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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 333/34, A61K 31/38	A1	**(11) International Publication Number:** WO 94/05651 **(43) International Publication Date:** 17 March 1994 (17.03.94)

(21) International Application Number: PCT/US93/08006

(22) International Filing Date: 25 August 1993 (25.08.93)

(30) Priority data:
07/939,189 2 September 1992 (02.09.92) US

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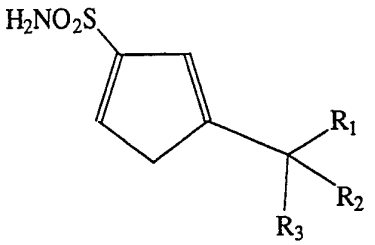
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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 5-SUBSTITUTED 3-THIOPHENE SULFONAMIDES AS ANTIGLAUCOMA AGENTS



(1)

(57) Abstract

The present invention provides novel carbonic anhydrase inhibitors represented by structural formula (1) wherein R_1 and R_2 are independently (a) hydrogen; or (b) OR_4 wherein R_4 is hydrogen or C_{1-7} alkyl; or (c) NR_5R_6, wherein R_5 and R_6 are independently hydrogen, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen or OR_4; or (d) $-COR_7$, wherein R_7 is hydrogen, C_{1-7} alkyl, or NR_5R_6; or (e) $-SR_8$, wherein R_8 is hydrogen or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4; or (f) C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4 or NR_5R_6; or (g) R_1 and R_2 are together, (i) $=O$, or (ii) $=NOR_8$ or (iii) $=S$; and R_3 is (h) C_{1-7} alkyl or C_{1-7} substituted with one or more halogen, OR_4 or NR_5R_6; or (i) aryl, wherein said aryl comprises up to 10 carbon atoms and is an unsubstituted carbocyclic aryl or heterocyclic aryl radical, or said carbocyclic aryl or heterocyclic aryl radical is substituted with one or more halogen, or OR_4, or NR_5R_6, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4, or NR_5R_6; or (j) $-COR_9$, wherein R_9 is R_7 or an usubstituted carbocyclic or heterocyclic radical, wherein said unsubstituted carbocyclic or heterocyclic radical comprises up to 10 carbon atoms, or said carbocyclic or heterocyclic radical is substituted with one or more halogen, or OR_4, or NR_5R_6 or C_{1-7} or C_{1-7} alkyl substituted with one or more halogen, OR_4 or NR_5R_6.

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DESCRIPTION

5-SUBSTITUTED 3-THIOPHENE SULFONAMIDES AS ANTIGLAUCOMA AGENTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to thiophenesulfonamides that have carbonic anhydrase inhibition activity and are useful as anti-glaucoma agents.

BACKGROUND OF THE ART

Glaucoma is an ocular disorder associated with elevated intraocular pressures which are too high for normal function and may result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. Indeed, few advances were made in the treatment of glaucoma since pilocarpine and physostigmine were introduced. Only recently have clinicians noted that many β-adrenergic blocking agents are effective in reducing intraocular pressure, they also have other characteristics, e.g. membrane stabilizing activity, that are not acceptable for chronic ocular use. (S)-1-tert-Butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol, a β-adrenergic blocking agent, was found to reduce intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other β-adrenergic blocking agents, e.g., to be devoid of local anesthetic properties, to have a long duration of activity, and to display minimal tolerance.

Although pilocarpine, physostigmine and the β-adrenergic blocking agents mentioned above reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase and, thereby, impeding the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

Agents referred to as carbonic anhydrase inhibitors, block or impede this inflow pathway by inhibiting the enzyme, carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by oral, intravenous or other systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular pressure, or when no other agent is effective.

Topically effective carbonic anhydrase inhibitors are reported in U.S. Patent No. 4,386,098; 4, 416,890; and 4,426,388. The compounds reported therein are 5 (and 6)-hydroxy-2-benzothiazolesulfonamides and acyl esters thereof.

Additionally, U.S. Patent 4,544,667 discloses a series of benzofuran-2-sulfonamides, and U.S. Patent Nos. 4,477,466; 4,486,444; 4,542,152; and 4,585,787 disclose 5-phenylsulfonylthiophene-2-sulfonamides and 5-benzoylthiophene-2-sulfonamides and alkanoyloxy derivatives thereof which are reported to be topically effective carbonic anhydrase inhibitors useful in the treatment of elevated intraocular pressure and glaucoma.

Finally, U.S. Patent 4,914,111 reports that thiophene or furan-2-sulfonamides, having a 4-benzyl substituent are effective for the topical treatment of elevated intraocular pressure and glaucoma.

In view of the above, it is clear that a great deal of research has been carried out on the use of sulfonamides for the topical treatment of glaucoma. Furthermore, certain thiophenesulfonamides have been suggested for the topical treatment of glaucoma. However, the use of 3-thiophenesulfonamides has not been suggested for use in the topical treatment of glaucoma.

Therefore, it is one objective of this invention to provide 3-thiophenesulfonamides for the treatment of glaucoma.

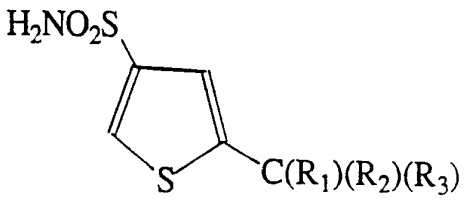
It is another object of this invention to provide compounds having carbonic anhydrase inhibition activity.

Another object of this invention is to provide a method of inhibiting carbonic anhydrase activity to thereby treat glaucoma.

Other objects and advantages of the instant invention will become apparent from a careful reading of the specification below.

SUMMARY OF THE INVENTION

The present invention provides novel compounds having carbonic anhydrase inhibition activity and useful in the treatment of glaucoma. These compounds are represented by the structural formula:



wherein R_1 and R_2 are independently

(a) hydrogen; or

(b) OR_4 wherein R_4 is hydrogen or C_{1-7} alkyl; or

(c) NR_5R_6 wherein R_5 and R_6 are independently hydrogen, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen or OR_4; or;

(d) -COR_7, wherein R_7 is hydrogen, C_{1-7} alkyl, or NR_5R_6; or

(e) -SR_8, wherein R_8 is hydrogen or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen or OR4; or

(f) C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4 or NR; or

(g) R_1 and R_2 are together

(i) =O, or

(ii) =NOR_8, or

(iii) =S;

and R_3 is

(h) C_{1-7} alkyl or C_{1-7} substituted with one or more halogen, OR_4 or NR_5R_6; or

(i) aryl, wherein said aryl comprises up to 10 carbon atoms and is an unsubstituted carbocyclic aryl or heterocyclic aryl, which may be selected from the group consisting of phenyl, thienyl, furyl, pyridyl, pyrryl, piperidyl, pyrrolidyl, morpholinyl, or said carbocyclic aryl or heterocyclic aryl is substituted with one or more halogen, or OR_4, or NR_5R_6, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4, or NR_5R_6; or

(j) $-COR_9$, wherein R_9 is R_7 or a carbocyclic or a heterocyclic radical, e. g. aryl, wherein said carbocyclic or a heterocyclic radical comprises up to 10 carbon atoms and may be selected from the group consisting of phenyl, cyclopentyl, cyclohexyl, thienyl, furyl, pyridyl, pyrryl, piperidyl, pyrrolidyl, morpholinyl or said carbocyclic aryl or heterocyclic aryl radical is substituted with one or more halogen, or OR_4, or NR_5 R_6, or C_{1-7} or C_{1-7} alkyl substituted with one or more halogen, OR_4 or NR_5R_6.

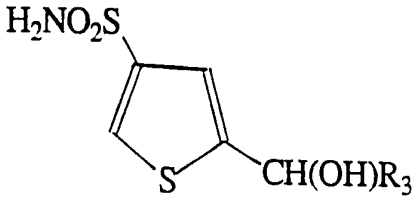
Preferably, in the novel compounds of the invention R_1 and R_2, together, represent O; or at least one of R_1 or R_2 is hydrogen and the other is OH, $OCOCH_3$, NOH, or H. (That is, the novel compounds of this invention may include an alpha carbonyl or hydroxy, or acetoxy, or hydroxyamino, etc. group at the 5 position on the thiophene ring.) R_3 preferably represents C_1 to C_6 alkyl or phenyl or phenyl substituted with one or more, more preferably one, hydroxy, methoxy, acetoxy, acetoxymethylene, carboxy, hydroxymethyl, formyl, N, N-dimethylaminomethyl fluoro, chloro or bromo radicals.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of the invention may be prepared by the following general reaction scheme:

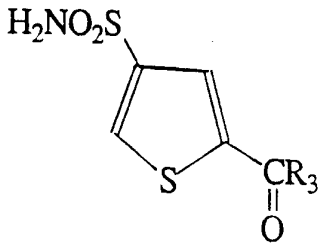
4-Bromo-2-thiophenecarboxaldehyde is reacted with R_3Li or R_3MgX, wherein X is a halogen, e.g., bromo or iodo, in tetrahydrofuran, or any other dipolar, aprotic solvent, e.g. diethylether, dioxane, etc., at a temperature of from about O° C. to -78° C., to yield an alkoxide of the addition product. This

intermediate is reacted with trimethylsilylchloride, at a temperature of from about O° C. to -78° C., to provide a "protected" alcohol. The protected intermediate is consecutively reacted with n-butyl lithium in tetrahydrofuran at a temperature of about -100° C. to yield the 3-lithio compound. The lithio compound is reacted with SO_2 at a temperature of about -100° C. in THF, or other aprotic solvent, to yield the lithio sulfinate. The lithium sulfinate is reacted with N-chloro succinimide (NCS) at ambient temperatures in dichloromethane to yield the sulfonyl chloride. The sulfonyl chloride is consecutively reacted with NH_4OH and tetra-n-butyl ammonium fluoride to yield a novel compound of the invention represented by the general formula:



I

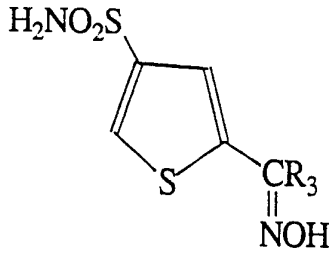
I may be oxidized by Jones' reagent to yield a novel compound of the invention represented by the general formula:



II

That is, II represents the alpha carbonyl derivatives of the invention, i.e., wherein R1 and R2 together, represent O (oxygen).

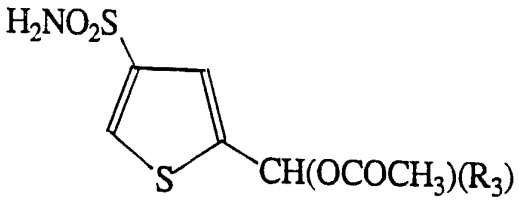
II may be reacted with H2NOH • HCl in pyridine to provide compounds of the invention represented by the general formula:



III

That is, in the compounds represented by Formula III, R_1 and R_2, together, represent NOH.

Alternatively, compounds represented by Formula I may be reacted with acetic anhydride in pyridine to yield compounds of the invention represented by the general formula:

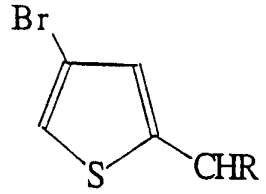


IV

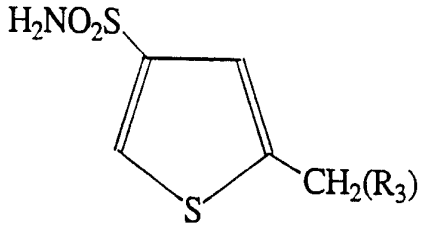
That is, in the compounds represented by Formula IV, R_1 represents OCOCH3 and R_2 represents hydrogen. Of course, other anhydrides may be used, e.g. benzoic anhydride, to provide compounds wherein R_1 represents a radical derived from said other anhydride, e.g. R1 is OCOC6H5.

An alternative to the above general reaction scheme relies on the Wittig reaction as follows:

(Alkyl)triphenylphosphonium bromide is reacted with 4-bromo-2-thiophene carboxaldehyde in THF, in the presence of potassium tertiary butoxide to yield



wherein R is an unsaturated alkenyl radical derived from the above alkyl phosphonium bromide. The 2-(alk-1-enyl)-4-bromothiophene of Formula V may be hydrogenated in the presence of Wilkenson's catalyst to yield the saturated derivative. The saturated derivative is consecutively reacted with n-butyl lithium, SO_2, NCS and NH_4OH/tetra-n-butyl ammonium fluoride to yield



wherein R1=R2=H and R3 is alkyl.

Specific compounds within the scope of this invention include:

1-[5-(3-sulfamoyl thienyl)] pentanone oxime
5-(4-hydroxybenzoyl)3-thiophene sulfonamide
5-(3-N,N-dimethylamino-4-hydroxybenzhydrol)-3-thiophene sulfonamide
5-(1-hydroxy-n-pentyl)-3-thiophene sulfonamide
5-(1-hydroxy-n-heptyl)-3-thiophene sulfonamide
5-(4-acetoxymethylbenzhydrol)-3-thiophene sulfonamide
5-(4-formylbenzhydrol)-3-thiophene sulfonamide
5-(4-carboxylbenzhydrol)-3-thiophene sulfonamide
5-(benzhydrol)-3-thiophene sulfonamide
5-(4-methoxybenzhydrol)3-thiophene sulfonamide
5-(2-methoxybutyl)-3-thiophene sulfonamide
5-(4-chlorohexyl)-3-thiophene sulfonamide
5-(3-phenylpentyl)-3-thiophene sulfonamide
5-(3-methylpentyl)-3-thiophene sulfonamide

5-benzoyl-3-thiophene sulfonamide
5-[benzhydrol]-3-thiophene sulfonamide

When administered for the treatment of elevated intraocular pressure of glaucoma, the active compound is most desirably administered topically to the eye, although systemic treatment is also satisfactory.

When given systemically, the drug can be given by any route, although the oral route is preferred. In oral administration the drug can be employed in any of the usual dosage forms such as tablets or capsules, either in a contemporaneous delivery or sustained release form. Any number of the usual excipients or tableting aids can likewise be included.

The active drug of this invention is most suitably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as a suspension, ointment, or as a solid insert. Formulations of these compounds may contain from 0.01 to 15% and especially 0.5% to 3% of medicament. Higher dosages as, for example, about 10%, or lower dosage can be employed provided the dose is effective in reducing or controlling elevated intraocular pressure. As a unit dosage from 0.001 to 10.0 mg, preferably 0.005 to 2.0 mg, and especially 0.1 to 1.0 mg of the compound is generally applied to the human eye, generally on a daily basis in single or divided doses so long as the condition being treated exists.

The herein before described dosage values are believed accurate for human patients and are based on the known and presently understood pharmacology of the compounds, and the activity of other similar entities in the human eye. As with all medications, dosage requirements are variable and must be individualized on the basis of the disease and the response of the patient.

The pharmaceutical preparation which contains the active compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and

other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, buffering ingredients such as sodium chloride, sodium borate, sodium acetate, and other conventional ingredients such as sorbitan monolaurate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a solid insert.

While many patients find liquid medication to be entirely satisfactory, others may prefer a solid medicament that is topically applied to the eye, for example, a solid dosage form that is suitable for insertion into the cul-de-sac. To this end the carbonic anhydrase inhibiting agent can be included with a non-bioerodable insert, i.e., one which after dispensing the drug remains essentially intact, or a bioerodable insert, i.e., one that either is soluble in lachrymal fluids, or otherwise disintegrates.

For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, or a hydroxy lower alkyl cellulose such a hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and the like; acrylates such as polyacrylic acid salts, ethyl acrylates, polyacrylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxyethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, and mixtures of said polymers.

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and is not intended as limiting the scope of the appended claims.

Example 1

2-(n-Hex-1-enyl)-4-bromo thiophene

2.0 grams (10.5 mmols) of (n-pentyl) triphenyl phosphonium bromide was added to 105 ml. of tetrahydrofuran (THF) with stirring. 1.86 gms (15.8 mmol.) of potassium tertiary butoxide was then added to the mixture while stirring at room temperature under an argon atmosphere. After one hour of continued stirring, 2.0 gms (10.5 mmol) of 4-bromo-2-thiophene carboxaldehyde, dissolved in 20 ml of THF, was added to the phosphonium bromide solution. After an additional one hour, the reaction was quenched with water. The organic layer was then separated, washed twice with water and then with brine. After drying over MgSO4 and filtering, the filtrate was concentrated. The concentrate was flushed through a silica plug and eluted with hexane to yield 2.2 gms of a yellow liquid. This liquid included a mixture of cis and trans isomers of the named compound and had the following NMR spectra:

^{1}HNMR($CDCl_3$):
7.12 (s), 6.98 (s), 6.88 (s), 6.42 (app. d), 6.03-6.14 (m), 5.52-5.64 (m), 2.322-2.42 (m), 2.12-2.22 (m),1.28-1.74 (m), 0.90-0.98 (m).

Example 2

2-(hexyl)-4-bromo thiophene

2.2 gms (9.0 mmol) of the product of Example 1 were dissolved in 25 ml of ethanol and 0.22 gms of Wilkenson's catalyst were added. (Wilkenson's catalyst is tris(triphenylphosphine) rhodium (I) chloride.) The mixture was stirred at room temperature under atmospheric hydrogen pressure overnight. The reaction product was concentrated and separated by flash chromatography, using hexane, as the eluant, to yield 2.2 gms of a colorless liquid. The NMR spectra of said liquid was as follows:

1HNMR(CDCl3):
7.01(s), 6.98 (s), 6.78 (s), 6.71 (s), 6.42 (d,J=15 Hz), 6.09 (d,t,J=8, 15Hz), 2.77 (t, J=7 Hz), 2.12-2.22 (m). 1.60-1.70 (m), 1.29-1.35 (m), 0.87-0.91 (m).

From said spectra it was determined that 2-(n-hex-1-enyl)-4-bromo-thiophene was still present in the reaction product. The reaction product was again treated with Wilkenson's Catalyst and hydrogen, overnight. The re-treated reaction mixture was passed through a silica gel plug and eluted with hexane to yield 2.1 gms of a clear, colorless liquid having the following NMR spectra:

7.01 (s, 1H), 6.71 (s, 1H), 2.77 (t=7 Hz, 2H), 1.65 (m, 2H), 1.29-1.35 (m, 6H), 0.89 (t, J=7 Hz, 3H).

Example 3

5-n-Heptyl-3-thiophene sulfonamide

1.93 gms (7.8 mmol) of the bromothiophene of Example 2 were added to 78 ml. of THF and the solution was cooled to -100° C, while under an argon atmosphere. 4.9 ml of a 1.6 M solution of n-butyl lithium (n-BuLi) in hexane were added to the cooled solution and stirred at -100° C. under an argon atmosphere. After a few minutes, SO_2 was bubbled into the solution. When the solution became saturated with SO_2, it was allowed to warm to room temperature and 20 ml. of ethyl ether were then added. After about two and one-half hours, the solution was transferred to a roto-evaporator and concentrated. The resulting concentrate was dissolved in 78 ml of methylene dichloride (CH_2Cl_2) and 1.15 gms (8.6mmol) of N-chlorosuccinimide (NCS) were added. The resulting mixture was stirred, under argon, at room temperature for two hours. The resulting mixture was filtered and the filtrate was concentrated. The concentrate was dissolved in 50 ml of acetone and 10 ml of concentrate NH_4OH (aqueous) were added. After 10 minutes, the mixture was diluted with ethyl acetate and washed with water three times and then with a saturated salt solution. i.e. brine. The organic phase was separated, dried over $MgSO_4$, filtered and the filtrate concentrated. The concentrate was subjected to flash chromatography utilizing a 3 to 1, by volume, mixture of hexane and ethyl acetate eluant to yield 1.24 gms of a light yellow solid having the following NMR spectra:

^{1}H NMR ($CDCl_3$):
7.76 (d, J=1.4 Hz, 1H), 7.07 (d, J=1.4 Hz, 1H), 5.21 (bs,2H), 2.76 (q, J=7.7 Hz, 2H), 1.65 (p, J=7.7 Hz, 2H), 1.28-1.38 (m, 6H), 0.87 (t, J=6.8 Hz, 3H).

Example 3(a)

5-n-Pentyl-3-thiophene sulfonamide

The reactions set forth in Examples 1 through 3 are repeated except that (n-butyl)triphenylphosphine bromide is substituted for (n-pentyl) triphenylphosphine bromide to yield the named compound.

Example 3(b)

5-(3-methylpentyl-3-thiophene sulfonamide

The reactions set forth in Examples 1 through 3 are repeated except that (2-methylbutyl)triphenylphosphine bromide is substituted for (n-pentyl)triphenylphosphine bromide to yield the named compound.

Example 3(c)

5-(3-phenylpentyl)-3-thiophene sulfonamide

The reactions set forth in Examples 1 through 3 are repeated except that (2-phenylbutyl)triphenylphosphine bromide is substituted for (n-pentyl)triphenylphosphine bromide to yield the named compound.

Example 3(d)

5-(4-chlorohexyl)-3-thiophene sulfonamide

The reactions set forth in Examples 1 through 3 are repeated except that (3-chloropentyl)triphenylphosphine bromide is substituted for (n-pentyl) triphenylphosphine bromide to yield the named compound.

Example 3(e)

5-(2-methoxybutyl)-3-thiophene sulfonamide

The reactions set forth in Examples 1 through 3 are repeated except that (3-methoxypropyl)triphenylphosphine bromide is substituted for (n-pentyl) triphenylphosphine bromide to yield the named compound.

Example 4

5-[4-t-butyldimethylsiloxyphenyl)(trimethylsiloxy)methyl]-3-bromothiophene

5.9 gms (0.02 mol) of 4-bromo t-butyldimethylsiloxybenzene were dissolved in 42 ml of dry THF. The solution was cooled to -78° C. while under an argon atmosphere and 13.1 ml (0.02) of a 1.6M solution of n-butyl lithium in hexane were added. After stirring for fifteen minutes under argon the solution was combined over a twenty-five-minute period with a solution of 4.0 gms (0.02 mol) of 4-bromo-2-thiophene carboxaldehyde in 50 ml. of THF at -78° C. The resulting solution was stirred for one hour and fifteen minutes at -78° C. 1.95 ml of trimethylsilylchloride (TMSCl) were added and the solution was allowed to warm to room temperature overnight with stirring. An additional 10 ml of TMSCl were added and the solution was stirred for six hours. The reaction was quenched with water; the organic phase was separated from the brine, dried over $MgSO_4$, filtered, concentrated and separated by flash chromatography, utilizing hexane as the eluant. 2.5 gms of a clear colorless liquid were recovered having a NMR spectra of:

^1H NMR (acetone-d_6):
7.21 (d, J=8.5 Hz, 2H), 7.11 (d, J=1.5 Hz, 1H), 6.80 (d, J=8.5 Hz, 2H), 6.65 (d, J=11.5 Hz, 1H), 5.84 (s, 1H), 0.99 (s, 3H), 0.21 (s., 6H), 0.10 (s, 9H).

Example 5

5-(4-hydroxybenzhydrol)3-thiophene sulfonamide

2.34 gms (5.0 mmol) of the bromothiophene, prepared in Example 4, were dissolved in 50 ml of dry THF. The resulting solution is cooled to -78°C while under an argon atmosphere. 3.1 ml of a 1.6 M solution of n-BuLi, in hexane, is

added and stirring was continued for a few minutes. SO_2 was bubbled into the solution until the solution was saturated with SO_2. 20ml of ethyl ether were added and the solution was allowed to warm to room temperature. After about two hours at room temperature, the solution was concentrated, the residue dissolved in 50 ml of methylene dichloride and 0.73 gms (5.5 mmol) of NCS were added. After about one-half hour, the resulting mixture was filtered, the filtrate concentrated and the concentrate was dissolved in a solution of 5 ml concentrated NH_4OH (aqueous) and 25 ml of acetone. After one-half hour, the resulting solution is diluted with ethyl acetate, washed with water, three times, and then with brine. The resulting organic phase is separated, dried over $MgSO_4$, filtered and the filtrate concentrated. The concentrate was subjected to flash chromatography utilizing a 3:1 mixture of hexane and ethyl acetate, as the eluant, to yield 1.41 gms of a light yellow oil having the following NMR spectra:

1H NMR (acetone-d6):
7.88 (s, 1H), 7.33 (d, J=9 Hz, 2H), 7.10 (s, 1H), 6.88 (d, J=9 Hz, 2H), 6.55 (bs, 2H), 6.07 (s, 1H), 0.97 (s, 9H), 0.20 (s, 6H), 0.07 (s, 9H).

0.52 (1.1 mmol.) of the product light yellow oil was dissolved in 11 ml of THF and 2.3 ml of a 1.0 M solution of tetra-n-butyl ammonium fluoride (TBAF) in THF was added. After one-half hour, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed three times with water and then with brine. The organic phase was separated, dried over $MgSO_4$, filtered and the filtrate concentrated. The concentrate was subjected to flash chromatography, utilizing the above hexane/ethyl acetate mixture to yield 0.26 gms of a white foam having the following NMR spectra:

^1H NMR(acetone-d_6):
8.43 (bs, 1H), 7.88 (s, 1H), 7.28 (d, J=9Hz, 2H), 7.05 (s, 1H), 6.82 (d, J=9Hz, 2H), 6.57 (bs, 2H), 5.95 (s, 1H), 5.32 (bs, 1H).

Example 5(a)

5-(4-methoxybenzhydrol)3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that 4-methoxybromobenzene is substituted for 4-bromo t-butyldimethyl-siloxy-benzene to yield the named compound which has the following NMR spectra:

^{1}H NMR (acetone-d_6):
7.88 (d, J=1.5 Hz, 1H), 7.38 (d, J=8.6 Hz, 2H), 7.07 (m, 1H), 6.92 (d, J=8.6 Hz, 2H), 6.54 (bs, 2H), 5.99 (d, J=4.3 Hz, 1H), 5.34 (d, J=4.3 Hz, 1H), 3.78 (s, 3H).

Example 5(b)

5-(benzhydrol)-3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that bromobenzene is substituted for 4-bromo t-butyldimethylsiloxybenzene to yield the named compound. This compound may be subsequently reacted with acetic anhydride in the presence of pyridine, as described above, to yield the acylated derivative, i. e. 5-[(phenyl)(acetoxy)methyl]-3-thiophene sulfonamide, having the following NMR spectra:

^{1}H NMR (acetone-d_6):
7.90 (s, 1H), 7.30-7.50 (m, 5H), 7.10 (s, 1H), 6.55 (bs, 2H), 6.05 (d, J=4.3 Hz, 1H), 5.46 (d, J=4.3 Hz, 1H).

Example 5(c)

5-(1-hydroxy-n-heptyl)-3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that 1-bromohexane is substituted from 4-bromo 5-butyldimethylsiloxybenzene to yield the named compound, having the following NMR spectra:

^{1}H NMR ($CDCl_3$):
7..88 (s, 1H), 7.24 (s, 1H), 5.06 (bs, 2H), 4.88-4.89) (m, 1H), 2.43-2.45 (m, 1H), 1.79-1.81 (m, 2H), 1.25 -1.31 (m, 8H), 0.86-0.88 (m, 3H).

Example 5(d)

5-(1-hydroxy-n-pentyl)-3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that 1-bromobutane is substituted for 4-bromo t-butyldimethylsiloxybenzene to yield the named compound, having the following NMR spectra:

^1H NMR ($CDCl_3$

7.82 (s, 1H), 7.20 (s, 1H), 5.35 (bs,2H), 4.80 (t, J=4.5 Hz, 1H), 1.70-2.88 (m, 2H), 1.24-1.48 (m, 4H) 0.88 (t, J=4.5 Hz, 3H).

Example 5(d)

5-(1-hydroxy-n-pentyl)-3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that 1-bromobutane is substituted for 4-bromo t-butyldimethylsiloxybenzene to yield the named compound, having the following NMR spectra:

^1H NMR ($CDCl_3$):

7.82 (s, 1H), 7.20 (s, 1H) 5.35 (bs, 2H) 4,80 (t, J=4.5 Hz, 1H), 1.70-2.88 (m, 2H), 1.24-1.48 (m, 4H), 0.88 (t, J=4.5 Hz, 3H).

Example 5(e)

5-n-Heptyl-3-thiophene sulfonamide

The reactions set forth in Examples 4 and 5 are repeated except that 3-bromo t-butyldimethylsiloxy is substituted for 4-bromo t-butyldi-methylsiloxybenzene to yield the named compound, having the following NMR spectra:

^1H NMR (acetone-d_6):

8.40 (bs, 1H), 7.89 (d, J=1.5 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 7.11 (d, J=1.5 Hz, 1H), 6.92-6.97 (m, 2H), 6.75-6.78 (m, 1H) 6.56 (bs, 2H), 5.97 (s, 1H), 5.40 (bs, 1H).

Example 6

5-(4-hydroxybenzoyl)-3-thiophene sulfonamide

0.10 gms (0.35 mmol) of 5-(4-hydroxybenzhydrol) 3-thiophene sulfonamide, as prepared in Example 5, were dissolved in 5 ml of acetone and to this solution 0.13 ml (0.35 mmol) of a 2.67 M solution of Jones' Reagent were added. (Jones'

Reagent is aqueous chromic acid.) The resulting mixture was stirred for about forty minutes at room temperature and then quenched with isopropyl alcohol. The resulting solution was diluted with ethyl acetate, washed three times with water and then with brine. The organic layer was separated, dried over MgSO4, filtered and the filtrate concentrated. The concentrate was subjected to flash chromatography, utilizing a 1:1 mixture of hexane and ethyl acetate, as the eluant, to yield 78 mg of a clear colorless oil having the following NMR spectra:

^{1}H NMR (acetone-d_6):
9.45 (bs, 1H), 8.43 (d, J=1.3 Hz, 1H), 7.95 (d, J-1.3 Hz, 1H), 7.89 (d, J=9 Hz, 2H), 7.04 (d, J=9 Hz, 2H), 6.81 (bs, 2H).

Example 6(a)-(i)

The compounds of Examples 5(a)-(j) are converted into the corresponding alpha carbonyl derivatives by the method of Example 6. The compounds were identified by the NMR spectra given below.

Example 6(a)
5-(4-methoxybenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):
8.43 (s, 1H), 7.92-7.95 (m, 3H), 7.12 (d, J=9.0 Hz, 2H), 6.77 (bs, 2H), 3.93 (s, 3H).

Example 6(b)
5-benzoyl-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):
8.48 (s, 1H), 7.90-7.95 (m, 3H), 7.60-7.75 (m, 3H), 6.80 (bs, 2H).

Example 6(c)
5-(1-heptanoyl)-3-thiophene sulfonamide

^{1}H NMR ($CDCl_3$):
8.21 (s, 1H), 7.94 (s, lH), 5.01 (bs, 2H), 2.89 (t, J=7.3 Hz, 2H), 1.73 (p, 7.2 Hz, 2H), 1.30-1.34 (m, 6H), 0.88 (t, J=8.3 Hz, 3H).

Example 6(d)

5-(1-pentanoyl)-3-thiophene sulfonamide

^{1}H NMR ($CDCl_3$):

8.22 (s, 1H), 7.96 (s, 1H), 5.10 (bs, 2H) 2.90 (t, J=7.5 Hz, 2H), 1.73 (p, J=7.5 Hz, 2H), 1.40 (sex., J=7.5 Hz, 2H), 0.95 (t, J=7.5 Hz, 3H).

Example 6(e)

5-(3-hydroxybenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

8.46 (d, J=1.3 Hz, 1H), 7.93 (d, J=1.4 Hz, 1H), 7.32-7.46 (m, 3H), 7.15-7.19 (m, 1H), 6.86 (bs, 2H).

Examples 6(f) to (j) were prepared by a process analogous to the preparation of Examples 6(a) to (e) with the appropriate bromo reactant substituted for the 4-bromotrimethylsiloxybenzene.

Example 6(f)

5-(4-butylbenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

8.45 (d, J=1.4 Hz, 1H), 7.93 (d, J=1.4 Hz, 1H), 7.85 (d, J=8.2 Hz, 2H), 7.45 (d, J=8.2 Hz, 2H), 6.78 (bs, 2H), 2.74 (t, J=7.5 Hz, 2H), 1.60-1.68 (m, 2H), 1.38 (sex., J=7.8 Hz, 2H), 0.93 (t, J=7.3 Hz, 3H).

Example 6(g)

5-(3-trifluoromethylbenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

8.52 (d, J=1.4 Hz, 1H), 8.22 (d, J=7.9 Hz, 1H), 8.17 (s, 1H), 8.06 (d, J=8.3 Hz, 1H), 7.95 (d, J=1.4 Hz, 1H), 7.88 (t, J=7.8 Hz, 1H), 6.78 (bs, 2H).

Example 6(h)

5-(2-fluorobenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):
8.50 (d, J=1.2 Hz, 1H), 7.79 (t, J=1.5 Hz, 1H) 7.68-7.73 (m, 2H), 7.34-7.44 (m, 2H), 6.80 (bs, 2H).

Example 6(i)

5-(3-fluorobenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):
8.49 (s, 1H), 7.95 (s, 1H), 7.60-7.77 (m, 3H), 7.47-7.53 (m, 1H), 6.79 (bs, 2H).

Example 6(j)

5-(3.5-difluorobenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):
8.51 (s, 1H), 7.99 (s, 1H), 7.49-7.56 (m, 2H), 7.37-7.44 (m, 1H), 6.79 (bs, 2H).

Example 7

5-(4-hydroxy-3-(N,N-dimethylaminomethyl)benzoyl)-3-thiophene sulfonamide

5-(4-hydroxy-3,5-(bis-N,N-dimethylaminomethyl)benzoyl)-3-thiophene sulfonamide

0.25 g (0.88 mmol) of 5-(4-hydroxybenzoyl)-3-thiophene sulfonamide, 0.21 mL (2.6 mmol) of aqueous formaldehyde (37%) and 0.89 mL (7.9 mmol) of aqueous dimethylamine (40%) were added to 3mL of ethanol. The solution was heated at reflux for 15 1/2h and then cooled to room temperature. Solvent was removed under vacuum and the crude product subjected to flash chromatography. Utilizing 5:1 chloroform/methanol as the eluant 49 mg of 5-(4-hydroxy-3-(N,N-dimethylaminomethyl)benzoyl)-3-thiophene sulfonamide was recovered as a yellow color solid.

The eluant was switched over to 2:1 methanol/chloroform (with 5% triethylamine) and 0.13 g of 5-(4-hydroxy-3, 5-(bis-N, N-dimethylamino-methyl) benzoyl)-3-thiophene sulfonamide was recovered as a yellow color solid.

^{1}H NMR (acetone-d_6):

8.39 (d, J=1.4 Hz, 1H), 7.93 (d, J=1.4 Hz, 1H), 7.75 (s, 2H), 3.66 (s, 4H), 2.32 (s, 12H).

Example 8

4-bromo-2-[tetrahydropyronyl)(4-t-butyldimethylsiloxymethylphenyl)methyl] thiophene

6.5g (22mmol) of 4-bromobenzyl alcohol, t-butyldimethylsilyl ether was added to 40mL of THF. The solution was cool to -78°C. 15.3 mL (22 mmol) of a 11.42M n-BuLi solution was added. The solution was transferred via cannula to 4.2g (22 mmol) of 4-bromo-2-thiophene carboxaldehyde in 70mL THF at -78°C. Reaction was stirred at -78° for 30 min. before quenching with 5mL of saturated NH4Cl. The reaction was diluted with ethyl acetate and washed with water (3x) followed with brine. Solution was dried over $MgSO_4$ and the solvent removed under vacuum. The product, 10mL (0.11 mol) of DHP and a catalytic amount of TsOH were added to 88mL of dichloromethane. The reaction was stirred at rt for 18 1/2h. The reaction was washed with water (3x) followed with brine. The solution was dried over MgSO4 and the solvent removed under vacuum. Flash chromatography utilizing 20:1 hexane/ethyl ether as the eluant recovered 9.3g of the product as a light yellow color oil.

^{1}H NMR ($CDCl_3$):

mixture of diastereomers-

7.27-7.40 (m), 7.12-7.18 (m), 6.90 (s), 6.58 (s), 5.95 (s), 5.90 (s), 4.84-4.88 (m), 4.75 (s) 4.72 (s), 4.62-4.66 (m), 3.96-4.05 (m), 3.74-3.82 (m), 3.48-3.62 (m), 1.48-2.02 (m), 0.94 (s), 0.93 (s), 0.12 (s), 0.10 (s).

Example 9

5-[(tetrahydropyranyl)(4-t -butyldimethylsiloxymethylphenyl)methyl] 3-thiophene sulfonamide

8.8g (18 mmol) of the product obtained in Example #8 was added to 180mL of THF. The solution was cooled to -100°C. 12.7mL (18 mmol) of a 1.42M n-BuLi solution was added dropwise. After a few minutes SO_2 was passed through the reaction flask until the solution became saturated. 30mL of ethyl ether was added and the liquid nitrogen/ethyl ether bath removed. After 2h the solvent was

removed under vacuum. The crude product and 2.6g (19.8 mmol) NDS were added to 180mL of dichloromethane. After stirring at rt for 1 1/2 h the mixture was filtered and the filtrate concentrated. The crude product was added to 30mL of concentrated ammonium hydroxide in 180mL of acetone. Upon stirring for 3 1/2 h the solution was diluted with ethyl acetate and washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 2:1 hexane/ethyl acetate recovered 2.9g of the product as a yellow color oil.

^1H NMR ($CDCl_3$):
7.96 (s), 7.94 (s), 7.49-7.34 (m), 7.01 (s), 6.07 (s), 6.01 (s), 4.83-4.86 (m), 4.78 (s), 4.60-4.64 (m), 3.90-3.99 (m), 3.68-3.77 (m), 3.43-3.58 (m), 1.43-1.98 (m), 0.96 (s), 0.15 (s), 0.13 (s).

Example 10

5-(4-hydroxymethylbenzhydrol)-3-thiophene sulfonamide

0.36g (0.72 mmol) of the product from Example #9 and a catalytic amount of TsOH were added to 10mL of methanol. After 2h of stirring at rt the solution was diluted with ethyl acetate and washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 2:1 ethyl acetate/hexane as the eluant recovered 87 mg of 5-(4-hydroxymethylbenzhydrol)-3-thiophene sulfonamide as a clear colorless oil.

1H NMR (acetone-d_6):
7.88 (d, J=1.4 Hz, 1H), 7.44 (d, J=7.5 Hz, 2H), 7.35 (d, J=7.5 Hz, 2H), 7.08 (d, J=1.4 Hz, 1H), 6.54 (bs, 2H), 6.04 (d, J=4.3 Hz, 1H), 5.42 (d, J=4.3 Hz, 1H), 4.62 (d, J=5.7 Hz, 2H), 4.19 (t, J=5.8 Hz, 1H).

Example 11

5-(4-carboxybenzoyl)-3-thiophene sulfonamide

0.53g (1.8 mmol) of 5-(4-hydroxymethylbenzhydrol)-3-thiophene sulfonamide was added to 8.8 mL of acetone. The solution was cooled to 0°C and 1.35mL (3.7 mmol) of Jone's reagent was added. After 15 min. the solvent was

removed under vacuum and the mixture filtered. The solid was washed with water. Flash chromatography utilizing 20% methanol/chloroform as the eluant recovered 0.48g of 5-(4-carboxybenzoyl)-3-thiophene sulfonamide as a white solid.

1H NMR (acetone-d_6):
8.51 (d, J=1.4 Hz, 1H), 8.23 (d, J=8.3 Hz, 2H), 8.01 (d, J=8.3 Hz, 2H), 7.94 (d, J=1.4 Hz, 1H), 6.79 (bs, 2H).

Example 11(a)

5-(3-carboxylbenzoyl)-3-thiophene sulfonamide

1H NMR (acetone-d_6):
8.51 (d, J-1.4 Hz, 1H), 8.50 (s, 1H), 8.34 (d, t, J=7.8, 1.3 Hz, 1H), 8.16 (d, t, J=7.8, 1.3 Hz, 1H), 7.96 (d, J=1.3 Hz, 1H), 7.77 (t, J=7.8 Hz, 1H), 6.81 (bs, 2H).

Example 12

5-[(tetrahydropyranyl)(4-hydroxymethyphenyl)-methyl] -3-thiophene sulfonamide

10.45g (0.91 mmol) of the product from Example #9 was added to L of THF. 1.0mL (1.0 mmol) of a 1M tetra-n-butylammonium fluoride solution was added. After stirring at rt for 1h the solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 1:1 hexane/ethyl acetate as the eluant recovered 0.33 g of the product as a clear colorless oil.

^1H NMR (acetone-d_6):
mixture of diastereomers-
7.97 (s), 7.95 (s), 7.32-7.48 (s), 6.97 (s), 6.60 (bs), 6.55 (bs), 6.05 (s), 5.98 (s), 4.82-4.85 (m), 4.58-4.68 (m), 4.17-4.28 (m), 3.90-33.97 (m), 3.68-3.75 (m), 3.40-3.56 (m), 1.44-1.98.

Example 13

5-(4-acetoxymethylbenzhydrol)-3-thiophene sulfonamide

0.74g (1.9 mmol) of the product from Example #12, 0.23 mL (2.9 mmol) of pyridine and 0.23 mL (2.9 mmol) of acetic anhydride were added to 19 mL of dichloromethane. After stirring at rt for 15h the solution was diluted with ethyl acetate and washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. The 0.60g of the crude product and a catalytic amount of TsOH were added to 14 mL of methanol. After stirring at rt for 3 1/2h the solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 1:1 hexane/ethyl acetate as the eluant recovered 0.37g of 5-(4-acetoxymethyl-benzhydrol)-3-thiophene sulfonamide as a clear colorless oil.

^1H NMR (acetone-d_6):
7.90 (s, 1H), 7.48 (d, J=7.5 Hz, 2H), 7.37 (d, J=7.5 Hz, 2H), 7.12 (s, 1H), 6.55 (bs, 2H), 6.08 (s, 1H), 5.50 (bs, 1H), 5.10 (s, 2H), 2.08 (s, 3H).

Example 14

5-(4-acetoxymethylbenzoyl)-3-thiophene sulfonamide

0.20g (0.6 mmol) of 5-(4-acetoxymethylbenzhydrol)-3-thiophene sulfonamide was added to 6mL of acetone. 0.22 mL (0.6 mmol) of a 2.67 M TBAF solution was added. After stirring at rt for 15 min. the reaction was quenched with isopropyl alcohol. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Recrystallization from ethyl acetate/hexane afforded 0.17g of 5-(4-acetoxymethylbenzoyl)-3-thiophene sulfonamide as white crystals.

^1H NMR (acetone-d_6):
8.47 (d, J=1.4 Hz, 1H), 7.93 (s, 1H), 7.92 (d, J=8.3 Hz, 2H), 7.62 (d, J=8.3 Hz, 2H), 6.80 (bs, 2H), 5.22 (s, 2H), 2.10 (s, 3H).

Example 15

5-(4-hydroxymethylbenzoyl)-3-thiophene sulfonamide

14 mg (41.3 mmol) of 5-(4-acetoxymethylbenzoyl)-3-thiophene sulfonamide and 9 mg (61.8 mmol) of K2CO3 were added to 3 mL of methanol. After stirring at rt for 11h the solution was diluted with ethyl acetate and washed with lN HCl followed with water (2x) and brine. The solvent was removed under vacuum to afford 12.5 mg of 5-(4-hydroxymethylbenzoyl)-3-thiophene sulfonamide as a white solid.

^{1}H NMR (acetone-d_6):

8.46 (d, J=1.4 Hz, 1H), 7.93 (d, J=1.4 Hz, 1H), 7.89 (d, J=8.3 Hz, 2H), 7.59 (d, J=7.9 Hz, 2H), 6.79 (bs, 2H), 4.77 (d, J=5.4 Hz, 2H), 4.51 (t, J=5.7 Hz, 1H).

Example 16

5-(4-formylbenzoyl)-3-thiophene sulfonamide

30 mg (0.1 mmol) of 5-(4-hydroxymethylbenzoyl)-3-thiophene sulfonamide and 300 mg of MnO2 were added to 5mL of THF. After stirring at rt for 30 min. the mixture was filtered through a bed of celite and eluted with ethyl acetate. The filtrate was concentrated and the crude product subjected to flash chromatography utilizing 1:1 ethyl acetate/hexane as the eluant to recover 16 mg of 5-(4-formylbenzoyl)-3-thiophene sulfonamide as a yellow solid.

^{1}H NMR (acetone-d_6):

10.21 (s, 1H), 8.52 (d, J=1.3 Hz, 1H), 8.12 (q, J=9.7 Hz, 4H), 7.94 (d, J=1.3 Hz, 1H), 6.79 (bs, 2H).

Example 16(a)

5-(3-formylbenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

10.18 (s, 1H), 8.52 (d, J=1.3 Hz, 1H), 8.14 (s, 1H), 8.23 (d, t, J=114, 8.0 Hz, 2H), 7.97 (d, J=1.4 Hz, 1H), 7.85 (t, J=8.0 Hz, 1H), 6.80 (bs, 2H).

Example 17

5-(4-formylbenzhydrol)-3-thiophene sulfonamide

0.12 g (0.32 mmol) of the product from Example #12, 4Å molecular sieves and 56mg (0.48 mmol) of NMO were added to 6mL of dichloromethane. After stirring at rt for 15 min. 5.6 mg (0.016 mmol) of TPAP was added. After 4h at rt the mixture was filtered through a plug of celite and eluted with ethyl acetate. The filtrate was concentrated and the crude product subjected to flash chromatography utilizing 1:1 ethyl acetate/hexane as eluant to recover 42 mg of the desired product and 41 mg of starting material.

63 mg (0.17 mmol) of the product and a catalytic amount of TsOH were added to 5mL of methanol. After 4h at rt the solution was diluted with ethyl acetate and washed with saturated $NaHCO_3$ followed with water (3x) and brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum to afford 47 mg of 5-(4-formylbenzhydrol)-3-thiophene sulfonamide as a clear colorless oil.

^1H NMR (acetone-d_6):
10.04 (s, 1H), 7.94 (d, J=8.3 Hz, 2H), 7.93 (s, 1H), 7.73 (d, J=8.3 Hz, 2H), 7.18 (s, 1H), 6.58 (bs, 2H), 6.20 (d, J=4 Hz, 1H), 5.77 (d, J=4 Hz, 1H).

Example 18

5-[(methoxy)(3-trifluoromethylphenyl)methyl]-3-thiophene sulfonamide

0.20g (0.6 mmol) of 5-(3-trifluoromethylbenzhydrol)-3-thiophene sulfonamide and 0.11g (0.6 mmol) of TsOH were added to 10mL of methanol. The solution was heated at reflux for 12 h. The solvent was removed under vacuum and the crude product subjected to flash chromatography utilizing 2:1 hexane/ethyl acetate as the eluant to recover 0.16g of 5-[(methoxy)(3-trifluoromethylphenyl)methyl]-3-thiophene sulfonamide as a white solid.

^1H NMR (acetone-d_6):
7.99 (d, J=1.5 Hz, 1H), 7.66-7.80 (m, 4H), 7.23-7.24 (m, 1H), 6.59 (bs, 2H), 5.76 (s, 1H), 3.41 (s, 3H).

Example 18(a)

5-[(methoxy)(4-hydroxymethylphenyl)methyl]-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

7.94 (d, J=1.1 Hz, 1H), 7.39 (s, 4H), 7.08 (d, J=1.1 Hz, 1H), 6.56 (bs, 2H), 5.56 (s, 1H), 4.64 (d, J=5.9 Hz, 2H), 4.24 (t, J=5.9 Hz, 1H), 3.35 (s, 3H).

Example 19

5-(1-pentanoyl)-3-thiophene sulfonamide, oxime

0.10 gm (0.4 mmol) of 5-(1-pentanoyl)-3-thiophene sulfonamide and 0.28 gm (4 mmol) of $NH_2OH \cdot HCl$ were dissolved in 5 ml of pyridine. The reaction vessel was sealed and heated at 60° C overnight. The reaction solution was cooled to room temperature, diluted with ethyl acetate, washed three times with water and finally with brine. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated. Thin liquid chromatography showed that the starting compounds were present. The concentrate was redissolved in 5 ml of pyridine, 0.25 gm of $NH_2OH \cdot HCl$ were added and the reaction vessel was sealed and heated at 60° C overnight. The resulting reaction solution was cooled to room termperature, extracted with ethyl acetate, washed with water and brine as described above. After drying with $MgSO_4$ and filtering, the organic phase was concentrated and subjected to flash chromatography, utilizing a 2 to 1 mixture of hexane and ethyl acetate, as the eluant, to yield 78 mg. of a white solid having the following NMR spectra:

^{1}H NMR (acetone-d_6):

mixture of Isomers-

11.11 (bs), 10.50 (bs), 8.16 (s), 7.92 (s), 7.78 (s), 7.55 (s), 6.64 (bs), 2.68-2.80 (m), 1.35-1.67 (m), 0.89-0.95 (m).

Example 19(a)-(b)

The compounds of Examples 6(a) and (b) are converted into the corresponding oxime derivatives by the method of Example 19.

Example 19(a)

5-(4-methoxybenzoyl)-3-thiophene sulfonamide, oxime

^{1}H NMR (acetone-d_6):

11.55 (s), 10.58 (s), 8.22 (d, J=111.4 Hz), 7.96 (d, J=11.4 Hz), 7.40-7.47 (m), 7.00-7.07 (m), 6.61-6.64 (m), 3.87 (s), 3.86 (s).

Example 19(b)

5-(4-methoxybenzoyl)-3-thiophene sulfonamide, oxime

^{1}H NMR (acetone-d_6):

mixture of Isomers-

11.69 (bs), 10.65 (bs), 8.24 (d, J=1.4 Hz), 7.98 (d, J=1.4 Hz), 7.37-7.59 (m), 7.02 (d, J=1.4 Hz), 6.58-6.64 (m).

Example 20

5-(4-ethoxycarbonylbenzoyl)-3-thiophene sulfonamide

0.1g (0.32 mmol) of 5-(4-carboxylbenzoyl)-3-thiophene sulfonamide was added to 0.19g (1.13 mmol) of N, N'-diisopropyl-O-ethylisourea in 1.6 mL of THF. Solution was heated at 50°C for 48h. The mixture was filtered through a plug of celite and the filtrate collected and concentrated. Flash chromatography (35% ethyl acetate/hexane) recovered 80 mg of 5-(4-ethoxycarbonylbenzoyl)-3-thiophene sulfonamide as a white color solid.

^{1}H NMR (acetone-d_6):

8.50 (d, J=1.4 Hz, 1H), 8.20 (d, J=8 Hz, 2H), 8.10 (d, J=8 Hz, 2H), 7.92 (d, J=1.4 Hz, 1H), 6.80 (bs, 2H), 4.40 (q, J=7 Hz, 2H), 11.39 (t, J=7 Hz, 3H).

Example 20(a)

5-(3-butoxycarbonylbenzoyl)-3-thiophene sulfonamide

8.50 (d, J=1.4 Hz, 1H), 8.43 (m, 1H), 8.25 (m, 1H), 8.12 (m, 1H), 7.94 (d, J=1.4 Hz, 1H), 7.74 (m, 1H), 6.80 (bs, 2H), 1.60 (s, 9H).

Example 20(b)

5-(4-(2-N,N-dimethylamino-1-ethoxy)carbonylbenzoyl)-3-thiophene sulfonamide

^{1}H NMR (CD_3OD):

8.47 (d, J=1.4 Hz, 1H), 8.29 (d, J=8.5 Hz, 2H), 8.00 (d, J=8.5 Hz, 2H), 7.89 (d, J=1.4 Hz, 1H), 4.73 (t, J=5 Hz, 2H), 3.65 (t, J=5 Hz, 2H), 3.03 (s, 6H).

Example 20(c)

5-(4-t-butoxycarbonylbenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

8.50 (d, J= 1.4 Hz, 1H), 8.16 (d, J=8.5 Hz, 2H), 8.00 (d, J=8.5 Hz, 2H), 7.93 (d, J=1.4 Hz, 1H), 6.79 (bs, 2H), 1.61 (s, 9H).

Example 21

5-(4-acetoxybenzoyl)-3-thiophene sulfonamide

58mg (0.20 mmol) of 5-(4-hydroxybenzoyl)-3-thiophene sulfonamide, 81 mL (1.0 mmol) of pyridine and 94 mL (1.0 mmol) of acetic anhydride were added to 4 mL of THF. The reaction was stirred at rt for 1 1/4h and then diluted with ethyl acetate. The organic phase was washed with water (2x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 1:1 hexane/ethyl acetate as the eluant recovered 51 mg of 5-(4-acetoxybenzoyl)-3-thiophene sulfonamide as tan color crystals.

^{1}H NMR (acetone-d_6):

8.47 (d, J=1.3 Hz, 1H), 7.98 (d, J=8.6 Hz, 2H), 7.96 (d, J=1.3 Hz, 1H), 7.37 (d, J=8.6 Hz, 2H), 6.78 (bs, 2H), 2.32 (s, 3H).

Example 21(a)

5-(3-acetoxybenzoyl)-3-thiophene sulfonamide

^{1}H NMR (acetone-d_6):

8.22 (d, J=1.3 Hz, 1H), 7.69 (d, J=1.3 Hz, 1H), 7.53 (d, d, J=7.8, 1.3 Hz, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.39 (s, 1H), 7.18-7.22 (m,1H), 6.50 (bs, 2H), 2.04 (s, 3H).

Example 22
5-(4-propionoxybenzoyl)-3-thiophene sulfonamide

0.10g (0.35) mmol) of 5-(4-hydroxybenzoyl)-3-thiophene sulfonamide, 85 mL (1.05 mmol) of pyridine, 26mL (0.35 mmol) of propionic acid and 70 mg (0.37 mmol) of EDCI were added to 3.5 mL of THF. The reaction was stirred at rt for 46h. The solution was diluted with ethyl acetate and washed with water (3x) followed with brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum. Flash chromatography utilizing 1:1 ethyl acetate/hexane recovered 77 mg of 5-(4-propionoxybenzoyl)-3-thiophene sulfonamide as a clear colorless oil.

^1H NMR (acetone-d_6):
8.47 (s, 1H), 7.99 (d, J=8.7 Hz, 2H), 7.95 (s, 1H), 6.79 (bs, 2H), 2.67 (q, J=7.4 Hz, 2H), 1.21 (t, J=7.4 Hz, 3H).

Example 22(a)
5-(3-benzoxybenzoyl)-3-thiophene sulfonamide

^1H NMR (acetone-d_6):
8.50 (d, J=1.4 Hz, 1H), 8.21 (d, J=7.2 Hz, 2H), 8.00 (d, J=1.4 Hz, 1H), 7.59-7.88 (m, 7H), 6.78 (bs, 2H).

The compounds of the invention were assayed for biological activity as follows:

Carbonic anhydrase activity was assayed according to the micromethod of Maren (*J. Pharmacol. Exptl. Therap.*, 130, 26-29, 1960). All solutions and reagents were maintained at 0-4°C. The final assay mixture contained 16 mM phenol red, added enzyme and 62.5 mM sodium carbonate/bicarbonate. Its volume was kept constant at 0.8mL. The time required for the added enzyme to lower the pH of CO2-saturated carbonate/bicarbonate buffer from pH 9.9 to 6.8 was measured using the color change of phenol red as endpoint. T1 is the time recorded for the reaction containing no enzyme. T2 is the time recorded for the reaction containing pure CA11 enzyme from human erythrocyte, or an

unknown amount in a sample. Enzyme activities (unit) were calculated using the formula:

$$Unit/ug=(T_1-T_2)(T_2*ug\ protein\ used\ in\ assay)$$

IC50 of a carbonic anhydrase inhibitor is the concentration that lowers the enzyme activity to half.

The results of this assay are reported in Table 1, below.

Table I

Structures	IC50nM
5-(4-acetoxybenzoyl)-3-thiophene sulfonamide	12nM
5-(4-hydroxy-3-(N,N-dimethylaminomethyl)benzoyl)-3-thiophene sulfonamide	30nM
5-(4-hydroxy-3,5-(bis-N,N-dimethylaminomethyl) benzoyl)-3-thiophene sulfonamide	155nM
5-(hydroxymethylbenzoyl)-3-thiophene sulfonamide	17nM
5-(4-propionoxybenzoyl)-3-thiophene sulfonamide	9nM
5-(3-hydroxybenzoyl)-3-thiophene sulfonamide	6.7nM
5-(3-carboxybenzoyl)-3-thiophene sulfonamide	11.14nM
5-(3-formylbenzoyl)-3-thiophene sulfonamide	7.3nM
5-(4-butylbenzoyl)-3-thiophene sulfonamide	8.7nM
5-(3-trifluoromethylbenzoyl)-3-thiophene sulfonamide	8.3nM
5-(2-N,N-dimethylamino-3-ethoxy)carbonylbenzoyl)-3-thiophene sulfonamide	25nM

5-(3-butoxycarbonylbenzoyl)-3-thiophene sulfonamide	25nM
5-(4-acetoxybenzoyl)-3-thiophene sulfonamide	3.6nM
[5-(3-sulfonamidothienyl)][2-pyridyl]ketone	19nM
5-(4-ethoxycarbonylbenzoyl)-3-thiophene sulfonamide	6nM
5-(4-t-butoxycarbonylbenzoyl)-3-thiophene sulfonamide	3nM
5-(3-benzoxybenzoyl)-3-thiophene sulfonamide	5.3nM
5-(4-formylbenzoyl)-3-thiophene sulfonamide	13nm
5-benzoyl-3-thiophene sulfonamide	13nM
5-(4-methoxybenzoyl]-3-thiophene sulfonamide	26nM
5-(1-heptanoyl)-3-thiophene sulfonamide	14nM
5-(1-pentanoyl)-3-thiophene sulfonamide	27nM
5-(4-carboxybenzoyl)-3-thiophene sulfonamide	3.4,5nM
5-(4-hydroxybenzoyl)-3-thiophene sulfonamide	17nM
5-(4-acetoxymethylbenzoyl)-3-thiophene sulfonamide	6nM
5-(2-fluorobenzoyl)-3-thiophene sulfonamide	18nM
5-(3-fluorobenzoyl)-3-thiophene sulfonamide	12nM
5-(3,5-difluorobenzoyl)-3-thiophene sulfonamide	15nM
5-(1-hydroxypentyl)-3-thiophene sulfonamide	32nM

5-(4-hydroxymethylbenzhydrol)-3-thiophene sulfonamide	41nM
5-(4-formylbenzhydrol)-3-thiophene sulfonamide	18nM
5-(1-hydroxyheptanyl)-3-thiophene sulfonamide	31nM
5-(4-methoxybenzhydrol)-3-thiophene sulfonamide	16nM
5-benzhydrol-3-thiophene sulfonamide	74nM
5-(4-acetoxymethylbenzhydrol)-3-thiophene sulfonamide	21nM
5-(4-hydroxybenzhydrol)-3-thiophene sulfonamide	26nM
5-(3-hydroxybenzhydrol)-3-thiophene sulfonamide	37nM
5-[(hydroxy)(pyridyl)methyl]-3-thiophene sulfonamide	240nM
5-(acetoxyphenylmethyl)-3-thiophene sulfonamide	90nM
5-(4-methoxybenzoyl)-3-thiophene sulfonamide, oxime	31nM
5-heptyl-3-thiophene sulfonamide	21nM
5-(1-pentanoyl)-3-thiophene sulfonamide, oxime	22nM
5-[(methoxy)(4-hydroxymethylphenyl)]methyl-3-thiophene sulfonamide	18nM
5-benzoyl-3-thiophene sulfonamide, oxime	53nM

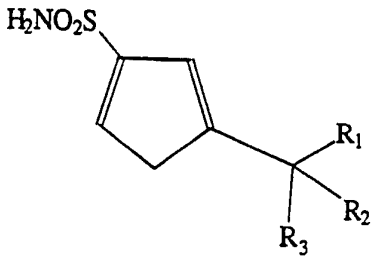
While particular embodiments of the invention have been described it will be understood of course that the invention is not limited thereto since many obvious modifications can be made and it is intended to include within

this invention any such modifications as will fall within the scope of the appended claims.

CLAIMS

Having now described the invention, what is claimed is:

1. Compounds represented by the structural formula:



wherein R_1 and R_2 are independently

(a) hydrogen; or

(b) OR_4 wherein R_4 is hydrogen of C_{1-7} alkyl; or

(c) NR_5R_6 wherein R_5 and R_6 are independently hydrogen, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen or OR_4; or

(d) $-COR_7$, wherein R_7 is hydrogen, C_{1-7} alkyl, or NR_5R_6; or

(e) $-SR_8$, wherein R_8 is hydrogen or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4; or

(f) C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4 or NR_5R_6; or

(g) R_1 and R_2 are together

(i) = O, or

(ii) = NOR_8 or

(iii) = S;

and R_3 is

(h) C_{1-7} alkyl or C_{1-7} substituted with one ore more halogen, OR_4 or NR_5R_6; or

(i) aryl, wherein said aryl comprises up to 10 carbon atoms and is an unsubstituted carbocyclic aryl or heterocyclic aryl radical, or said carbocyclic aryl or heterocyclic aryl radical is substituted with one or more halogen, or OR_4, or NR_5R_6, or C_{1-7} alkyl, or C_{1-7} alkyl substituted with one or more halogen, or OR_4, or NR_5R_6; or

(j) $-COR_9$, wherein R_9 is R_7 or an unsubstituted carbocyclic or heterocyclic radical, wherein said unsubstituted carbocyclic or heterocyclic radical comprises up to 10 carbon atoms, or said carbocyclic or heterocyclic

radical is substituted with one or more halogen, OR_4 or NR_5R_6, or C_{1-7} alkyl substituted with one or more halgen, OR_4 or NR_5R_6.

2. The compound of claim 1 wherein R_1 and R_2, together, represent O or at least one of R_1 or R_2 is hydrogen and the other is selected from the group consisting of hydroxy, acetoxy, oxime and hydrogen.

3. The compound of claim 2 wherein R_3 is C_1 to C_6 alkyl or phenyl or phenyl substituted with at least one hydroxy, methoxy, acetoxy, acetoxymethylene, carboxy, hydroxymethyl, formyl, N, N-dimethylaminomethyl, fluoro, chloro or bromo radicals.

4. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R_3 is phenyl.

5. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R_3 is p-methoxyphenyl.

6. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R_3 is hydroxyphenyl.

7. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R_3 is p-acetoxyphenyl.

8. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R3 is p-acetoxymethylphenyl.

9. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R3 is p-carboxylic phenyl.

10. The compound of claim 3 wherein R_1 and R_2, together, are oxygen and R_3 is n-butyl.

11. The compound of claim 3 wherein R_1 and R2, together, are oxygen and R_3 is n-hexyl.

12. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is phenyl.

13. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-methoxyphenyl.

14. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-hydroxyphenyl.

15. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-acetoxyphenyl.

16. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-acetoxymethylphenyl.

17. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-carboxylic phenyl.

18. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is n-butyl.

19. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is n-hexyl.

20. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is p-formylphenyl.

21. The compound of claim 3 wherein R_1 is hydrogen, R_2 is hydroxy and R_3 is 4-hydroxy-3-N, N-dimethylaminomethylphenyl.

22. The compound of claim 3 wherein R_1 is hydrogen, R_2 is acetoxy and R_3 is phenyl.

23, The compound of claim 3 wherein R_1 and R_2, together, are oxime and R_3 is butyl.

24. The compound of claim 3 wherein R_1 and R_2, together, are oxime and R_3 is p-methoxyphenyl.

25. The compound of claim 2 wherein R_1 and R_2 are hydrogen and R_3 is n-butyl.

26. The compound of claim 1 wherein R_3 is aryl.

27. The compound of claim 26 wherein R_3 is selected from the group consisting of phenyl, thienyl, furyl, pyridyl, pyrryl, piperidyl, pyrrolidyl and morpholinyl.

28. The compound of claim 1 wherein R_3 is -COR_9.

29. The compound of claim 28 wherein R_9 is aryl.

30. The compound of claim 28 wherein R_9 is selected from the group consisting of phenyl, cyclopentyl, cyclohexyl, thienyl, furyl, pyridyl, pyrryl, piperidyl, pyrrolidyl, morpholinyl.

31. A method of treating the elevated intraocular pressure of a patient which comprises administering to said patient an effective amount of a compound according to claim 1.

32. The method of claim 31 which comprises topically administering said compound of claim 1.

33. A method of treating the elevated intraocular pressure of glaucoma in a patient which comprises administering to said patient an effective amount of a compound according to claim 1.

34. The method of claim 33 which comprises topically administering said compound of claim 1.

35. The method of claim 34 which comprises administering a unit it dosage of from 0.001 to 10.0 mg of the compound of claim 1 on a daily basis.

36. A pharmaceutical composition for treating a patient having glaucoma, by topical administration, which comprises an effective amount of a compound according to claim 1 in a pharmaceutically-acceptable carrier.

37. The composition of claim 36 comprising from 0.01 to 15% of said compound of claim 1.

38. A method of inhibiting carbonic anhydrase activity in a patient which comprises administering to said patient an effective amount of a compound according to claim 1.

39. The method of claim 31 which comprises topically administering said compound of claim 1.

40. The method of claim 39 which comprises administering a unit dosage of from 0.001 to 10.0 mg of the compound of claim 1 on a daily basis.

INTERNATIONAL SEARCH REPORT

Inte· ɔnal Application No
PCI/US 93/08006

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D333/34 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 268 396 (MERCK & CO., INC.) 25 May 1988 see claims ---	1,31-40
A	EP,A,0 228 237 (MERCK & CO., INC.) 8 July 1987 see claims ---	1,31-40
A	EP,A,0 467 613 (ELI LILLY AND COMPANY) 22 January 1992 see claim 12; example 18A --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 1993	- 3. 12. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	CHOULY, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 130 109 (MERCK & CO., INC.) 2 January 1985 see claims & US,A,4 477 466 cited in the application & US,A,4 486 444 cited in the application & US,A,4 542 152 cited in the application & US,A,4 585 787 cited in the application	1,31-40
A	GB,A,2 202 532 (MERCK & CO., INC.) 28 September 1988 see claims & US,A,4 914 111 cited in the application	1,31-40
A	GB,A,1 461 729 (CHEVRON RESEARCH COMPANY) 19 January 1977 see claims	1

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 93/08006

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 31-35,38-40 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compounds/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 93/08006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP-A-0228237	08-07-87	JP-A- 62158273	14-07-87
		US-A- 4929637	29-05-90
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		JP-A- 4234382	24-08-92
EP-A-0130109	02-01-85	US-A- 4486444	04-12-84
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		EP-A,B 0130109	02-01-85
US-A-4542152	17-09-85	CA-A- 1219867	31-03-87
		EP-A,B 0130109	02-01-85
		JP-A- 60013785	24-01-85
		US-A- 4585787	29-04-86
US-A-4585787	29-04-86	US-A- 4542152	17-09-85
		CA-A- 1219867	31-03-87
		EP-A,B 0130109	02-01-85
		JP-A- 60013785	24-01-85
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US-A-4914111	03-04-90	GB-A- 2202532	28-09-88
GB-A-1461729	19-01-77	US-A- 3888879	10-06-75
		DE-A- 2528952	19-02-76

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte ional Application No
PC1/US 93/08006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1461729		FR-A,B 2280636	27-02-76
		JP-A- 51015626	07-02-76
		US-A- 3998961	21-12-76