated sulfuric acid were added to the mixture and reflux was continued another 24 h. The mixture was allowed to cool to room temperature under a drying tube and potassium carbonate (10 g) was added followed by saturated aqueous sodium bicarbonate (300 mL) and hexane (1 L) The organic phase was separated and the aqueous was extracted with hexane (3 × 400 mL). The combined hexane extracts were washed with brine (6 × 500 mL), dried over $MgSO_4$, treated with decolorizing carbon, filtered through celite and evaporated under reduced pressure. The residue was distilled through a 12 inch Vigreux column to provide 120 g (71%) of the ketal as a colorless liquid that solidified on standing: bp 88° C./0.1 mmHg).

Step B: 3-Acetyl-N-methyl-2-thiophenesulfonamide

A solution of the compound from Step A (50.0 g, 0.236 mol) in hexane (400 mL) was cooled to −60° C. under nitrogen. n-Butyllithium (1.3 eq, 120 mL of a 2.5 M hexane solution) was added over 15 min while the temperature was maintained at −60° C. The cold bath was removed, and the reaction mixture was allowed to warm to room temperature, taking 30 min. After the mixture had stirred at room temperature for 30 min, it was again cooled to −60° C., at which point tetrahydrofuran (100 mL) was added. After the mixture had returned to −60° C., sulfur dioxide gas was bubbled into the reaction until the mixture was acidic, and the mixture was stirred overnight while warming to room temperature. N-Chlorosuccinimide (40 g, 1.3 eq) was added in one portion and stirring was continued at room temperature for 6 h. Methylamine gas was then bubbled into the mixture until the sulfonyl chloride was no longer present as indicated by TLC. (silica, 30% ethyl acetate/hexane). The reaction mixture was then concentrated on the rotary evaporator under reduced pressure, and the residue was diluted with tetrahydrofuran (400 mL) and 1 M aqueous hydrochloric acid (400 mL) and refluxed for 1 h. The mixture was then cooled, basified using solid sodium bicarbonate, and partitioned between water (1 L) and ethyl acetate (500 mL). The organic phase was separated and the aqueous layer was further extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with saturated aq. sodium bicarbonate (4 × 500 mL), dried over $MgSO_4$, treated with decolorizing carbon, filtered through celite, and so concentrated. The residual oily solid was leached with diethyl ether (500 mL) resulting in a solid that was collected by filtration, washing with ether, to provide, after air drying, 31 g (60%) of the sulfonamide: mp 101°-103° C.

over $MgSO_4$, treated with decolorizing carbon (Norite A), filtered through celite, and concentrated under reduced pressure, to provide 5.2 g (73%) of the sulfonamide.

Step G:

(−)-4-Ethylamino-3,4-dihydro-2-methyl-2H-thieno[3,-2,e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

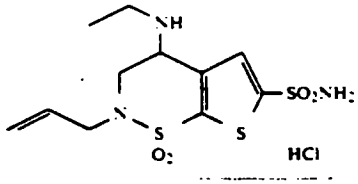
The compound from Step F (27.0 g, 83.1 mmol) (94% ee) was dissolved in n-propanol (800 mL) and the solution was filtered through a sintered glass filter. The filtrate was heated to about 80° C., and an 80° C. solution of di-p-toluoyl-D-tartaric acid (15.7 g, 40.7 mmol) in n-propanol (500 mL) was added. The mixture was allowed to stand at room temperature overnight before it was cooled in an ice-water bath for 1 h. The crystals were collected by filtration, washed with cold n-propanol, and dried to provide 39.2 g (93%) of the di-p-toluoyl-D-tartrate salt of greater than 98% ee. Because this material was somewhat colored, it was recrystallized from n-propanol (1.5 L) to provide a first crop of 34.8 g. This solid was added to a saturated aqueous solution of sodium bicarbonate (500 mL), and the mixture was stirred for 1 h. The mixture was then extracted with ethyl acetate (4×400 mL), and the combined extracts were dried over 4A molecular sieves, filtered, and concentrated on the rotary evaporator at reduced pressure to provide 20.2 g (75% recovery) of the (−)-sulfonamide of greater than 98% ee.

Step H:

(−)-4-Ethylamino-3,4-dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The compound from Step G (20.2 g, 62.2 mmol) was treated with 2 M ethanolic hydrogen chloride (40 mL), and then the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in water (200 mL) and evaporated to dryness to provide the hydrochloride salt which was washed with ethyl acetate and dried under high vacuum at 78° C. for 6 h. The yield of the hydrochloride salt was 21.7 g (94%) as the hemihydrate.

Example 12



2-Allyl-4-ethylamino-3,4-dihydro-2H-thieno[3.2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide-hydrochloride

Step A:

2-Allyl-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step C of Example 2 (4.0 g, 19.5 mmol) was dissolved in anhydrous DMF (70 mL) cooled to −10° C. and sodium hydride (21.5 mmol) was added. After stirring for five minutes allyl bromide (2.53 mL, 29.25 mmol) was added and this mixture stirred for 2 h at 0° C. The reaction mixture was poured onto ice water (100 mL) and this solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a crude product which was purified by column chromatography (silica, methylene chloride:methanol, 20:1) to provide the desired product (4.2 g, 88%) as a syrup.

Step B:

2-Allyl-4-(1-ethoxy)ethoxy-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step A (4.2 g, 17.1 mmol) was dissolved in tetrahydrofuran (75 mL) and cooled to 0° C. at which point p-toluenesulfonic acid (163 mg, 0.6 mmol) was added followed by ethylvinyl ether (3.3 mL, 34.3 mmol). This mixture was stirred at 0° C. for 2 h, diluted with cold ethyl acetate (100 mL) and washed with saturated sodium bicarbonate (70 mL) and brine (70 mL). The organic layer was dried ($MgSO_4$) and evaporated to provide 5.2 g of crude product which was used in the next step without further purification.

Step C:

2-Allyl-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step B (5.0 g, 15.8 mmol), dissolved in anhydrous tetrahydrofuran (125 mL) and cooled to −60° C., was treated dropwise with n-butyllithium (2.5 M, 7.6 mL, 18.9 mmol). This mixture was stirred at −40° C. for 40 min and then sulfur dioxide gas was bubbled over the surface for 20 min after which time the mixture was warmed to room temperature. After 30 min at room temperature the mixture was concentrated and the residue was dissolved in water (150 mL), cooled to 0° C. and sodium acetate trihydrate (6.4 g, 47.3 mmol) was added followed by hydroxylamine-O-sulfonic acid (3.2 g, 28.4 mmol). The reaction mixture was stirred at room temperature for 18 h after which time was basified with solid sodium bicarbonate and extracted with ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and the solvent evaporated to give the desired intermediate (5.0 g). This residue was dissolved in tetrahydrofuran (70 mL), cooled to 0° C. and then 1N HCl (70 mL) was added. After stirring at room temperature for 1 h the tetrahydrofuran was evaporated and the solution was neutralized with saturated sodium bicarbonate solution. The product was extracted into ethyl acetate and the combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by chromatography (silica, 5% methanol:methylene chloride) to give a syrup (1.2 g).

Step D: 2 -

Allyl-4-ethylamino-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

The product from Step C (1 g, 3 mmol) was dissolved in tetrahydrofuran (50 mL) containing triethylamine (1.7 mL, 12.0 mmol) and the solution was cooled to −16° C. Tosyl chloride (1.1 g, 6.0 mmol) was added and the mixture stirred for 18 h at room temperature after which time it was cooled to 0° C. and ethylamine (10 mL) was added. After heating at reflux for 1 h the solvent was evaporated and the residue dissolved in ethyl acetate (50 mL) and washed with 1N HCL (3×20 mL). The combined aqueous washes were basified (sodium bicarbonate) and extracted with ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate solution (3×15 mL) and brine (3×15 mL), dried ($MgSO_4$) and evaporated to give the desired free

3: $R_1=(CH_2)_2CH_3$; $R_2=(CH)_2O(CH_2)_2OCH_3$: 3,4-Dihydro-4-propylamino-2-[2-(methoxyethoxy)ethyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride: mp 174°-178° C.;

4: $R_1=CH_2CH_3$; $R_2=(CH_2)_3O(CH_2)_2OCH_3$: 4-Ethylamino-3,4-dihydro-2-[3-(2-metnoxy)ethoxy]-propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride: mp 209°-211° C.;

5: $R_1=(CH_2)_2CH_3$; $R_2=(CH_2)_3O(CH_2)_2OCH_3$: 3,4-Dihydro-4-propylamino-2-[3-(2-methoxy)ethoxy)-propyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide maleate: mp 150°-152° C.

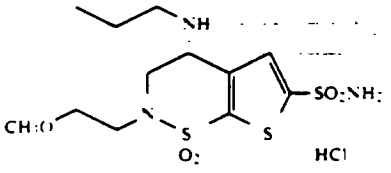
Using the procedures described in Examples 13 and 14 but substituting the appropriate alkylhaloether in Step A and the desired alkylamine in Step D the following compounds can be prepared:

6: $R_1=(CH_2)_2CH_3$; $R_2=(CH_2)_2OCH_2CH_3$: 2-(2-Ethoxy)ethyl-3,4-dihydro-4-propyl amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride;

7: $R_1=CH_2CH_3$; $R_2=(CH_2)_3OCH_2CH_3$: 2-(3-Ethoxy)propyl-4-ethylamino-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride.

8. $R_1=(CH_2)_2CH_3$;$R_2=(CH_2)_3OCH_3$: 3,4-Dihydro-2-(3-methoxy)propyl-4-propyl amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride.

EXAMPLE 17



R-(−)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A:

3,4-Dihydro-2-(2-methoxy)ethyl-4-oxo-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of the product of Example 13, Step C (1.0 g, 2.92 mmol), in acetone (65 mL) was added over 3 min Jones reagent (1.1 M, 2.66 mL, 2.92 mmol). After 20 min the mixture was evaporated to dryness and the residue was triturated with ethyl acetate (3×80 mL) and the combined organics were washed with brine and dried over molecular sieves. Concentration gave the desired product (0.92 g).

Step B: (−)-3,4-Dihydro-4-hydroxy-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of the product from Step A (550 mg, 16.2 mmol) in tetrahydrofuran (200 mL) cooled to −65° C. was added dropwise a solution of (+)-β-chlorodiisopinocampheyl borane (25.6 g, 79.8 mmol) in anhydrous tetrahydrofuran (30 mL) over 5 min. After the addition was completed the mixture was stored at −22° C. for 3 days. Diethanolamine (11.06 g, 105.2 mmol) was added and the mixture stirred for 30 min and then evaporated to dryness. The residue was mixed with a saturated solution of sodium bicarbonate (100 mL) and extracted with ethyl acetate (3×150 mL). Concentration of the organics gave a viscous liquid which was chromatographed (silica, hexane to 50% hexane:ethyl acetate to 10% methanol:methylene chloride) to give the desired subject (5.23 g, 95%): mp 131°-133° C.; $[\alpha]_D$ −3.31° (C- 1.18, MeOH).

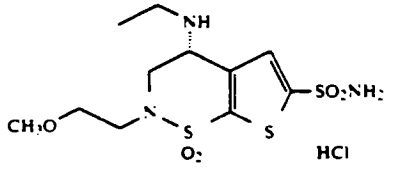
Step C:

(+)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

To a solution of the product form Step B (2.68 g, 784 mmol) and triethylamine (3.19 g, 31.3 mmol) in anhydrous tetrahydrofuran (100 mL) cooled to −20° C. was added tosyl chloride (2.99 g, 15.7 mmol) over 5 min. This mixture was placed in an ice bath for 18 h and after which time an excess of propylamine (10.0 g, 169 mmol) was added. The mixture was stirred at ambient temperature for 1 h followed by heating at reflux for an additional 2 h. Evaporation of the mixture gave a crude product which was mixed with saturated sodium bicarbonate (100 mL) and extracted with ethyl acetate (3×100 mL) The combined extracts were evaporated and the residue chromatographed (silica, 5% methanol:-methylene chloride) to give the free base (1.7 g, 57%). The free base was dissolved in ethyl acetate (20 mL) and treated with a solution of 1.5 N ethanolic HCl in ethanol (4.5 mL). The solution was evaporated to dryness and the residue dissolved in methanol (2 mL) and methylene chloride (80 mL) was added. After crystallization was complete the solid was collected and dried (65° C. in vacuo) to give the desired product (1.45 g, 36%): mp 205°-206° C.; $[\alpha]_D$ +6.02° (C=1.03, H_2O).

Analysis calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.31; H, 5.27; N, 10.01 Found: C, 33.99; H, 5.12; N, 9.81

Example 18

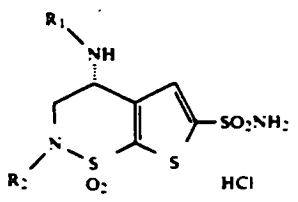


R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methoxy)ethyl-2H-thieno[3,2-e]- 1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Using essentially the same procedure as described in Example 17 except substituting an equimolar amount of ethyl amine for propylamine the desired subject is produced: mp 224°-227° C.; $[\alpha]_D$ +5.86° (C=1.11, H_2O).

Analysis calculated for C, 31.84; H, 5.10; N, 10.13 Found: C, 31.97; H, 4.97; N, 10.15

EXAMPLE 19



added a solution of n-butyllithium in pentane (20.6 mL of a 2.0 M solution) at −78° C. over a period of 20 minutes. After stirring this solution for 45 min, a stream of SO_2 gas was passed over the surface of the solution (20 min). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2 hr. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 2 hr. The solvent was evaporated to give a residue which was dissolved in methylene chloride (200 mL), cooled to 0° C., and N-chlorosuccinamide (7.4 g, 0.055 mol) was added in portions. After one hour the reaction mixture was allowed to warm to room temperature; stirring continued for two more hours, at which point the methylene chloride was removed by evaporation and the residue dissolved in THF (100 mL). This solution was cooled (0° C.) and a solution of t-butylamine (7.8 mL, 0.075 mol) in THF (50 mL) was added dropwise followed by stirring for 8 hr at room temperature. After removal of excess amine by evaporation, 2N HCl (10 mL) was added and the reaction mixture stirred at room temperature for 8 hr. Water (50 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to provide crude product which was purified by column chromatography (silica; 5% CH_3OH/CH_2Cl_2) to give the desired product as a yellow syrup (7.3 g, 72%).

Step B:

2-(2-Bromoethyl)-3,4-dihydro-4-hydroxy-2H-thieno3,2-e]-1,2-thiazine-6-(N-t-butyl)-sulfonamide-1,1-dioxide

To a suspension of NaH (1.9 g, 0.049 mol) in DMF (10 mL) was added a solution of the product from Step A (8.3 g, 24.4 mmol) in DMF (20 mL) at 0° C. This mixture was stirred for 40 minutes and 1,2-dibromoethane (8.34 mL, 0.098 mol) was added dropwise after which the reaction mixture was stirred for 4 hr at room temperature. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated to give an oil which was purified by chromatography (silica; 50% ethyl acetate/hexane) to give 8.8 g (81%) of the desired product.

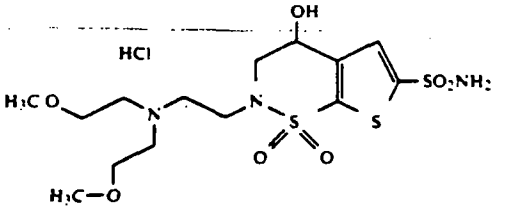
Step C:

2-[1-(4-Acetyl-piperazinyl)ethyl-3,4-dihydro-4-hydroxy-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide maleate

To a solution of the product from Part B (2.02 g, 4.5 mmol) in 3-methyl-2-butanone (15 mL) was added 1-acetylpiperazine (2.23 g, 17.5 mmol), sodium carbonate (1.8 g, 17.5 mmol), and potassium iodide (200 mg); this mixture was heated at 95° C. for 4 hr. The solvent was evaporated and a saturated aqueous solution of ammonium chloride (30 mL) was added to the residue. This solution was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give an oil which was dissolved in trifluoroacetic acid (20 mL). After stirring at room temperature for 24 hr, the trifluoroacetic acid was removed by evaporation and the residue dissolved in a saturated aqueous solution of sodium bicarbonate (30 mL) which was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give an oil which was purified by column chromatography (silica; 10% CH_3OH/CH_2Cl_2) to give 1.2 g (60%) of free base. The free base (500 mg, 1.12 mmol) was dissolved in THF (10 mL) and added to a solution of maleic acid (172 mg, 1.48 mmol) in ether (10 mL). The solid which readily formed was collected by filtration, washed with an excess of ether, and dried to give the desired salt; mp 210° C. Analysis. Calculated for $C_{18}H_{26}N_4O_{10}S_3H_2O$: C,37.75; H, 4.93; N,9.78. Found: C,37.77; H,4.88; N,9.74.

The 2-bromoethyl derivative described in Step B or analogous compounds such as that described in Example 25, Step A, or their corresponding acetals (represented by the compound in Example 25, Step B) are key starting materials for the incorporation of a number of the heterocyclic rings found in the novel compounds of Structure [1]. Many of the simplified rings which correspond to the general structure of NR_5-R_6 where R_5 and R_6 form a 5 or 6 member ring can be obtained commercially. In other cases the desired heterocyclic component can be prepared from these simplified rings or by other methods which are known to one skilled in the art. Important lead references which disclose the synthesis of these heterocyclic rings are: "Comprehensive Heterocyclic Chemistry," A. R. Katritzky et al., Volumes 2–6, and references cited therein.

EXAMPLE 22



3,4-Dihydro-hydroxy-2-[2-(N,N-dimethoxyethyl-)aminoethyl]-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

To a solution of the product from Example 21, Part B (1.70 g, 4.0 mmol) in 3-methyl-2-butanone (10 mL) was added bis(2-methoxyethyl)amine (2.2 mL, 11.0 mmol), sodium carbonate (1.2 g, 11.0 mmol), and potassium iodide (200 mg); this mixture was heated at 100° C. for 8 hr. The solvent was evaporated and water (50 mL) was added to the residue. This solution was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give an oil which was dissolved in trifluoroacetic acid (24 mL). After stirring at 45° C. for 20 hr, the trifluoroacetic acid was removed by evaporation and the residue dissolved in a saturated aqueous solution of sodium bicarbonate (50 mL) which was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give an oil which was purified by column chromatography (silica; 10% CH_3OH/CH_2Cl_2) to give 1.1 g (58%) of free base. The free base (460 mg, 1.04 mmol) was dissolved in ethanol (10 mL) to which a solution of hydrochloric acid in ethanol (5 mL) was added; this solution was stirred for 30 min and evaporated. The solid was recrystallized (CH_3OH/Et_2O) to give the desired salt; mp 205° C.

Step B:
2-(3-Bromo)propyl-4-(1-ethoxy)ethoxy-3,4-dihydro-2H-thieno-[3,2-e]-1,2-thiazine

The product from Step A (10.1 g, 30.1 mmol) and p-toluenesulfonic acid (1.1 g) were dissolved in THF (100 mL) and cooled to −20° C. at which point ethylvinyl ether (5.8 mL, 60.2 mmol) was added. This mixture was allowed to warm to 0° C. and kept at this temperature for 1.5 hr followed by dilution with cold ethyl acetate (200 mL). The organic layer was separated, washed with saturated sodium bicarbonate (3×50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated to provide 9.5 g (79%) of crude product which was used in the next step without further purification.

Step C:
4-(1-Ethoxy)ethoxy-3,4-Dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine

The product from Step B (9.5 g, 23.8 mmol) was dissolved in methanol (200 ml) and sodium methoxide (6.5 g, 119 mmol) was added: the mixture was heated at reflux temperature for 18 hr. Evaporation of the solvent gave the crude product which was dissolved in ethyl acetate (300 mL). This solution was washed with water (3×50 mL) and brine (3×35 mL), dried ($MgSO_4$) and evaporated to provide the curde product which was purified by column chromatography [silica: CH_3OH/CH_2Cl_2(20:1)] to give 6.5 g (78%) of product as a syrup.

Step D:
3,4-Dihydro-4-hydroxy-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

The product from Step C (6.5 g, 18.6 mmol) was dissolved in THF (40 mL), cooled to −78° C. and treated sequentially with n-butyllithium, sulfur dioxide, and hydroxylamine-O-sulfonic acid in a manner essentially identical to that described in Example 2, Step D to provide the desired crude product which, after purification by column chromatography, provided 4.1 g (62%) of an amber syrup.

Step E:
3,4-Dihydro-2-(3-methoxy)propyl-4-oxo-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

To a solution of the product from Step D (3.8 g, 10.7 mmol) in acetone (40 mL) at room temperature was added Jones reagent [9.7 mL (prepared by dissolving CrO_3 (7 g) in H_2O (50 mL) and adding H_2SO_4 (6.1 mL)]. This mixture was stirred at room temperature for one hour, diluted with ethyl acetate (200 mL) and washed with a 5% solution of sodium bisulfite (2×100 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica: CH_3OH/CH_2Cl_2(20:1)] to give 2.7 g (70%) of the desired product: mp 115°–117° C.

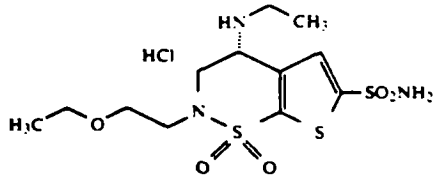
Step F:
(+)-3,4-Dihydro-4-hydroxy-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

To a solution of the product of Step E (2.6 g, 7.34 mmol) in THF (30 mL) at −78° C. was added a solution of (+)-β-chlorodiisopinocampheylborane (11.8 g, 36.7 mmol) in THF (10 mL). The reaction mixture was allowed to warm to −20° C. and kept at this temperature for 4 days. Diethanolamine (4.2 mL, 44 mmol) was added to the reaction mixture and the solution stirred for 30 min, diluted with EtOAc (150 mL), washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica: CH_3OH/CH_2Cl_2(20:1)] to give 2.4 g (92%) of the desired compound as a colorless foam.

Step G:
(−)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

To a solution of the product from Step F (2.4 g, 6.74 mmol) and triethylamine (3.8 mL, 27 mmol) in anhydrous tetrahydrofuran (20 mL) cooled to −20° C. was added tosyl chloride (2.6 g, 13.5 mmol); this mixture was allowed to warm to room temperature and stirred for 18 hr. The reaction mixture was cooled to −60° C. and ethylamine (10 mL) was added and the mixture was again allowed to warm to room temperature. After 18 hr the reaction mixture was diluted with ethyl acetate (200 mL), washed with a saturated aqueous solution of sodium bicarbonate (3×50 mL), dried ($MgSO_4$), and evaporated to give the crude product which was purified by column chromatography [silica: CH_3OH/CH_2Cl_2(20:1)] to give 1.3 g (52%) of the desired amine. The free base was dissolved in ethanol (5 mL) and treated with a 2M solution of hydrochloric acid in ethanol (4 mL) at room temperature. Evaporation of the solvent provided a solid which was recrystallized from methanol: methylene chloride to give 950 mg (34%) of the desired product; mp 175°–177° C.; $[\alpha]_D$ 17.1° (C=1.00, H_2O). Analysis. Calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.32; H, 5.28; N, 10.00 Found: C, 34.26; H, 5.23; N, 9.92.

EXAMPLE 26



(+)-2-(2-Ethoxy)ethyl-4-ethylamino-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

By following essentially the same procedure as used for the preparation of Example 25 but using instead 2-bromoethylethyl ether for the alkylation reaction in Step A, and omitting step C, the desired compound was prepared; mp 211°–213° C., $[\alpha]_D$ +9.4° (C=1.00, CH_3OH). Analysis. Calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.32; H, 5.28; N, 10.00. Found: C, 34.27; H, 5.28; N, 9.92.

a blanket of nitrogen was added imidazole (300 mg, 4.4 mmol) and tert-butyldimethylsilyl chloride (904 mg, 6 mmol). The reaction mixture was stirred at room temperature for 5 hr and the solvent removed by evaporation to give a residue. The residue was dissolved in ethyl acetate (150 mL) and the solution washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by a column chromatography silica; CH_3OH/CH_2Cl_2(10:1)] to give 1.05 g (58%) of product as an oil.

Step E:

2-[3-(tert-Butyldimethylsilyloxy)propyl]-4-ethylamino-3,4-dihydro-2H-thieno[3.2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

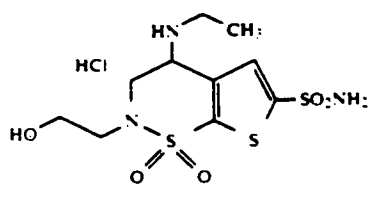
To a solution of the product of Step D (1.4 g, 3 mmol) and triethylamine (1.7 mL, 12 mmol) in THF (10 mL) at −20° C. was added p-toluenesulfonyl chloride (1.2 g, 6 mmol) and the reaction mixture was stirred at 0° C. for 5 hr. The reaction mixture was cooled to −78° C. at which point ethylamine (10 mL) was added; this mixture was allowed to warm to reflux temperature for 2 hr and then maintained at room temperature for 40 hr. After removing the solvent the crude product was diluted with ethyl acetate (150 mL), washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 900 mg (64%) as a colorless foam.

Step F:

4-Ethylamino-2-(3-hydroxy)propyl-3,4-dihydro-2H-thieno[3.2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

The product from Step E (900 mg, 1.86 mmol) was dissolved in a 1M solution of tetrabutylammonium fluoride in THF (10 mL) and stirred at room temperature for 20 hr under a nitrogen atmosphere. After removal of the solvent, the residue was dissolved in ethyl acetate (100 mL) and this solution was washed with a saturated aqueous solution of sodium bicarbonate (2×50 mL), water (3×25 mL) and brine (3×25 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(10:1)] to give 600 mg (87%) of free base as a syrup. This syrup was dissolved in ethanol (3 mL), and a 2M solution of hydrochloric acid in ethanol (2 mL) was added followed by evaporation to provide a solid which was dissolved in water (5 mL) and evaporated. Recrystallization from methanol/methylene chloride gave 480 mg of the desired product: mp 203°-205° C. Analysis Calculated for $C_{11}H_{20}ClN_3O_5S_3$: C, 32.55; H, 4.96; N, 10.35. Found C, 32.43; H, 4.92; N, 10.28.

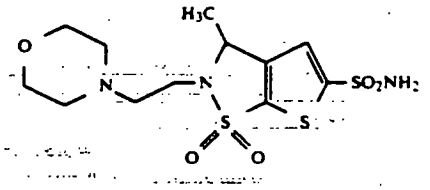
EXAMPLE 30



4-Ethylamino-3,4-dihydro-2-(2-hydroxy)ethyl-2H-thieno[3.2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

By following the same procedure as that described in Example 29, but substituting 2-bromoethanol for 3-bromopropanol in Step A, the desired compound was obtained as a crystalline solid: mp 228°-230° C. Analysis Calculated for $C_{10}H_{18}ClN_3O_5S_3$: C, 30.65; H, 4.63; N, 10.72. Found C, 30.78; H, 4.68, N, 10.59.

EXAMPLE 31

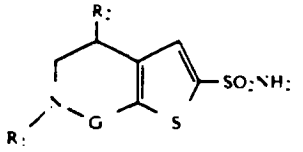


2,3-Dihydro-3-methyl-2-[2-(4-morpholinyl)ethyl]-thieno[3,2-d]isothiazole-5-sulfonamide-1,1-dioxide

Step A: 3-Methylthieno[3,2-d]isothiazole

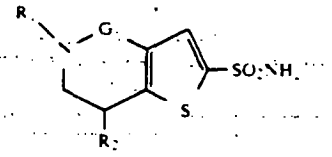
The product from Example 2, Step A (10.37 g, 48.8 mmol) was dissolved in anhydrous ether (100 mL), cooled to −20° C. and a 2.5M solution of n-butyllithium in hexanes (21.5 mL, 49 mmol) was slowly added. The mixture was allowed to warm to 0° C. and stirred at this temperature for two hours, again cooled to −20° C. at which point sulfur (1.56 g, 48.8 mmol) was added in small portions. The cooling bath was removed and the mixture was allowed to warm to room temperature over a two hour period followed by the addition of 2 N HCl (10 mL). The ether layer was separated, washed with brine (3×25 mL) and evaporated to a residue which was mixed with THF (100 mL) and 2N HCl (10 mL) and heated at 45° C. for 45 min followed by the addition of solid sodium bicarbonate to neutralize the mixture. The organic layer was separated, washed with brine (3×25 mL), dried ($MgSO_4$), and evaporated to a solid which was recrystallized from methylene chloride/hexane to give 4.6 g (60%) of a solid (150°-152° C.). This solid was suspended in dioxane (400 mL), water (5 mL) was added, and the mixture degassed under nitorgen. Concentrated hydrochloric acid (1 mL) was added to this mixture followed by triphenylphosphine (18.7 g, 71.2 mmol). This mixture became homogenous after 15 min and was stirred for one additional hour, diluted with water (IL, and extracted with ether (4×100 mL). The combined extracts were washed with water (3×100 mL), brine (2×100 mL), and evaporated to a residue which was dissolved in aqueous THF (400 mL, 1:1) to which was added hydroxylamine-O-sulfonic acid (8.1 g, 71.2 mmol). This mixture was stirred for 45 min followed by the addition of sodium carbonate (18.9 g, 178 mmol) and stirring continued at room temperature for 18 hr. The reaction mixture was diluted with water (500 mL) and extracted with ether (3×150 mL). The combined extracts were dried (Na_2CO_3) and evaporated to a residue which was purified by column chromatography (silica, hexane/ethyl acetate) to provide 22.1 g (65%) of the desired compound as an amber oil.

TABLE 1-continued



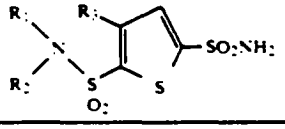
G	R_1	R_2
SO_2	n-Pr	HNEt
SO_2	i-Pr	HNEt
SO_2	CH_2CHCH_2	HNEt
SO_2	CH_2CCH	HNEt
SO_2	$(CH_2)_2OMe$	HNEt
SO_2	$(CH_2)_2OMe$	$EtNC(=O)OEt$
SO_2	$(CH_2)_2OMe$	$EtNC(=O)CH_3$
SO_2	$(CH_2)_2OH$	HNEt
SO_2	$(CH_2)_2OEt$	HNEt
SO_2	$(CH_2)_2OEt$	HNn-Pr
SO_2	$(CH_2)_2OH$	HNEt
SO_2	$(CH_2)_2OH$	HNn-Pr
SO_2	$(CH_2)_2OC(=O)CH_3$	HNEt
SO_2	$(CH_2)_2OMe$	HNn-Pr
SO_2	$(CH_2)_2OEt$	HNEt
SO_2	$(CH_2)_2OEt$	HNn-Pr
SO_2	$(CH_2)_3OMe$	HNEt
SO_2	$(CH_2)_3OMe$	HNn-Pr
SO_2	$(CH_2)_3OMe$	HNi-Bu
SO_2	$(CH_2)_2O(CH_2)_2OMe$	HNEt
SO_2	$(CH_2)_2O(CH_2)_2OMe$	HNn-Pr
SO_2	$(CH_2)_2O(CH_2)_2OMe$	HNi-Bu
SO_2	$(CH_2)_3O(CH_2)_2OMe$	HNEt
SO_2	$(CH_2)_3O(CH_2)_2OMe$	HNn-Pr
SO_2	$(CH_2)_3O(CH_2)_2OMe$	HNi-Bu
SO_2	$CH_2CHCHCH_2OMe$ (trans)	HNEt
SO_2	$CH_2CHCHCH_2OMe$ (trans)	HNn-Pr
SO_2	$CH_2CHCHCH_2OMe$ (trans)	HNi-Bu
SO_2	$CH_2CHCHCH_2OMe$ (cis)	HNEt
SO_2	$CH_2CHCHCH_2OMe$ (cis)	HNn-Pr
SO_2	$CH_2CHCHCH_2OMe$ (cis)	HNi-Bu
SO_2	Me	$HNCH_2CHCH_2$
SO_2	Me	HNC_3H_5
SO_2	Me	$HNCH_2C_3H_5$
SO_2	Me	HNn-Pr
SO_2	Me	HNi-Bu
SO_2	Me	$HN(CH_2)_2OH$
SO_2	Me	$HN(CH_2)_2OMe$
SO_2	Me	OH
SO_2	Me	OMe
SO_2	Me	Oi-Bu
SO_2	Me	$O(CH_2)_2N(CH_2CH_2)_2O$
SO_2	Me	$O(CH_2)_2N(CH_2CH_2)_2NCOMe$
SO_2	Me	4-Cl—Ph
SO_2	Me	$3\text{-}N(Me)_2$—Ph
SO_2	Me	$3\text{-}CH_2N(CH_2CH_2)_2O$—Ph
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OH
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2NCOMe$	CH_2OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2NCOMe$	OEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2NCOMe$	OH
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	CONHEt
SO_2	$(CH_2)_3Me$	HNEt
SO_2	$(CH_2)_3OMe$	HNEt
SO_2	$CH_2CONHMe$	HNEt
SO_2	Ph	HNEt
SO_2	4-Cl—Ph	HNEt
SO_2	4-CONHMe—Ph	HNEt
SO_2	$4\text{-}SO_2NMe_2$—Ph	HNEt
SO_2	$3\text{-}SO_2Me$—Ph	HNEt
SO_2	$4\text{-}OCF_2H$—Ph	HNEt
SO_2	4-OMe—Ph	HNEt
SO_2	$4\text{-OH, }3\text{-}CH_2NMe_2$—Ph	HNEt
SO_2	4-NHCOMe—Ph	HNEt
SO_2	CH_2-4-pyridyl	HNEt
SO_2	$(CH_2)_2OH$	HNEt
SO_2	$(CH_2)_2OEt$	HNEt
SO_2	$(CH_2)_2COMe$	HNEt
SO_2	$CH_2CON(CH_2CH_2)_2NCH_2OMe$	OEt
SO_2	CH_2CO_2-i-Pr	HNEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OH

TABLE 2-continued



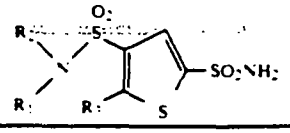
G	R_1	R_2
SO_2	$(CH_2)_2CONHMe$	HNEt
SO_2	Ph	HNEt
SO_2	4-Cl—Ph	HNEt
SO_2	4-CONHMe—Ph	HNEt
SO_2	4-SO_2NMe_2—Ph	HNEt
SO_2	3-SO_2Me—Ph	HNEt
SO_2	4-OCF_2H—Ph	HNEt
SO_2	4-OMe—Ph	HNEt
SO_2	4-OH, 3-CH_2NMe_2—Ph	HNEt
SO_2	4-NHCOMe—Ph	HNEt
SO_2	$(CH_2)_2OH$	HNEt
SO_2	$(CH_2)_2OEt$	HNEt
SO_2	$(CH_2)_2COMe$	HNEt
SO_2	$CH_2CON(CH_2CH_2)_2N(CH_2)_2OMe$	OEt
SO_2	CH_2CO_2-i-Pr	HNEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OH
CO	H	HNMe
CO	H	HNEt
CO	Me	HN-n-Pr
CO	Me	HN-i-Bu
CO	Me	$HN(CH_2)_2OH$
CO	Me	$HN(CH_2)_2OMe$
CO	Me	OH
CO	Me	OMe
CO	Me	O-i-Bu
CO	Me	$O(CH_2)_2N(CH_2CH_2)_2O$
CO	Me	$O(CH_2)_2N(CH_2CH_2)_2NCOMe2$
CO	Me	4-Cl—Ph
CO	Me	3-NMe_2—Ph
CO	Me	3-$CH_2N(CH_2CH_2)_2O$—1
CO	$(CH_2)_2N(CH_2CH_2)_2O$	OMe
CO	$(CH_2)_2N(CH_2CH_2)_2O$	OEt
CO	$(CH_2)_2N(CH_2CH_2)_2NCOMe$	CH_2OMe
CO	$(CH_2)_2N(CH_2CH_2)_2NCOM_e$	OEt
CO	$(CH_2)_2N(CH_2CH_2)_2O$	CONHEt
CO	$(CH_2)_2Me$	HNEt
CO	$(CH_2)_2OMe$	HNEt
CO	$CH_2CONHMe$	HNEt
CO	Ph	HNEt
CO	4-Cl—Ph	HNEt
CO	4-CONHMe—Ph	HNEt
CO	4-SO_2NMe_2—Ph	HNEt
CO	3-SO_2Me—Ph	HNEt
CO	4-OCF_2H—Ph	HNEt
CO	4-OMe—Ph	HNEt
CO	4-OH, 3-CH_2NMe_2—Ph	HNEt
CO	4-NHCOMe—Ph	HNEt
CO	$(CH_2)_2OH$	HNEt
CO	$(CH_2)_2OEt$	HNEt
CO	$(CH_2)_2COMe$	HNEt
CO	$CH_2CON(CH_2CH_2)_2N(CH_2)_2OMe$	OEt
CO	CH_2CO_2-i-Pr	HNEt
CO	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OH

TABLE 3



R_1	R_2	R_3
$(CH_2)_2N(CH_2CH_2)_2O$	H	H
$(CH_2)_2N(CH_2CH_2)_2O$	H	H
$(CH_2)_2N(CH_2CH_2)_2O$	Et	H
$(CH_2)_2N(CH_2CH_2)_2O$	Me	H
$(CH_2)_2N(CH_2CH_2)_2O$	Me	Me
$(CH_2)_2N(CH_2CH_2)_2O$	H	Cl
$(CH_2)_2N(CH_2CH_2)_2O$	H	Br

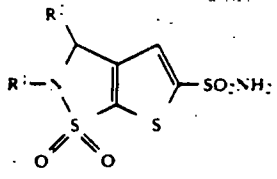
TABLE 4-continued



$(CH_2)_2N(CH_2CH_2)_2O$	Me	$CH_2CONHEt$
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	H
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	H
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	Me	H
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	Me	Me
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	Cl
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	Br
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2OEt
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2OMe
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2O-i-Pr
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2O-t-Bu
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2OH
$(CH_2)_5Me$	H	$CH_2N(CH_2CH_2)_2O$
$(CH_2)_2OMe$	H	$CH_2N(CH_2CH_2)_2O$
$(CH_2)_2OH$	H	$CH_2N(CH_2CH_2)_2O$
$(CH_2CONHMe$	H	$CH_2N(CH_2CH_2)_2O$
Ph	H	$CH_2N(CH_2CH_2)_2NCOMe$
4-Cl—Ph	H	Me
4-CONHMe—Ph	H	Me
4-SO_2NMe_2—Ph	H	Me
3-SO_2Me—Ph	H	Me
4-OCF_2H—Ph	H	Me
4-OMe—Ph	Me	Me
4-OH, 3-CH_2NMe_2—Ph	Me	Me
4-NHCOMe—Ph	Me	Me
$(CH_2)_2OH$	Me	Me
$(CH_2)_2OEt$	Me	Me
$CH_2CON(CH_2CH_2)_2N(CH_2)_2OMe$	Me	H
CH_2CO_2-i-Pr	Me	Me
$(CH_2)_2N(CH_2CH_2)_2O$	H	CH_2CH_2OH
$(CH_2)_2N(CH_2CH_2)_2NCOMe$	H	CH_2CH_2OH

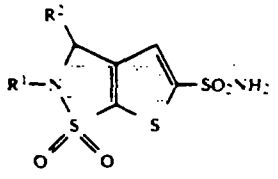
R_1 and R_2	R_3
$-(CH_2CH_2)_2N(CH_2)_2OMe$	H
$-(CH_2CH_2)_2N(CH_2)_2OMe$	Me
$-(CH_2CH_2)_2N(CH_2)_2OMe$	Cl
$-(CH_2CH_2)_2N(CH_2)_2OMe$	CH_2OH
$-(CH_2CH_2)_2N(CH_2)_2OM$	CH_2OMe
$-(CH_2CH_2)_2NCH_2CONHMe$	H
$-(CH_2CH_2)_2N(CH_2)_2CONHMe$	H

TABLE 5



R^1	R^2
Me	CH_2NHMe
Me	CH_2NHEt
Et	CH_2NHEt
n-Pr	CH_2NHEt
Et	CH_2NHMe
n-Pr	CH_2NHMe
$CH_2CH{=}CH_2$	CH_2NHMe
Me	$CH_2NHCH_2CH_2OCH_3$
Et	$CH_2NHCH_2CH_2OCH_3$
n-Pr	$CH_2NHCH_2CH_2OCH_3$
Et	$CH_2NHCH_2CH_2OH$
$CH_2CH_2OCH_3$	CH_2NHMe
$CH_2CH_2OCH_3$	CH_2NHEt
$CH_2CH_2CH_2OH$	CH_2NHMe
$CH_2CH_2CH_2OH$	CH_2NHEt
$CH_2CH_2CH_2OCH_3$	CH_2NHEt
C_6H_5	$CH_2NHCH_2CH_2OH$
C_6H_5	$CH_2NHCH_2CH_2OCH_3$
C_6H_4(3-SO_2CH_3)	CH_2NHEt
C_6H_4(3-OH)	CH_2NHEt
C_6H_4[3-$SO_2N(CH_3)_2$]	CH_2NHEt

TABLE 5-continued



R^1	R^2
$CH_2C_6H_5$	CH_2NHEt
2-thenyl	CH_2NHEt
2-thenyl(5-SO_2CH_3)	CH_2NHEt
$CH_2CH_2N(CH_2CH_2)_2O$	H
$CH_2CH_2N(CH_2CH_2)_2O$	CH_3
$CH_2CH_2N(CH_2CH_2)_2O$	CH_2OH
$CH_2CH_2N(CH_2CH_2)_2O$	CH_2OCH_3
$CH_2CH_2N(CH_2CH_2)_2O$	CH_2CH_2OH
$CH_2CH_2N(CH_2CH_2)_2O$	$CH_2OCH_2CH_2OH$
$CH_2CH_2N(CH_2CH_2OH)_2$	CH_3
$CH_2CH_2N(CH_2CH_2OCH_3)_2$	CH_3
$CH_2CH_2N(CH_3)CH_2CH_2OCH_3$	CH_3
$CH_2CH_2N(CH_2CH_2)_2NCOCH_3$	H
$CH_2CH_2N(CH_2CH_2)_2NCOCH_3$	CH_3
$CH_2CH_2N(CH_2CH_2)_2NCOCH_3$	CH_2OH
$CH_2CH_2N(CH_2CH_2)_2NCOCH_3$	CH_2CH_2OH
$CH_2CH_2NHCH_2CH_2F$	CH_3
$CH_2CH_2NHCH_2CH_2F$	CH_2CH_2OH
$CH_2CH_2N(CH_2CH_2)_2NCHO$	H
$CH_2CH_2N(CH_2CH_2)_2NCHO$	CH_3
$CH_2CH_2N(CH_2CH_2)_2NCH_2CH_2OCH_3$	H

-continued

Ingredient	Concentration (wt %)
Benzalkonium Chloride	0.01%
Carbopol	3.0%
HCl/NaOH	pH 5.0
Purified Water	q.s.

The mannitol (0.18 g), benzalkonium chloride (0.05 mL), Compound (0.1 g) and carbopol (0.15 g) can all be added to water (4.3 mL) and mixed well. The pH can be adjusted to pH 5.0 and purified water (q.s. to 5 mL) can be added and mixed well to form a gel.

EXAMPLE 35

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-4-Ethylamino-3,4-dihydro-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (Compound)	2.27%
Hydroxypropylmethylcellulose	3.3%
Sodium Acetate Dihydrate	0.1%
Mannitol (Osmolality = 282 mOsm)	2.44%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 5.0

The sodium acetate (0.2 g), disodium edta (0.02 g), benzylalkonium chloride (2.1 g of a 1% solution) and mannitol (5.32 g) were dissolved in water for injection (115 mL). The pH was adjusted to 5.0 with 1N sodium hydroxide and the final volume was adjusted to 117 mL with water for injection. Hydroxypropylmethylcellulose (83.0 g of an 8% solution) was mixed with the 117 mL of the acetate buffer solution to furnish the vehicle. To prepare the final formulation, 0.068 g of the Compound was diluted with vehicle to make 3.0 mL total volume and the pH was adjusted to 5.0 with 1N sodium hydroxide (5 μL).

EXAMPLE 36

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methoxyethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	1.69%
Hydroxypropylmethylcellulose	3.0%
Sodium Acetate trihydrate	0.1%
Mannitol (Osmolality = 317 mOsm)	2.4%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 6.4

The above ingredients were mixed together in substantially the same manner as described in Example 35 to furnish the ophthalmic solution.

EXAMPLE 37

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(2-methoxyethyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.19%
Hydroxypropylmethylcellulose	3.0%
Sodium Acetate trihydrate	0.1%
Mannitol (Osmolality = 286 mOsm)	2.4%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 0.5

The above ingredients were mixed together in substantially the same manner as described in Example 35 to furnish the ophthalmic solution.

EXAMPLE 38

Ophthalmic Suspension

Ingredient	Concentration (wt %)
(−)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.0%
Hydroxypropylmethylcellulose	0.5%
Dibasic Sodium Phosphate	0.2%
Disodium Edetate	0.01%
Sodium Chloride	0.8%
Purified Water	q.s.
Benzalkonium Chloride	0.01%
Polysorbate 80	0.1%
NaOH/HCl	pH 7.1

The above ingredients can be mixed together in substantially the same manner as described in Example 32 to furnish the ophthalmic suspension.

We claim:

1. A compound selected from the group consisting of:
3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
2-(2-Ethoxyethyl-)-4-ethylamino-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
2-(2-Ethoxy)ethyl-3,4-dihydro-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
3,4-Dihydro-2-(3-methoxy)propyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
3,4-Dihydro-2-[2-(methoxyethoxy)ethyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-syulfonamide 1,1-dioxide;
4 Ethylamino-3,4-dihydro-2-[2-(methoxyethoxy)ethyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide;
4-Ethylamino-3,4-dihydro-2-[3-(methoxyethoxy)-propyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; and
3,4-Dihydro-2-[3-(methoxyethoxy)propyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide.

2. The compound of claim 10 which is
3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide.

US005378703A

United States Patent [19]

Dean et al.

[11] Patent Number: 5,378,703

[45] Date of Patent: * Jan. 3, 1995

[54] **SULFONAMIDES USEFUL AS CARBONIC ANHYDRASE INHIBITORS**

[75] Inventors: **Thomas R. Dean**, Wentherford; **Hwang-Hsing Chen**; **Jesse A. May**, both of Fort Worth, all of Tex.

[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[*] Notice: The portion of the term of this patent subsequent to Aug. 31, 2010 has been disclaimed.

[21] Appl. No.: **19,011**

[22] Filed: **Feb. 18, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 775,313, Oct. 9, 1991, Pat. No. 5,240,923, which is a continuation-in-part of Ser. No. 618,765, Nov. 27, 1990, Pat. No. 5,153,192, which is a continuation-in-part of Ser. No. 506,780, Apr. 9, 1990, abandoned.

[51] **Int. Cl.**[6] C07D 513/04; A61K 31/54

[52] **U.S. Cl.** 514/222.8; 544/48

[58] **Field of Search** 544/48; 514/222.8

[56] **References Cited**

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Primary Examiner—John M. Ford

Attorney, Agent, or Firm—Sally Yeager

[57] **ABSTRACT**

Sulfonamides and pharmaceutical compositions containing the compounds useful in controlling intraocular pressure are disclosed. Methods for controlling intraocular pressure through administration of the compositions are also disclosed.

14 Claims, No Drawings

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated, is substituted optionally with H or C alkyl or in which said carbon is substituted optionally with C alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl , Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkylC_{3-5}cycloalkyl; C(=O)R_7 or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O , S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, C(=O)R_7, C_{6-1} alkyl. C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(=O)R_7 or on nitrogen with C_{1-4} alkoxy, C(:O)R_7, S(=O)$_m$$R_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(:O)R_7 or on sulfur by (=O)$_m$, wherein m is 0–2.

R_7 is C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_9; C_{1-4} alkoxy; alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, S(=O)$_m$$R_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0–2.

R_8 is C_{2-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_7.

R_9 C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino; and

R_{10} is a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine.

G is C(=O) or SO_2.

In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where i and j are numbers from 1 to 8 for example. This C_{i-j} definition includes both the straight and branched chain isomers. For example, C_{1-4} alkyl would designate methyl through the butyl isomers; and C_{1-4} alkoxy would designate methoxy through the butoxy isomers.

The term "halogen," either alone or in compound words such as "haloalkyl, " means fluorine, chlorine, bromine or iodine Further, when used in compound words such as "haloalkyl," said alkyl may be partially or fully substituted with halogen atoms, which may be the same or different.

Structure *I* includes isomers, wherein R_3 and GNR_1R_2 are attached to the 4 and 5 position respectively or R_3 is attached to the 5 position and GNR_1R_2 is attached to the 4 position. Many of the novel compounds of Structure I possess one or more chiral centers and this invention includes all enantiomers, diastereomers and mixtures thereof.

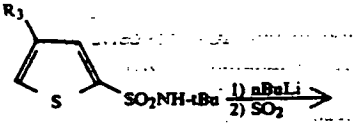
In addition to the following teaching, U.S. Pat. Nos. 5,153,192 and U.S. Pat. No. 5,240,923, the parents of this case which are commonly assigned, are incorporated herein by reference, particularly for their synthesis teaching and their many specific examples.

Compounds of the present invention can be prepared using a variety of procedures, a number of which are described below.

Many of the novel compounds of Structure I can be prepared from 5-sulfamoyl-thiophene-2-sulfonyl chlorides or 3-substituted 5-sulfamoyl-thiophene-2-sulfonyl chlorides, or where it is particularly advantageous for subsequent reactions in a specific preparation that the sulfonamide group be protected, 3-substituted 5-(N-t-butylsulfamoyl)-thiophene-2-sulfonyl chlorides can be used. These thiophene-2-sulfonyl chlorides can be readily prepared by a variety of procedures known in the art, for example see Gronowitz et al in *Thiophene and its Derivatives*, Vol. 44, Pt. 3, p135. The preparative sequence for novel compounds of Structure I using a protected sulfonamide is illustrated in Equation 1. In general, N-t-butyl-thiophene-2-sulfonamides can be selectively metallated at C5 using a strong organometallic base such as n-butyllithium, subsequent condensation with sulfur dioxide gas produces the intermediate lithium sulfinate salts (Equation 1a). The intermediate sulfinate salt can be readily converted to the corresponding sulfonyl chloride with an appropriate chlorinating agent such as N-chlorosuccinimide; amination of the sulfonyl chloride with a primary alkylamine, primary arylamine, or secondary alkylamine, bearing the desired R_1 and R_2 substituents, provides, following deprotection, the novel compounds of Structure I (Equation 1b).

In many cases it is more advantageous initially to prepare simplified primary or secondary sulfonamides as described above, but then append the more complex R_1 or R_2 substituents using standard alkylation reactions (Equation 1c). This sequence can furnish directly certain novel compounds of Structure I; however, subsequent modification of the substituents R_1, R_2, and R_3 can furnish yet other novel compounds of Structure I including novel fused bicyclic compounds; all of which can be prepared using methods known to one skilled in the art. Primary sulfonamides can be prepared from the corresponding sulfonyl chlorides by amination with ammonia or directly from the lithium sulfinate salts using hydroxylamine-O-sulfonic acid (HOSA) (Equation 1d). Equation 1

a)



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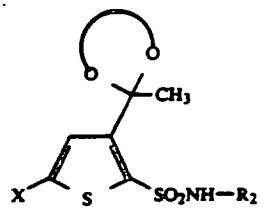
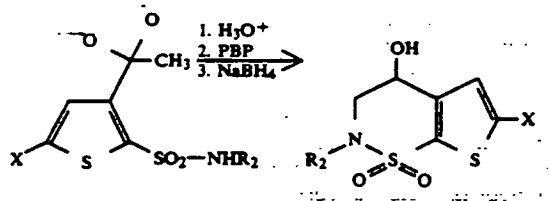


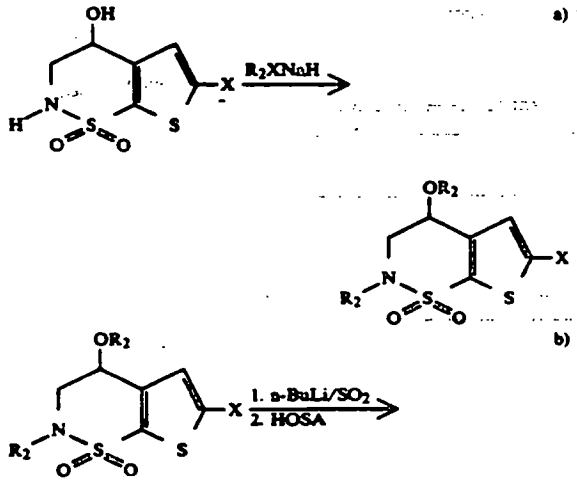
Conversion of these acyclic sulfonamides into the desired thienothiazine compounds can be accomplished using a variety of procedures well known in the art; e.g. acid hydrolysis of the ketal followed by bromination of the ketone and subsequent base catalyzed cyclization of the e-bromoketone (Equation 4).

Equation 4



Certain desired bicyclic compounds of Structure I can be readily prepared by a sequence which involves initial alkylation with an appropriate alkyl halide in the presence of a suitable base (Equation 5a) followed by introduction of the sulfamoyl group by procedures analogous to Equations 1a–d, that is metallation of the alkylated product of Equation 4 with a strong organometallic base such as n-butyllithium, followed by treatment with sulfur dioxide to give the intermediate sulfinate salt which is aminated, e.g. by reaction with hydroxylamine-O-sulfonic acid (Equation 5b). Treatment of this intermediate with an appropriate alkyl nitrile in the presence of sulfuric acid provides an amide which upon reduction gives the desired amine [Equation 5c; R' is lower alkyl (C_{1-4})].

Equation 5



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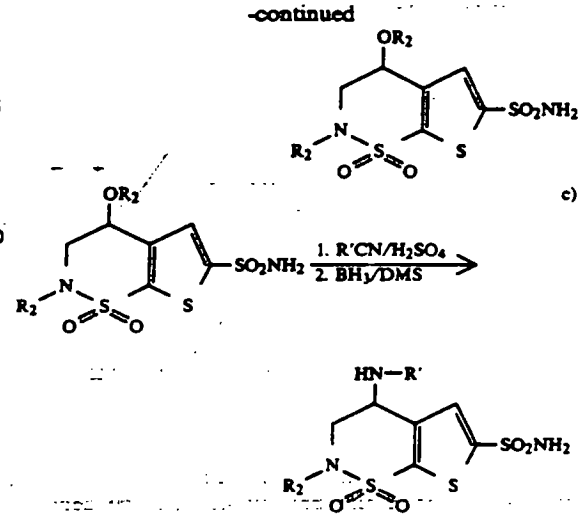
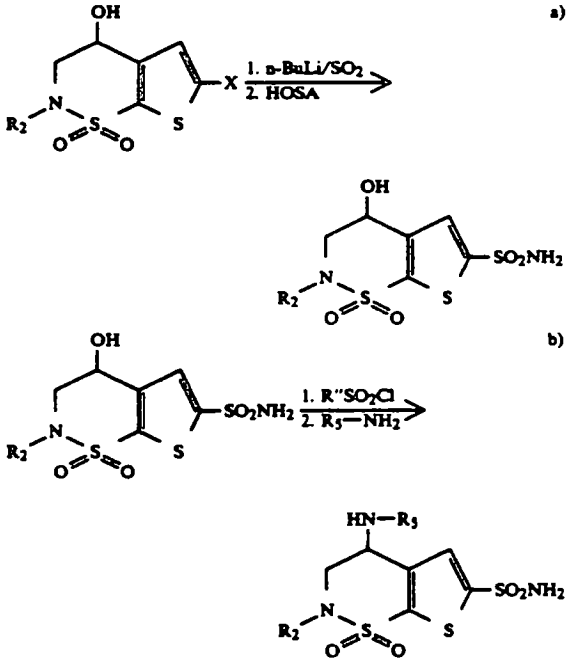


Yet other desirable compounds of Structure I are better prepared according to Equation 6 where the cyclic intermediate from Equation 4 is sulfamoylated (see Equation 5b) at position six (Equation 6a) followed by conversion of the hydroxyl group to a sulfonate ester (e.g. R'' is p-toluyl or methyl) and reaction of this intermediate with the desired alkylamine (Equation 6b).

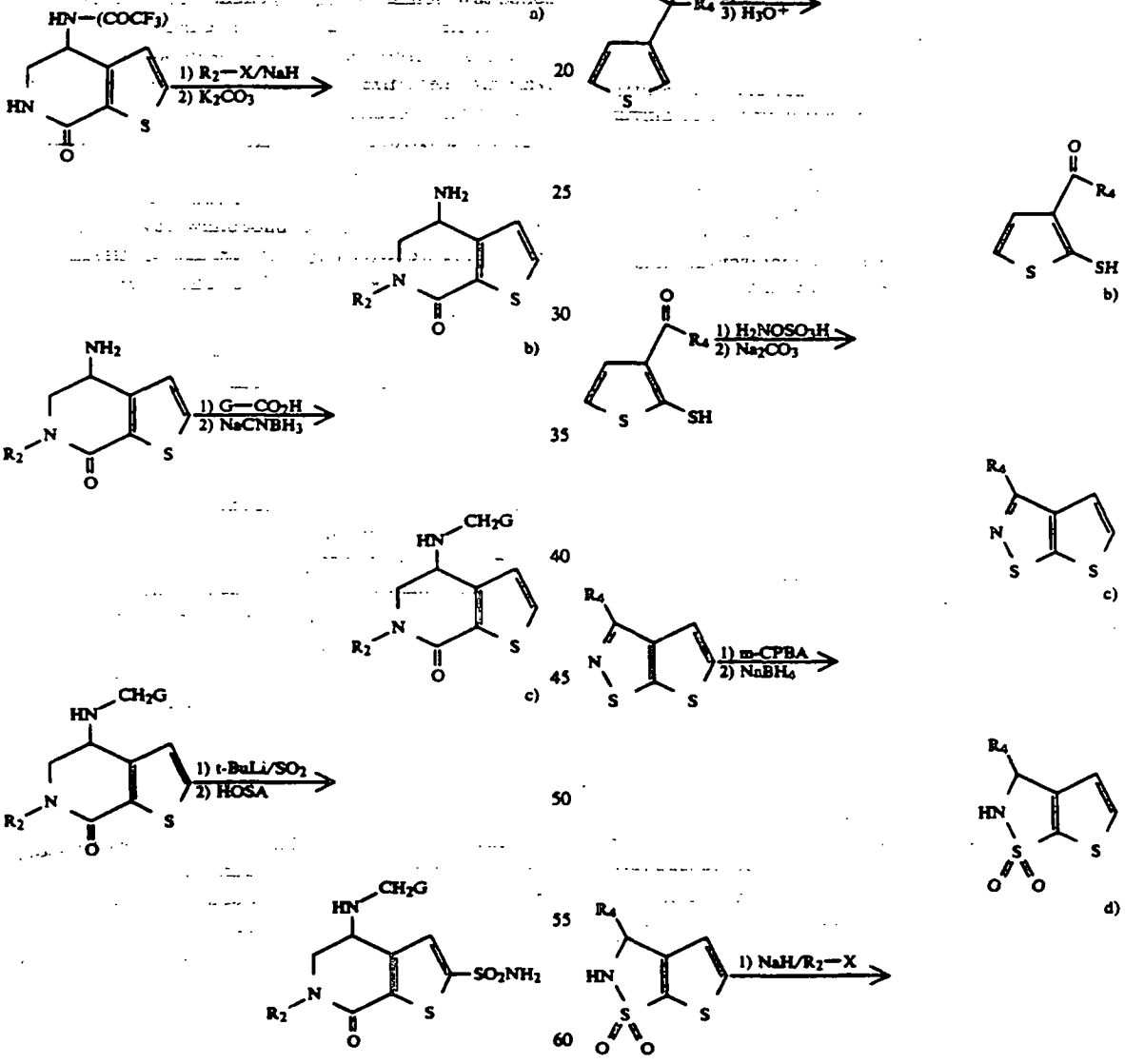
Equation 6



Still other desirable compounds of Structure I can be prepared (Equation 7) from an appropriate thienylethanol; these intermediate alcohols can be readily prepared by procedures well known in the art, e.g. reaction of thienyl-3-acetaldehyde with an appropriate Grignard reagent. Sulfamoylation of such alcohols by the procedures described in Equations 1a and 1d provide exclusively the desired thiophene-2-sulfonamide intermediates of Equation 7a. Cyclization to the desired bicyclic

b]pyridine [Heterocycles, 27, 1637 (1988)] with the requisite R_2 group using standard alkylation procedures followed by hydrolysis of the amide provides the primary amine as shown in Equation 9a. This intermediate primary amine can be selectively transformed to more desirable secondary amines using well known methods of reductive amination, that is treatment with the desired aldehyde and a suitable reducing agent, or reductive alkylation, that is reaction with the requisite carboxylic acid and a suitable reducing agent [Equation 9b; G is H or loweralkyl (C_{1-4})]. Introduction of the primary sulfonamide can be accomplished as previously described in Equations 1a, 1b, and 1d, but preferably using t-butyllithium as the base (Equation 9c).

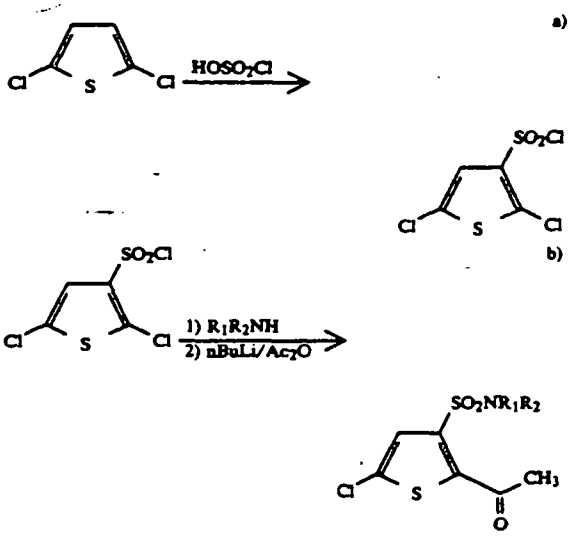
Equation 9



Certain cyclic compounds of Structure I, such as the 2,3-dihydrothienoisothiazoles, can be obtained through the modification of an existing cyclic compound (Equation 10). The metallated ketals of Equation 3 can be readily converted to the desired intermediate mercaptoketones as shown in Equation 10a, and the oxime O-esters of such compounds can be cyclized according to Equation 5b. Oxidation and subsequent reduction of the thienoisothiazole by procedures well known in the art provides the intermediate cyclic sulfonamides shown in Equation 10c. These cyclic sulfonamides can be substituted on nitrogen utilizing standard alkylation procedures such as demonstrated by Equation 10d. Incorporation of the primary sulfonamide into position five of these examples of Structure I can be accomplished under the basic conditions demonstrated by Equations 1a-d. Equation 10

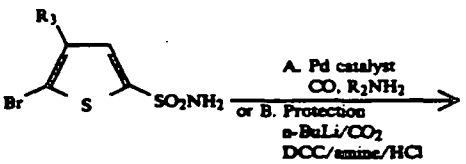
Chlorosulfonation of this starting material followed by amination using methods similar to those described in Equation 2 will provide the desired thiophene-3-sulfonamide (Equation 12a). Subsequent treatment of this intermediate with n-butyllithium at low temperature followed by quenching with acetic anhydride will give rise to the ketone of Equation 12b. This key intermediate can then be converted into the desired novel compounds of Structure I using substantially the same general methods described in Equations 4–6.

Equation 12



Still other desirable compounds of Structure I, such as 5-sulfamoyl-thiophene-2-carboxamides, can be prepared according to Equation 13. Treatment of the readily prepared 5-bromo-thiophene-2-sulfonamides under palladium mediated amidation reaction conditions [see for example *J. Org. Chem.*, 39, 3327 (1974)] in the presence of the desired amine component provides the novel compounds of Structure I. Alternately, 5-bromo-thiophene-2-sulfonamides can be initially protected, such as with the formamidine group, followed by treatment with a strong organometallic base, such as n-butyllithium or LDA, and carbon dioxide to give the intermediate carboxylic acid. Treatment of this intermediate acid with an activating agent, such as dicyclohexylcarbodiimide or triphenylphosphine triflate, followed by reaction with the desired amine component provides, following deprotection, the desired compounds of Structure I.

Equation 13



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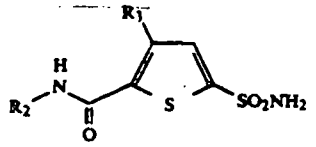
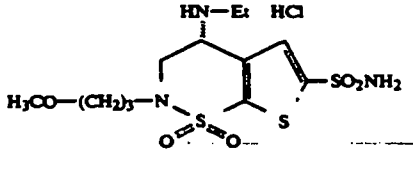


The compounds of Structure I can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride and water to form an aqueous, sterile ophthalmic suspensions or solutions. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940 or the like according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. Ophthalmic solution formulations may be prepared by dissolving the active ingredient in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the active ingredient. Furthermore, the ophthalmic solution may contain a thickener such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like to improve the retention of the medicament in the conjunctival sac.

The compounds are preferably formulated as topical ophthalmic suspensions or solutions, with pH of about 4.5 to 7.8. The compounds will normally be contained in these formulations in an amount of 0.1% to 10% by weight, but preferably in an amount of 0.25% to 5.0% by weight. Thus, for topical presentation 1 to 3 drops of these formulations would be delivered to the surface of the eye 1 to 4 times a day according to the routine discretion of a skilled clinician.

The following examples, which are in no way limiting, illustrate the preparation of selected examples of the novel compounds of Structure I. The compounds set forth in Examples 1, 4–4, 4–5, 4–8, 4–9, 5–2, 5–4, 7, and 8 represent the preferred thiophene sulfonamides of this invention. The compounds represented in Examples 1, 7, and 8 are most preferred.

Example 1



(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

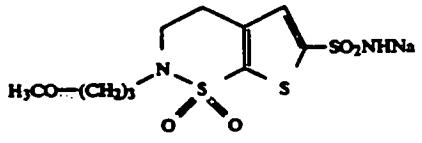
Step I:
(S)-3,4-Dihydro-4-hydroxy-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide

To a solution of the product of Step H (2.6 g, 7.34 mmol) in THF (30 mL) at −78° C. was added a solution of (+)-β-chlorodiisopinocampheylborane (11.8 g, 36.7 mmol) in THF (10 mL). The reaction mixture was allowed to warm to −20° C. and kept at this temperature for 4 days. Diethanolamine (4.2 mL, 44 mmol) was added to the reaction mixture and the solution stirred for 30 min, diluted with EtOAc (150 mL), washed with water (2×50 mL) and brine (2×50 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 2.4 g (92%) of the desired compound as a colorless foam.

Step J:
(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride

To a solution of the product from Step I (2.4 g, 6.74 mmol) and triethylamine (3.8 mL, 27 mmol) in anhydrous tetrahydrofuran (20 mL) cooled to −20° C. was added tosyl chloride (2.6 g, 13.5 mmol); this mixture was allowed to warm to room temperature and stirred for 18 hr. The reaction mixture was cooled to −60° C. and ethylamine (10 mL) was added and the mixture was again allowed to warm to room temperature. After 18 hr the reaction mixture was diluted with ethyl acetate (200 mL), washed with a saturated aqueous solution of sodium bicarbonate (3×50 mL), dried ($MgSO_4$), and evaporated to give the crude product which was purified by column chromatography [silica; CH_3OH/CH_2Cl_2(20:1)] to give 1.3 g (52%) of the desired amine. The free base was dissolved in ethanol (5 mL) and treated with a 2M solution of hydrochloric acid in ethanol (4 mL) at room temperature. Evaporation of the solvent provided a solid which was recrystallized from methanol: methylene chloride to give 950 mg (34%) of the desired product; mp 175°-177° C.; $[\alpha]_D$+10.35° (C=1.00, H_2O). Analysis. Calculated for $C_{12}H_{22}ClN_3O_5S_3$: C, 34.32; H, 5.28; N, 10.00 Found: C, 34.26; H, 5.23; N, 9.92.

EXAMPLE 2



3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide sodium salt

Step A:
3,4-Dihydro-4-hydroxy-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine- 1,1-dioxide

The product from Example 1, Step C (2.0 g, 9.74 mmol) was added to a suspension of sodium hydride (0.4 g, 10.0 mmol, of a 60% suspension in mineral oil) in DMF (30 mL) and the mixture was stirred for 1 hr. then cooled to 20° C. 3-Bromopropyl methyl ether (1.5 g, 9.74 mmol) was added and the mixture was stirred overnight then quenched with water (200 mL), and extracted with ethyl acetate (4×30 mL). The extracts were combined, washed with water (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure which provided an oil which was purified by column chromatography (silica, gradient: hexane to ethyl acetate) to give 1.7 g (63%) of a clear oil which was not purified further.

Step B:
3,4-Dihydro-2-(3-methoxypropyl)-4-O-phenoxythiocarbonyl-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step A (1.68 g, 6.06 mmol) and DMAP (1.48 g, 12.11 mmol) were dissolved in 1,2-dichloroethane (16 mL) and cooled in an ice bath. Phenoxythiocarbonyl chloride (1.26 mL, 9.09 mmol) was added slowly and the reaction mixture was stirred at room temperature overnight, then quenched with water (40 mL). The mixture was extracted with dichloromethane (3×10 mL) and the extracts were combined, washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica, gradient: nexane to 3:1 hexane/ethyl acetate) to give 1.75 g (70%) the desired product as an oil which was used in the next step.

Step C:
3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step B (1.75 g, 4.23 mmol) and AIBN (100 mg) were mixed with dry benzene (12 mL) and degassed under nitrogen. The mixture was heated to reflux and tributyltin hydride (1.2 mL, 4.44 mmol) was added rapidly dropwise to maintain a gentle reflux. Heating was continued for 30 min and the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica, gradient: hexane to 3:1 hexane/ethyl acetate) to provide the desired product (1.06 g, 95%) as a clear oil.

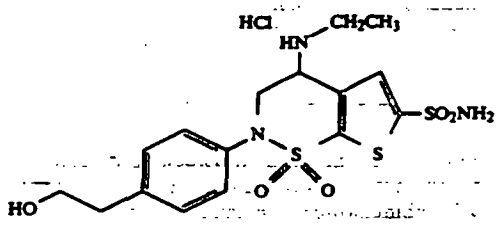
Step D:
3,4-Dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thinzine-6-sulfonamide 1,1-dioxide sodium salt

The product form Step C (1.03 g, 3.94 mmol) was dissolved in dry THF (20 mL) and cooled (−65° C.) under nitrogen. n-Butyllithium (2.1 mL of a 2.1M solution in hexanes) was added dropwise and the mixture was stirred for 45 min, then excess sulfur dioxide was introduced into the flask until the solution tested acidic to moist litmus paper. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (25 mL) and sodium acetate trihydrate (2.68 g, 19.7 mmol) then hydroxylamine-O-sulfonic acid (1.34 g, 11.8 mmol) were added and the mixture was stirred at room temperature for 16 hr followed by extraction with ethyl acetate (5×5 mL). The extracts were combined, washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica, gradient: 3:1 hexane/ethyl acetate to 7:3 methylene chloride/methanol) which gave the desired product (1.21 g, 69%) as an amber syrup which was converted to the sodium salt as follows: The residue was dissolved in 2N NaOH (1.78 mL, 3.56 mmol), then mixed with ethanol (1.8 mL) and cooled. Ethyl ether was added to the cloud point and the product precipitated from the solution. The solids were collected and

By following the above general procedure but using the appropriate arylalkyl halide in Step B and either n-propylamine or ethylamine in Step C the following compounds were prepared:

1. 3,4-Dihydro-2-(3-phenylpropyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 124°-127° C.
2. 3,4-Dihydro-2-(4-phenylbutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 120°-125° C.
3. 4-Ethylamino-3,4-dihydro-2-(2-thienyl)methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 182°-184° C.

EXAMPLE 4



4-Ethylamino-3,4-dihydro-2-[4-(2-hydroxyphenyl)phenyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A: 3-Acetyl-2-(phenylmethyl)thio-5-chlorothiophene

A mixture consisting of thiourea (858.4 g, 11.28 mol), benzyl bromide (1,930 g, 11.28 mol), THF (9000 ml), and water (3000 ml) was heated at reflux temperature for 2 hr followed by cooling to 50° C. To this solution was added 3-acetyl-2,5-dichlorothiophene (2000 g, 10.25 mol) and an aqueous solution of sodium hydroxide (2,200 g of 50% NaOH diluted to 3000 ml); this mixture was heated at reflux temperature for 4 hr, cooled to room temperature, and the two layers separated. The organic layer was diluted with ethyl acetate (6000 ml) and washed with water (3×2000 ml) and saturated aqueous sodium chloride, dried ($MgSO_4$), and the solvent evaporated to give a residue which was triturated with hexane. This solid was collected by filtration and dried to give the desired product (2,550 g, 88%): mp 86°-88° C.

Step B: 3-Acetyl -5-chloro-N-[4-(2-hydroxyethyl)phenyl]-thiophene-2-sulfonamide

The product from Step A (15 g, 0.058 mol) was dissolved in glacial acetic acid (150 mL), water (15 mL) was added and the solution cooled to 3° C. Chlorine gas was slowly passed through the solution until the temperature reached 15° C. at which point the mixture was cooled to 5° C. before the addition of chlorine was continued; this sequence was repeated four times. The reaction mixture was poured into ice water (400 mL) and extracted with methylene chloride (3×200 mL). The combined extracts were washed with cold saturated aqueous $NaHCO_3$ (2×250 mL), dried ($MgSO_4$), and evaporated. The sulfonyl chloride obtained from this procedure was dissolved in THF (50 mL) and added to a solution of 4-(hydroxyethyl)aniline (16 g, 0.116 mol) in THF (100 mL); this mixture was stirred for 2 days followed by evaporation of the solvent. The residue was suspended in 1M HCl and extracted with methylene chloride (2×100 mL). The combined extracts were washed with 1N HCl and then dried ($MgSO_4$), filtered, and evaporated to a syrup which was purified by column chromatography (silica, gradient: 3% to 5% ethanol/methylene chloride) to provide a yellow solid (11.6 g, 56%): mp 112°-116° C.

Step C: 6-Chloro-3,4-dihydro-2-[4-[2-(t-butyldiphenylsiloxy)ethyl]phenyl]-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step B (11.5 g, 0.032 mol) was added to DMF (100 mL) containing imidazole (5.44 g, 0.08 mol) and t-butyldiphenylsilyl chloride (9.34 mL, 0.035 mol) and stirred at room temperature for 18 hr. The reaction mixture was evaporated to dryness and the residue was suspended in methylene chloride and filtered. The filtrate was concentrated and chromatographed (silica, methylene chloride) to provide a solid which was dissolved in THF (200 mL) and cooled to 5° C. A solution of pyridinium bromide perbromide (11.23 g, 0.035 mol) in THF (50 mL) was added dropwise and this mixture was stirred at 5° C. for 1 hr, at ambient temperature for 1 hr, and then evaporated to dryness. The residue was suspended in ethanol (150 mL) and cooled to 5° C. followed by the addition of sodium borohydride (3.59 g, 95 mmol). The reaction mixture was maintained at room temperature for 1 hr and then heated at reflux temperature for 1.5 hr. Water was carefully added and the ethanol evaporated. The aqueous mixture was neutralized and extracted with ethyl acetate (2×200 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 15% ethyl acetate/hexane) to provide an amber syrup (8.2 g, 44%).

Step D: 2-[4-[2-(t-Butyldiphenylsiloxy)ethyl]phenyl]-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Step C (8.2 g, 14 mmol) was dissolved in dry THF (50 mL) along with p-toluenesulfonic acid (0.5 g) and the solution cooled to 5° C. with an ice bath. Ethyl vinyl ether (2.62 mL, 27 mmol) was added and the reaction mixture was stirred for 0.5 hr. Saturated aqueous sodium bicarbonate (75 mL) was added to the reaction mixture followed extraction with ethyl acetate (2×50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by-column chromatography (silica, 20% ethyl acetate/hexane) to provide an oil (7.62 g, 83%). This material was dissolved in dry THF (70 mL) under nitrogen and cooled to −65° C. n-BuLi (15 mL of a 1.76M solution, 26 mmol) was added dropwise, after 0.5 hr the reaction mixture was treated with sulfur dioxide until the dark solution turned yellow, stirring continued for 0.5 hr at room temperature. Evaporation of the solvent provided a residue which was suspended in water (50 mL) containing sodium acetate (7.7 g, 57 mmol) and hydroxylamine-O-sulfonic acid (3.88 g, 34 mmol). This mixture was stirred at room temperature for 18 hr and then treated with 6N HCl (5 mL) for 3 hr followed by extraction with ethyl acetate (2×60 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, gradient: 4% to 5% ethanol/methylene chloride)

from an additional funnel over 15 minutes, causing the temperature to rise to 15° C. The mixture was warmed to 20° C. over 30 minutes and then was stirred vigorously at ambient temperature for 15 hours without external temperature control. Water (5 L) was added, and the phases were split. The organic phase was washed sequentially with saturated aqueous sodium chloride (5 L), 10% aq. sodium bisulfite (5 L), saturated aqueous sodium chloride (5 L), 10% aq. sodium bicarbonate (10 L), and saturated aqueous sodium chloride (10 L). It was then dried over sodium sulfate (1 kg), filtered, and stripped of solvent by rotary evaporation. The residual solid was triturated with t-butyl methyl ether (3 L) and the mixture was chilled for 15 minutes. The solid was collected by filtration, washed with t-butyl methyl ether (1 L), and dried in air at ambient temperature to give the desired product (666 g, 79%): mp 178°-179° C.; Analysis. Calculated for $C_6H_6ClNO_3S_2$: C, 30.06; H, 2.52; N, 5.84; S, 26.75. Found: C, 30.19; H, 2.51; N, 5.80; S, 26.70.

Step B:
3-(2-Bromoacetyl)-5-chloro-thiophene-2-sulfonamide

A 50-L, 5-necked flask equipped with a mechanical stirrer, a thermometer, and a 1 L addition funnel was charged with the product from Step A (1.087 kg, 4.55 mol) and ethyl acetate (22 L). The pale yellow suspension was cooled to 1° C. over 45 minutes using an ice-water bath and 90% pyridinium bromide perbromide (1.305 kg, 3.67 mol) was added in one portion. Sulfuric acid (544 mL) was added via the addition funnel over 10 minutes causing the temperature to rise to 5° C. The reaction mixture was stirred and, after 1 hour, TLC analysis indicated complete reaction. Thirty minutes later, water (5 L) was added and the mixture was stirred for 5 minutes before the phases were split. The organic phase was washed with saturated aqueous sodium chloride until the pH of the wash was 3 (4×5 L), dried over sodium sulfate (1 kg), filtered, and stripped of solvent by rotary evaporation. The residue was triturated with methylene chloride (2 L) and chilled for 15 minutes before the solid was collected by filtration, washed with cold methylene chloride (2 L), and dried to give the desired product (1.041 kg, 72%): mp 147°-148° C. Analysis. Calculated for $C_6H_5BrClNO_3S_2$: C, 22.62; H, 1.58; N, 4.40; S, 20.13. Found: C, 22.66; H, 1.60; N, 4.35; S, 20.12.

Step C:
(S)-6-Chloro-3,4-dihydro-4-hydroxy-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

A 50-L, 5-necked flask equipped with a mechanical stirrer and a thermometer was flushed with nitrogen overnight. Working under nitrogen, the flask was charged with the product from Step B (855 g, 2.68 mol) and t-butyl methyl ether (MTBE, 12.5 L). The stirred suspension was cooled to −40° C. using a dry-ice/2-propanol bath and (+)-β-chlorodiisopino-campheylborane (4.5 L of a 1.2M solution in MTBE, 5.4 mol) was added via a cannula over 30 minutes, causing the temperature to rise to −32° C. The reaction mixture was maintained between −25 to −20° C. for 3.5 hours. The mixture was warmed to 0° C. and 1M sodium hydroxide (11 L) was added from an addition funnel over 10 minutes, causing the temperature to rise to 22° C. The biphasic mixture was stirred vigorously at ambient temperature for 2 hours, after which TLC analysis indicated complete cyclization. The phases were split, and the dark aqueous layer was extracted with t-butyl methyl ether (3 L), acidified to pH 1 using concentrated hydrochloric acid, and extracted with ethyl acetate (2×4 L).

The combined ethyl acetate extracts were washed with saturated aqueous sodium chloride (3 L), dried over sodium sulfate (1 kg), filtered, and concentrated to a volume of about 1 liter by rotary evaporation, at which point toluene (2 L) was added. As the remainder of the ethyl acetate was removed, the product crystallized from toluene. It was collected by filtration, washed with toluene (2 L) and methylene chloride (2 L), and dried in air at ambient temperature (498 grams 77%): mp 126°-127° C.; $[\alpha]^{25}_D$−5.9° (c=1, CH_3OH). Analysis. Calculated for $C_6H_6ClNO_3S_2$: C, 30.06; H, 2.52; N, 5.84. Found: C, 30.14; H, 2.56; N, 5.80.

Step D:
(S)-6-Chloro-3,4-dihydro-4-hydroxy-2-(2-phenylethyl)-2H-thieno[3,2-e]-1,2-thiazine 1,1-dioxide

The product from Step C (1.5 g, 6.2 mmol) was added to a suspension of potassium carbonate (2.14 g, 15.5 mmol) in ethanol (25 mL) and phenethyl bromide (2.1 mL, 15.4 mmol) was added in three equal portions over a 24 hr period; stirring continued for 64 hr. The reaction mixture was evaporated and the residue suspended in water which was extracted with ethyl acetate (30 mL). The organic layer was dried ($MgSO_4$) and evaporated to a residue which was partially purified by column chromatography (silica, 3% ethanol/methylene chloride) to give 2.16 g of crude product (consisting of a 1:2 mixture of phenethyl bromide and the desired product) as a yellow oil; this material was used in the next step without further purification.

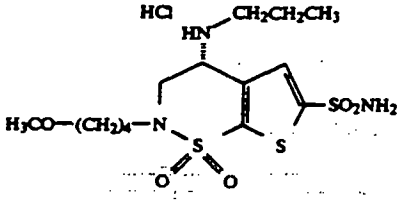
Step E:
(S)-3,4-Dihydro-4-hydroxy-2-(2-phenylethyl)-2H-thieno[3,2-e]-1,2thiazine-6-sulfonamide 1,1-dioxide

The product from Step D (1.36 g, 3.96 mmol) was dissolved in dry THF (25 mL) along with p-toluenesulfonic acid (0.11 g, 0.6 mmol) and the solution cooled to 5° C. at which point ethyl vinyl ether (1.16 mL, 12.1 mmol) was added. After stirring this mixture for 40 min, saturated aqueous sodium bicarbonate (15 mL) was added followed by extraction with ethyl acetate (40 mL). The organic layer was dried (Na_2SO_4), evaporated, and the residue dissolved in THF (40 mL) under nitrogen. The solution was cooled to 60° C. and n-BuLi (4.1 mL of a 1.76M solution, 7.2 mmol) was added dropwise followed by stirring for 30 min and the introduction of sulfur dioxide until the green solution turned yellow. The cooling bath was removed and the reaction mixture stirred for 1 hr.

Evaporation of the solvent provided a residue which was suspended in water containing sodium acetate (4.89 g, 36 mmol) and hydroxylamine-O-sulfonic acid (2.73 g, 24 mmol); this mixture was stirred for 5 hr. The reaction mixture was acidified to pH 1 with 6N HCl and stirred at room temperature for 18 hr followed by extraction with ethyl acetate (2×50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue which was purified by column chromatography (silica, 5% ethanol/methylene chloride) to give the desired product as an oil which crystallized upon standing (1.14 g, 75%): mp 117°-119° C.

2. 3,4-Dihydro-2-(2-methoxyethyl)-3-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide, mp 106°–108° C.

EXAMPLE 7



R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

Step A: N-(1,1-Dimethylethyl)-3,4-dihydro-4-hydroxy-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

The product from Example 3, Step A (8.75 g, 0.26 mol) was dissolved in DMF (25 mL) and the solution was cooled to −0° C. Sodium hydride (1.56 g of an oil dispersion, 0.03 mol) was added, stirred for 30 min, and then 4-methoxybutyl bromide (8.6 g,0.052 mol) in DMF (15 mL) was added; this mixture was warmed to room temperature and stirred for 15 hr. A saturated aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (5×50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography (silica, gradient: 50% to 60% ethyl acetate/hexane) to give the desired product (9.5 g, 86%) as a yellow oil.

Step B: N-(1,1-Dimethylethyl)-3,4-dihydro-2-(4-methoxybutyl)-4-oxo-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of the product from Step A (9.5 g, 0.022 mol) in acetone (20 mL) at −10° C. was added freshly prepared Jones reagent (10 mL) and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated and saturated aqueous sodium bicarbonate was added until the pH of the solution was 6. The aqueous mixture was extracted with ethyl acetate (4×50 mL). The combined extracts were washed with brine (2×10 mL), dried ($MgSO_4$) and evaporated to provide a yellow solid (7.5 g, 78%).

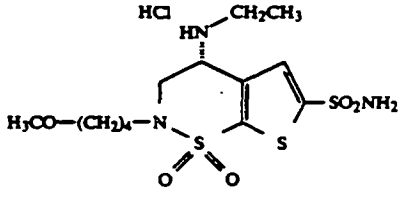
Step C: (S)-N-(1,1-Dimethylethyl)-3,4-dihydro-4-hydroxy-2-(4-methoxybutyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

To a solution of (+)-β-chlorodiisopinocamphenylborane (28.01 g, 0.087 mol) in THF (60 mL) at −20° C. was added a solution of the product from Step B (7.4 g, 0.017 mol) in THF (90 mL); this mixture was stirred for 40 hr while maintaining this temperature. Diethanolamine (9.13 g, 0.087 mol) was added to the reaction mixture which was allowed to warm to room temperature and stirred at this temperature for 2 hr. Evaporation of the THF gave a residue which was dissolved in ethyl acetate (100 mL); this solution was washed with water (100 mL). The aqueous layer was separated and extracted with ethyl acetate (3×50 mL). The ethyl acetate extracts were combined, washed with brine (2×20 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by column chromatography (silica, 60% ethyl acetate/hexane) to give an oil (6.4 g, 86%).

Step D: R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride

To a solution of the product from Step C (5.4 g,0.013 mol) in THF (40 mL) at 0° C. was added triethylamine (5.38 g, 0.053 mol) followed by p-toluenesulfonyl chloride (5.07 g,0.027 mol) and the mixture was stirred for 2 hr. The reaction mixture was divided into two equal volumes, one of which was treated with propylamine (15 mL) at 0° C. for 15 hr. The excess propylamine was evaporated and the solution diluted with water (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a crude product which was purified by column chromatography (silica, gradient: 50% to 70% ethyl acetate/hexane). The free base was dissolved in ethanol (10 mL) and treated with ethanolic hydrogen chloride. Evaporation gave a solid which was recrystallized from isopropanol to give the desired product as a white solid (1.4 g, 26%): mp 183°–185° C.; $[\alpha]_D$+27.2° (c=0.43, CH_3OH). Analysis: Calculated for $C_{14}H_{26}ClN_3O_5S_3$-0.5 H_2O: C, 36.79; H, 5.95; N, 9.19. Found: C, 37.08; H, 6.34; N, 8.82.

EXAMPLE 8



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

The second portion of the intermediate tosylate prepared in Example 7, Step D was treated with ethylamine (18 mL) at 0° C. for 15 hr. By proceeding in a manner analogous to that already described in Example 7, Step D the title compound was obtained (2.4 g, 46%): mp 129°–130° C.; $[\alpha]_D$+23.6° (c=0.49, CH_3OH). Analysis. Calculated for $C_{13}H_{24}ClN_3O_5S_3$: C, 35.97; H, 5.57; N, 9.68. Found: C, 35.80; H, 5.84; N, 9.41.

Using modifications of the procedures described above and in Examples 7 but substituting the appropriate alkyl halide in Step A and the desired alkylamine in Step D the following compounds were prepared:

1. R-(+)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 200°–201° C;
2. R-(+)-4-Allylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, 202°–205° C.;
3. R-(+)-3,4-Dihydro-2-(4-hydroxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, mp 197°–198° C.;

-continued

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

Step A:

(R)-3,4-Dihydro-4-hydroxy-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

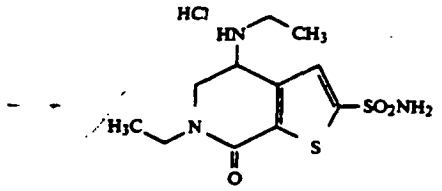
To a solution of (−)-β-chlorodiisopinocampheylborane (20.4 g, 63.5 mmol) in THF (20 mL) at −20° C. was added a solution of the product from Example 1, Step H (4.5 g, 12.7 mmol) in THF (60 mL) at −20° C.; this mixture was stirred for 48 hr maintaining this temperature. Diethanolamine (6,6 g, 63.5 mmol) was added and the solution allowed to warm to room temperature. The solvent was evaporated and the residue suspended in water (50 mL). This mixture was extracted with ethyl acetate (5×50 mL), and the combined extracts were washed with brine (15 mL), dried ($MgSO_4$), and evaporated to a syrup which was purified by column chromatography (silica, gradient: 50% to 60% ethyl acetate/-hexane) to give a white solid (3.9 g, 85%); mp 109°-111° C. Analysis: Calculated for $C_{10}H_{16}N_2O_6S_3$: C, 33.69; H, 4.53; N, 7.86. Found: C, 33.74; H, 4.48; N, 7.85.

Step B:

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

To a solution of the product from Part A (2.81 g, 7.9 mmol) in acetonitrile (10 mL) at room temperature was added dimethylformamide dimethyl acetal (1.16 mL, 8.6 mmol); this solution was stirred for 2 hr and evaporated to dryness. The crude product was purified by chromatography (silica, 50% ethyl acetate/hexane) to give the desired protected sulfonamide derivative. This compound (2.54 g, 5.6 mmol) was dissolved in DMF (15 mL), cooled to 0° C., and sodium hydride (0.33 9 of a 60% oil dispersion, 8.33 mmol) was added. After stirring for 30 min, ethyl iodide (1.3 g, 8.3 mmol) was added and stirring continued, but at room temperature, for 2 hr. A saturated aqueous solution of ammonium chloride (50 mL) was added and the mixture extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a residue which was dissolved in ethanol (3 mL), acetic acid (6 mL) and hydrazine (1.4 mL) were added and the mixture was heated at 55° C. for 24 hr. After cooling to room temperature, saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with ethyl acetate (4×50 mL) The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated to a residue which was purified by column chromatography (silica, gradient: 30% to 50% ethyl acetate/hexane) to give a syrup (500 mg). $[\alpha]_D$ −3.91° (c=0.67, CH_3OH). Analysis. Calculated for $C_{12}H_{20}N_2O_{63}$: C, 37.48; H, 5.24; N, 7.29. Found: C, 37.61; H, 5.25; N, 7.18.

EXAMPLE 11



6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine-2-sulfonamide hydrochloride

Step A: 6-Ethyl-4,5,6,7-tetrahydro-4-(trifluoroacetamino)-7-oxo-thieno[2,3-b]pyridine

After cooling a solution of 4,5,6,7-tetrahydro-4-(trifluoroacetamino)-7-oxo-thieno[2,3-b]pyridine (1.0 g, 3.8 mmol) in DMF (10 mL) to −20° C., sodium hydride (273 mg, 11.4 mmol of a 60% oil dispersion) was added followed by ethyl bromide (1.7 mL, 22.7 mmol). This mixture was allowed to warm to room temperature. Stirring continued at this temperature for an additional hour and then the mixture was poured into ice water (100 mL). This aqueous mixture was extracted with ethyl acetate (4×100 mL) and the combined extracts were washed with brine (2×50 mL), dried ($MgSO_4$), and concentrated to a crude oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give a yellow solid (0.85 g, 77%): mp 136°-138° C.

Step B:

6-Ethyl-4-amino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine

To a solution of the product from Step A (4.5 g, 15.4 mmol) in 50% aqueous methanol (80 mL) was added potassium carbonate (3.2 g, 23 mmol) and the mixture stirred at room temperature for 5 hr. The methanol was evaporated and the remaining aqueous mixture was acidified (pH 3), extracted with ethyl acetate (100 mL), the pH was adjusted to 9 and again extracted with ethyl acetate (3×200 mL). The combined extracts were evaporated to an oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give the desired product as a yellow oil (2.7 g, 70%).

Step C:

6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine

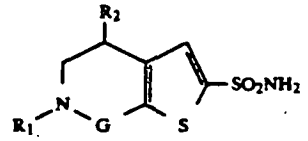
To a solution of the product from Step B (2.7 g, 13.8 mmol) in methanol (20 mL) at room temperature was added acetic acid (790 mL, 13.8 mmol) and sodium cyanoborohydride (867 mg, 13.8 mmol). After stirring this mixture for 18 hr concentrated HCl (1 mL) was added; when the evolution of gas ceased, the pH of the mixture was adjusted to 9 with 50% NaOH. The solvent was evaporated and the residue dissolved in ethyl acetate (200 mL); this solution was washed with brine (2×50 mL), dried ($MgSO_4$), and evaporated to an oil which was purified by column chromatography (silica, 5% methanol/methylene chloride) to give the desired product (1.85 g, 62%).

Step D:

6-Ethyl-4-ethylamino-4,5,6,7-tetrahydro-7-oxo-thieno[2,3-b]pyridine-2-sulfonamide hydrochloride

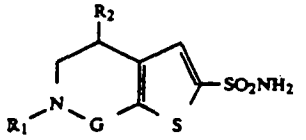
After cooling a solution of the product from Step C (1.7 g, 7.6 mmol) in THF (10 mL) to −78° C., a 1.7M

TABLE 1



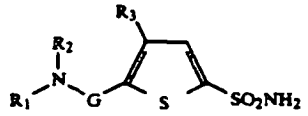
G	R_1	R_2
SO_2	CH_2CO_2-i-Pr	NH-n-Pr
SO_2	CH_2CO_2-i-Pr	NHEt
SO_2	$(CH_2)_3CO_2$-i-Pr	NHEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	H
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OH
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	OCH_2CH_2OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	CH_2CH_3
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	CH_2OMe
SO_2	$(CH_2)_2N(CH_2CH_2)_2S$	NHEt
SO_2	$(CH_2)_2N(CH_2CH_2)_2SO_2$	OH
SO_2	CH_2CCH	NHEt
SO_2	$CH_2CCCH_2OCH_3$	NHEt
SO_2	$CH_2CONHMe$	NHEt
SO_2	$(CH_2)_2CONH(CH_2)_2OH$	NHEt
SO_2	C_6H_4—(3-OEt)	NHEt
SO_2	C_6H_4—(3-OH)	NHEt
SO_2	C_6H_4—(3-OH)	NH-n-Pr
SO_2	C_6H_4—(3-OMe)	NHEt
SO_2	C_6H_4—(4-OH)	NHEt
SO_2	C_6H_4—(4-OMe)	NHEt
SO_2	C_6H_4—(3-$OCHF_2$)	NHEt
SO_2	C_6H_4—(4-SO_2Me)	NHEt
SO_2	C_6H_4—(4-NHCOMe)	NHEt
SO_2	C_6H_4—(4-$CONMe_2$)	NHEt
SO_2	C_6H_3—(4-OH)—(3-CH_2NMe_2)	OEt
SO_2	C_6H_3—(4-OH)—(3-CH_2NMe_2)	H
SO_2	C_6H_3—(3,4-OH)	NHEt
SO_2	C_6H_3—(3,4-OMe)	NHEt
SO_2	C_6H_4—(4-$COCH_3$)	NHEt
SO_2	$CH_2C_6H_4$—(3,4-OMe)	NHEt
SO_2	$CH_2C_6H_3$—(4-OH)—(3-CH_2NMe_2)	OEt
SO_2	$CH_2C_6H_4$—(4-OMe)	NHEt
SO_2	$CH_2C_6H_4$—(3-OH)	NHEt
SO_2	CH_2[(2-CO_2Et)-pyridin-4-yl]	NHEt
SO_2	CH_2[(5-CO_2iPr)-thieno-2-yl]	NHEt
SO_2	$(CH_2)_3OH$	OH
SO_2	$(CH_2)_4OH$	OH
SO_2	$(CH_2)_5OH$	OH
SO_2	$(CH_2)_6OH$	OH
SO_2	$(CH_2)_4OH$	OEt
SO_2	$(CH_2)_4OH$	NH-n-Pr
SO_2	$(CH_2)_4OH$	NH-i-Bu
SO_2	$(CH_2)_3OCH_3$	OEt
SO_2	$(CH_2)_2OCH_3$	OEt
SO_2	CH_2-2-thienyl	OH
SO_2	CH_2—C_6H_5	OH
SO_2	$(CH_2)_2CH(OH)CH_3$	NHEt
SO_2	$(CH_2)_3CH(OH)CH_3$	NHEt
SO_2	$(CH_2)_2CH(OCH_3)CH_3$	NHEt
SO_2	$(CH_2)_3OH$	H
SO_2	$(CH_2)_3OCH_3$	H
SO_2	$(CH_2)_3OCOCH_3$	NHEt
SO_2	$(CH_2)_4OCOCH_3$	NHEt
SO_2	$(CH_2)_4CO_2Et$	NHEt
SO_2	$(CH_2)_3CO_2Et$	NHEt
SO_2	$(CH_2)_2CO_2Et$	NHEt
SO_2	$(CH_2)_4CO_2$-i-Pr	NHEt
SO_2	$(CH_2)_5CH_3$	NHEt
SO_2	$(CH_2)_4CH_3$	NHEt
SO_2	$(CH_2)_3CH(CH_3)_2$	NHEt
SO_2	CH_2-2-thiazole	OH
SO_2	CH_2-2-oxazole	OH
SO_2	CH_2-2-pyrimidine	OH
SO_2	CH_2-3-pyridazine	OH
SO_2	CH_2-2-pyrazine	OH
SO_2	CH_2-3-isothiazole	OH
SO_2	CH_2-3-isoxazole	OH
CO	$(CH_2)_3CO_2$-i-Pr	NHEt
CO	C_6H_4—(3-OH)	NHEt
CO	C_6H_4—(3-OH)	NH-n-Pr
CO	C_6H_4—(3-OMe)	NHEt
CO	C_6H_4—(4-OH)	NHEt
CO	C_6H_4—(4-OMe)	NHEt
CO	C_6H_4—(3-$OCHF_2$)	NHEt

TABLE 1-continued



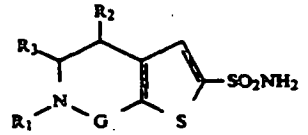
G	R_1	R_2
CO	C_6H_4—(4-SO_2Me)	NHEt
CO	C_6H_3—(4-OH)—(3-CH_2NMe_2)	OEt
CO	C_6H_3—(4-OH)—(3-CH_2NMe_2)	H
CO	C_6H_3—(3,4-OH)	NHEt
CO	C_6H_3—(3,4-OMe)	NHEt
CO	C_6H_4—(4-$COCH_3$)	NHEt
CO	$CH_2C_6H_4$—(3,4-OMe)	NHEt
CO	$CH_2C_6H_3$—(4-OH)—(3-CH_2NMe_2)	OEt
CO	$CH_2C_6H_4$—(4-OMe)	NHEt
CO	$CH_2C_6H_4$—(3-OH)	NHEt
CO	CH_2[(2-CO_2Et)-pyridin-4-yl]	NHEt
CO	CH_2[(5-CO_2iPr)-thieno-2-yl]	NHEt

TABLE 2



G	R_1	R_2	R_3
SO_2	$(CH_2)_2N(CH_2CH_2)_2O$	H	$COCH_3$
SO_2	$CH_2C_6H_4$—(3-OH)	CH_3	H
SO_2	$CH_2C_6H_4$—(3-OMe)	H	H
SO_2	$CH_2C_6H_4$—(4-OH)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-OMe)	H	H
SO_2	$CH_2C_6H_4$—(4-OH)	H	CH_2OEt
SO_2	$CH_2C_6H_4$—(4-$CONHMe$)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-SO_2NMe_2)	H	H
SO_2	$CH_2C_6H_4$—(3-SO_2Me)	H	CH_3
SO_2	$CH_2C_6H_4$—(4-$OCHF_2$)	CH_3	H
SO_2	$CH_2C_6H_3$—(4-OH)-3-(CH_2NMe_2)	CH_3	CH_3
SO_2	$CH_2C_6H_4$—(3-NHCOMe)	H	CH_3
SO_2	CH_2-4-pyridinyl	H	CH_3
SO_2	CH_2-2-pyridinyl	H	CH_3
SO_2	CH_2-2-thienyl	H	CH_3
SO_2	CH_2—(5-Me-2-thienyl)	H	H
CO	$(CH_2)_2N(CH_2CH_2)_2O$	H	$COCH_3$
CO	$CH_2C_6H_4$—(3-OH)	CH_3	H
CO	$CH_2C_6H_4$—(3-OMe)	H	H
CO	$CH_2C_6H_4$—(4-OH)	H	CH_3
CO	$CH_2C_6H_4$—(4-OMe)	H	H
CO	$CH_2C_6H_4$—(4-OH)	H	CH_3
CO	$CH_2C_6H_4$—(4-$CONHMe$)	H	CH_3
CO	$CH_2C_6H_4$—(4-SO_2NMe_2)	H	H
CO	$CH_2C_6H_4$—(3-SO_2Me)	H	CH_3
CO	$CH_2C_6H_4$—(4-$OCHF_2$)	CH_3	H
CO	$CH_2C_6H_3$—(4-OH)-3-(CH_2NMe_2)	CH_3	CH_3
CO	$CH_2C_6H_4$—(3-$NHCOMe$)	H	CH_3
CO	CH_2-4-pyridinyl	H	CH_3
CO	CH_2-2-pyridinyl	H	CH_3
CO	CH_2-2-thienyl	H	CH_3
CO	CH_2—(5-Me-2-thienyl)	H	H

TABLE 3



R_1	R_2	R_3
CH_3	H	$CH_2N(CH_2CH_2)_2O$
$(CH_2)_3OMe$	H	$CH_2N(CH_2CH_2)_2O$
$CH_2N(CH_2CH_2)_2O$	H	CH_2OH
$CH_2N(CH_2CH_2)_2O$	H	CH_2OMe
$CH_2N(CH_2CH_2)_2O$	H	CH_3

-continued

Ingredient	Concentration (wt %)
HCl/NaOH	pH 6.4

The above ingredients were mixed together in substantially the same manner as described in Example 18 to furnish the ophthalmic solution.

EXAMPLE 20

Ophthalmic Solution

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.19%
Hydroxypropylmethylcellulose	3.0%
Sodium Acetate trihydrate	0.1%
Mannitol (Osmolality = 288 mOsm)	2.4%
Benzalkonium Chloride	0.01%
Disodium Edetate	0.01%
Purified Water	q.s.
HCl/NaOH	pH 5.0

The above ingredients were mixed together in substantially the same manner as described in Example 18 to furnish the ophthalmic solution.

EXAMPLE 21

Ophthalmic Suspension

Ingredient	Concentration (wt %)
(+)4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride (Compound)	2.0%
Hydroxypropylmethylcellulose	0.5%
Dibasic Sodium Phosphate	0.2%
Disodium Edetate	0.01%
Sodium Chloride	0.8%
Purified Water	q.s
Benzalkonium Chloride	0.01%
Polysorbate 80	0.1%
NaOH/HCl	pH 7.1

The above ingredients can be mixed together in substantially the same manner as described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 22

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Hydroxypropylmethylcellulose	3.0%
Dibasic Sodium Phosphate	0.2%
Sodium Chloride	0.7%
Disodium EDTA	0.01%
Polysorbate 80	0.05
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients were mixed together using a procedure similar to that described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 23

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Hydroxypropylmethylcellulose	3.0%
Sodium acetate (trihydrate)	0.1%
Mannitol	4.1%
Disodium EDTA	0.01%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 5.0
Hydrochloric Acid	q.s. pH = 5.0
Water for Injection	q.s. 100%

The above ingredients were mixed together in a manner similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 24

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide (Compound)	2.0%
Carbomer 934P	0.5%
Sodium Chloride	0.4%
Mannitol	2.4%
Disodium EDTA	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients were mixed together using a method similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

EXAMPLE 25

Ophthalmic Suspension

Ingredient	Concentration (wt %)
R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride (Compound)	2.0%
Carbomer 934P	0.5%
Sodium Chloride	0.4%
Mannitol	2.4%
Disodium EDTA	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride Solution	0.01% + 5% xs
Sodium Hydroxide	q.s. pH = 7.2
Hydrochloric Acid	q.s. pH = 7.2
Water for Injection	q.s. 100%

The above ingredients can be mixed together using a method similar to the same general procedure described in Example 15 to furnish the ophthalmic suspension.

which can be unsubstituted or substituted optionally with C_1–C_3alkyl, C_1–C_3halo alkyl OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

5. The compound of Claim 4 wherein:

R_4 is OH; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; or NR_5R_6; phenyl, or R_{10} unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

6. The compound of Claim 1 wherein:

R_4 is OH; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; or NR_5R_6; phenyl, or R_{10}, unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0–2 and n is 0–2.

7. A compound selected from the group consisting of:

R-(+)-4-Ethylamino-3,4-dihydro-2-(3-methoxy)propyl-2H-thieno 1,2-thiazine-6-sulfonamide-1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-2-(4-hydroxy-phenyl)-3,4-dihydro-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxy-phenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(4-hydroxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-3,4-Dihydro-2-(4-methoxybutyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

R-(+)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno -1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxy-phenylmethyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-hydroxy-phenyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxy-phenyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-hydroxy-phenyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-hydroxy-phenyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-methoxybutyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(3-methoxypropyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(2-propenyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(4-methoxybutyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihyro-2-(3-methoxypropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-propyl-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(2-methylpropyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-4-Cyclopropylmethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-4-(2-methylpropyl)amino-2-propyl-2H-thieno-1,2-thiazine-6-sulfonamide 1,1 dioxide;

(R)-3,4-Dihydro-2-(4-hydroxybutyl)-4-(2-methylpropyl)amino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide;

(R)-3,4-Dihydro-2-(4-hydroxybutyl)-4-propylamino-2H-thieno-1,2-thiazine-6-sulfonamide 1,1-dioxide.

8. A formulation for controlling intraocular pressure comprising a therapeutically effective amount of the compound of Claim 1 in a pharmaceutically acceptable carrier.

9. A formulation for controlling intraocular pressure comprising a therapeutically effective amount of the compound of Claim 7 in a pharmaceutically acceptable carrier.

10. The formulation of Claim 8 wherein the compound concentration is between 0.1 and 10% by weight.

11. The formulation of Claim 9 wherein the compound concentration is between 0.1 and 10% by weight.

12. The formulation of Claim 10 wherein the compound concentration is between 0.1 and 10% by weight.

13. A method for controlling intraocular pressure which comprises topically administering to the affected eye a therapeutically effective amount of the compound of Claim 1.

14. A method for controlling intraocular pressure which comprises topically administering to the affected eye a therapeutically effective amount of the compound of Claim 7.

* * * * *

13-0056

US005461081A

United States Patent [19]

Ali et al.

[11] Patent Number: 5,461,081

[45] Date of Patent: Oct. 24, 1995

[54] **TOPICAL OPHTHALMIC PHARMACEUTICAL VEHICLES**

[75] Inventors: Yusuf Ali, Forth Worth, Tex.; Kenneth W. Reed, Lawrenceville, Ga.

[73] Assignee: Alcon Laboratories, Inc., Fort Worth, Tex.

[21] Appl. No.: 178,941

[22] Filed: Jan. 7, 1994

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 109,748, Aug. 20, 1993, abandoned, which is a continuation-in-part of Ser. No. 913,110, Jul. 14, 1992, abandoned, which is a continuation-in-part of Ser. No. 414,550, Sep. 28, 1989, abandoned.

[51] Int. Cl.[6] A61K 47/00; A61K 31/715

[52] U.S. Cl. 514/772.3; 514/54; 514/781; 514/782; 514/912

[58] Field of Search 514/772.3, 781, 514/782, 54, 912

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Primary Examiner—Zohreh Fay

Attorney, Agent, or Firm—Patrick M. Ryan; Sally Yeager

[57] **ABSTRACT**

Universal ophthalmic pharmaceutical vehicles which increase in viscosity upon instillation in the eye are disclosed. Ophthalmic compositions of the universal vehicle and a pharmaceutically active drug are also disclosed. In one embodiment, the vehicle gels upon instillation in the eye. In another embodiment, suspension vehicles having superior physical stability are provided.

19 Claims, 1 Drawing Sheet

TOPICAL OPHTHALMIC PHARMACEUTICAL VEHICLES

This application is a continuation-in-part of U.S. Ser. No. 08/109,748, filed Aug. 20, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/913,110, filed Jul. 14, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/414,550, filed Sep. 28, 1989, now abandoned.

BACKGROUND OF THE INVENTION

This invention is directed to liquid ophthalmic pharmaceutical vehicles which become viscous on contacting the eye. This invention also relates to topical ophthalmic compositions comprising the vehicle and a pharmaceutically active drug.

It is known that the addition of viscous or visco-elastic polymers to an eye drop pharmaceutical composition will increase the viscosity of the composition. This is usually desirable on the premise that an increased vehicle viscosity enhances drug delivery and duration of action; see, for example, *J. Pharm. Pharmacol.*, Vol. 34, pp. 464–466 (Jan. 7, 1982). However, it is frequently advantageous to administer ophthalmic compositions as a drop, that is, an aqueous solution or suspension rather than a thick, viscous gel or ointment which can be messy and may tend to blur vision. In addition, non-droppable compositions can present problems with patient compliance, especially with the elderly.

Another problem, in the case of suspension compositions, is their poor physical stability. Many marketed ophthalmic suspension products currently use the polymers hydroxypropyl methylcellulose, hydroxyethyl cellulose, and polyvinyl alcohol to increase the suspension's viscosity and thus decrease the settling rate of the drug particles. These suspensions are not well flocculated and, with time, the insoluble drug particles will completely settle forming a dense layer which will not resuspend easily. This in turn may undesireably lead to variable drug dosages.

SUMMARY OF THE INVENTION

The present invention provides for ophthalmic vehicles and compositions which can be administered as a drop, but whose viscosity increases upon instillation into the eye so that the composition provides for relatively better drug delivery and duration of action, referred to herein as bioavailability, of drug over aqueous compositions whose viscosity does not increase upon instillation. In one embodiment the vehicle gels upon instillation. In another embodiment, the vehicle provides an improved suspension vehicle.

This invention relates to ophthalmic pharmaceutical vehicles and compositions comprising the vehicle and a pharmaceutically active drug in which the vehicle comprises a charged polymer and oppositely charged electrolytes or molecules, hereinafter referred to collectively as "electrolytes", which can be administered as a drop and upon instillation, increase in viscosity. The polymer can be negatively charged, such as a carboxyvinyl polymer, in which case the vehicle will include positively charged electrolytes, such as calcium. Conversely, the polymer can be positively charged and then negatively charged electrolytes are used in the vehicle.

The suspension vehicles of the present invention possess improved suspension characteristics. They exhibit superior physical stability and permit easy resuspension of insoluble drug particles, thus resulting in greater uniformity of drug dosing. In addition to an ophthalmic dosage form, the vehicles and compositions of the present invention also provide for oral, parenteral and topical suspension dosage forms.

The vehicles of this invention can be used in composition with pharmaceutically active drugs. The term "drug", as used herein, means any therapeutic agent that is desirable to deliver to the eye. There is no limitation on the type of drug which can be incorporated into the compositions disclosed herein. The drugs can be charged, uncharged, water soluble or insoluble.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 compares the physical stability of two suspensions.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The vehicles disclosed herein comprise a charged polymer and oppositely charged electrolytes. Without intending to be bound by any theory, it is understood that the vehicle's viscosity is increased due to the decrease in electrolyte concentration when the vehicle is administered to the eye. In the case of a gelling vehicle, the concentrations of the polymer and electrolytes in the vehicle are optimal when a small change in electrolyte concentration will result in a dramatic increase in vehicle viscosity. The small change in electrolyte concentration on instillation is caused by the electrolytes being taken up by the cells in the eye, by diffusing out of the polymer vehicle or being eliminated in tear fluid or by a combination of these mechanisms. Whatever the mechanism, the concentration of electrolytes in the vehicle is reduced and the vehicle viscosity increases.

As used herein, "gels" means the vehicle's viscosity increases sufficiently to transform the drop into a semi-solid or gelatinous state.

Polymers which can be used in the vehicle disclosed herein include any nontoxic charged water soluble polymer. These polymers can either be negatively or positively charged. Typically, negatively charged polymers will include, but are not limited to, carboxy vinyl polymers, such as Carbopol®, sodium carboxy methylcellulose, pectin, gelatin (Type B), sodium hyaluronate, acacia, calcium carboxy methylcellulose, sodium alginate and polystyrene sulfonic acid (PSSA). These polymers are used in the vehicles at concentrations from about 0.1 to about 10.0 weight percent (wt. %).

Electrolytes which are used in conjunction with the charged polymers will be either cations or anions depending on the charged polymer being used. If negatively charged polymers are being used in the vehicle the electrolytes which are used to provide for the changing viscosity upon instillation will be positively charged. These cations will typically be Na^+, K^+, Mn^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++}, Al^{+++}, Li^+, Zn^{++} and Be^{++}. In addition, positively charged organic ions can be used, for example, lysineoHCl, arginineoHCl and histadineoHCl. These electrolytes will typically be present at a concentration of between 0.01 and ..0 wt. %.

If a positively charged polymer is used, such as gelatin (Type A) or polyvinyl amine, the electrolyte used in conjunction therewith to provide for viscosity changes will be an anion. These anions will typically be PO_4^{-3}, HPO_4^{-2}, $H_2PO_4^-$, I^-, Cl^-, F^-, SO_4^{-2}, HCO_3^- and negatively charged organic ions. Again, the polymer concentration will range from about 0.1–10.0 wt. % and the electrolytes will typically

5. QS to 100% of the final batch weight with purified water.

6. Steam sterilize the formulation.

The vehicles of Examples 2–6 were also prepared according to this compounding procedure.

EXAMPLE 2

"Universal" Ophthalmic Vehicle No. 2

Ingredient	Weight Percent
Carbopol ® 934P	0.40
Calcium Chloride	0.10
Mannitol	4.00
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

EXAMPLE 3

"Universal" Ophthalmic Vehicle No. 3

Ingredient	Weight Percent
Carbopol ® 934P	0.40
Calcium Chloride	0.05
Lysine HCl	0.225
Mannitol	4.00
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

EXAMPLE 4

"Universal" Ophthalmic Vehicle No. 4

Ingredient	Weight Percent
Carbopol ® 934P	1.00
Calcium Chloride	0.40
Mannitol	3.00
KOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

EXAMPLES 5–6:

Universal ophthalmic pharmaceutical suspension vehicles which exhibit superior physical stability. If charged drug particles are added to these suspension vehicles, an appropriate adjustment may have to be made to the electrolyte concentration.

EXAMPLE 5

"Universal" Pharmaceutical Vehicle No. 1

Ingredient	Weight Percent
Mannitol	1.80
Carbopol ® 934P	0.45
Polysorbate 80	0.05
Sodium Chloride	0.50
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

EXAMPLE 6

"Universal" Pharmaceutical Vehicle No. 2

Ingredient	Weight Percent
Carbopol ® 934P	0.70
Polysorbate 80	0.05
Sodium Chloride	0.80
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified water	q.s. 100%

EXAMPLE 7

Preferred Ophthalmic Gelling Solution

Ingredient	Weight Percent
Betaxolol HCl	28
Carbopol ® 934P	1.00
Calcium Chloride	75
Mannitol	1.5
Benzalkonium Chloride	0.01
EDTA	.05
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

EXAMPLE 8

Preferred Suspension Composition

Ingredient	Weight Percent
Rimexolone	1.0
Mannitol	1.80
Carbopol ® 934P	0.45
Polysorbate 80	0.05
Sodium Chloride	0.50
Edetate Disodium	0.01
Benzalkonium Chloride	0.01 + 5% excess
NaOH	pH 7.2 ± 0.2
Purified Water	q.s. 100%

The results of a sedimentation/settling study comparing the physical stability of the Rimexolone steroid suspension of Example 8 to the commercially available prednisolone acetate steroid suspension (1 wt. %), Econopred®, are shown in FIG. 1. The Econopred® suspension contains hydroxypropyl methylcellulose as its polymeric viscosity enhancer. As indicated above, Example 8 contains Carbopol® as its stearic stabilizer and viscosity enhancer. After standing for six months in a measuring glass cylinder, 2% of the Econopred® suspension settled to the bottom as a cake or sediment. The remaining 98% consisted of a single supernatant phase. In contrast, none of the suspension of Example 8 settled to the bottom as a cake or sediment after standing for six months. Substantially all of the suspension

ORIGINAL DECLARATION FOR PATENT 5,240,923

The undersigned declares that Patent 5,240,923 covers the formulation, composition, and/or method of use of Brinzolamide 1% Ophthalmic Suspension. This product is the subject of this application for which approval is being sought:

Sally S. Yeager - Applicant — Dec. 19, 1996 Date

13-0063

00024887 004●8

ORIGINAL DECLARATION FOR PATENT 5,378,703

The undersigned declares that Patent 5,378,703 covers the formulation, composition, and/or method of use of Brinzolamide 1% Ophthalmic Suspension. This product is the subject of this application for which approval is being sought:

Sally S. Yeager - Applicant

Dec. 19, 1996
Date

13-0064

00024887 004●8

ORIGINAL DECLARATION FOR PATENT 5,461,081

The undersigned declares that Patent 5,461,081 covers the formulation, composition, and/or method of use of Brinzolamide Ophthalmic Suspension. This product is the subject of this application for which approval is being sought:

Sally S. Yeager - Applicant

Dec 19, 1996
Date

13-0065

00024887 004●8

B. Exclusivity - Request for Five Year Exclusivity

The applicant requests a Five year period of market exclusivity based on the following information:

1. The active moiety of Brinzolamide 1% Ophthalmic Suspension, brinzolamide, is a new chemical entity which has not been previously approved in other applications under Section 505(b) of the Act after September 24, 1984.

2. New clinical investigations (other than bioavailability studies) have been conducted by the applicant that are essential to approval of the application.