

NOVEL BENZOTHIOPINES HAVING ACTIVITY AS INHIBITORS
OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

5

BACKGROUND OF THE INVENTION

Field of the Invention

10 The present invention relates to novel
benzothiepins, derivatives and analogs thereof,
pharmaceutical compositions containing them, and their
use in medicine, particularly in the prophylaxis and
treatment of hyperlipidemic conditions such as is
15 associated with atherosclerosis or
hypercholesterolemia, in mammals.

Description of Related Art

20 It is well-settled that hyperlipidemic conditions
associated with elevated concentrations of total
cholesterol and low-density lipoprotein cholesterol
are major risk factors for coronary heart disease and
particularly atherosclerosis. Interfering with the
circulation of bile acids within the lumen of the
25 intestinal tract is found to reduce the levels of
serum cholesterol in a causal relationship.
Epidemiological data has accumulated which indicates
such reduction leads to an improvement in the disease
state of atherosclerosis. Stedronsky, in "Interaction
30 of bile acids and cholesterol with nonsystemic agents
having hypocholesterolemic properties," Biochimica et
Biophysica Acta, 1210 (1994) 255-287 discusses the
biochemistry, physiology and known active agents
surrounding bile acids and cholesterol.

35 Pathophysiologic alterations are shown to be
consistent with interruption of the enterohepatic

circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology, 1982:83:804-11.

5 In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihner, E. et al, in " Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein
10 receptor expression in gallstone patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226 and Suckling et al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine
15 treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol
20 levels.

In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target for the treatment of hypercholesterolemia based on an
25 interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

30 In a series of patent applications, e.g. Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various
35 naturally occurring constituents of the enterohepatic circulation system and their derivatives, including

bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as
5 hypocholesterolemic agents.

In vitro bile acid transport inhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for
10 "Hypolipidemic Benzothiazepine Compounds"

Selected benzothiepinines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

15 Other selected benzothiepinines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is
20 limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

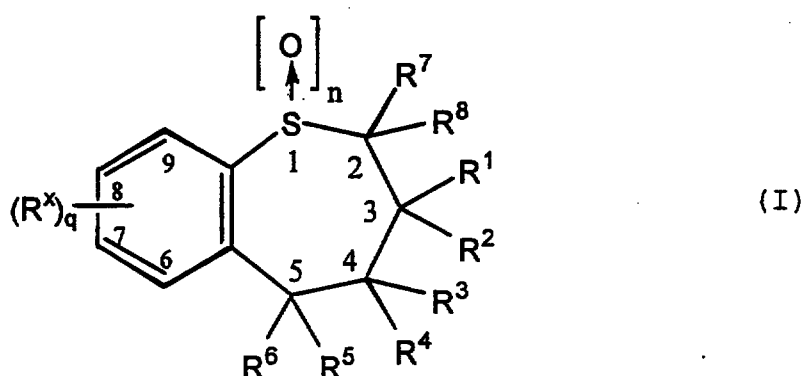
The above references show continuing efforts to find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their
25 usefulness as hypocholesterolemic agents.

Additionally selected benzothiepinines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO
30 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

The present invention furthers such efforts by
35 providing novel benzothiepinines, pharmaceutical compositions, and methods of use therefor.

SUMMARY OF THE INVENTION

Accordingly, among its various aspects, the present invention provides compounds of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^wA⁻, SR⁹, S⁺R⁹R¹⁰A⁻, P⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹, N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or

phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9 ,

SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle,

quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons

replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 ,
 $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene, and R^{13} , R^{14} , and R^{15}
 are independently selected from the group consisting
 of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl,
 5 polyether, aryl, arylalkyl, alkylarylalkyl,
 alkylheteroarylalkyl, alkylheterocyclalkyl,
 cycloalkyl, heterocycle, heteroaryl, quaternary
 heterocycle, quaternary heteroaryl, heterocyclalkyl,
 heteroarylalkyl, quaternary heterocyclalkyl,
 10 quaternary heteroarylalkyl, alkoxyalkyl,
 alkylammoniumalkyl, and
 carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl,
 heterocycle, and polyalkyl optionally have one or more
 15 carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 ,
 $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene,
 carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with
 one or more groups selected from the group consisting
 20 of hydroxy, amino, sulfo, carboxy, alkyl,
 carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl,
 quaternary heterocycle, quaternary heteroaryl,
 quaternary heterocyclalkyl, quaternary
 heteroarylalkyl, guanidinyll,

25 carboxyalkylheterocyclthio, OR^9 , NR^9R^{10} ,
 $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 ,
 CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$,
 $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected
 30 from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to
 which they are attached form a mono- or polycyclic

heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

5 R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

20 wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , 25 oxo, CO_2R^9 , CN , halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

30 wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are

substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen, OH, or SH and when R^5 is OH, R^1 , R^2 , R^3 , R^4 , R^7 and R^8 cannot be all hydrogen;

provided that when R^5 or R^6 is phenyl, only one of R^1 or R^2 is H;

provided that when $q = 1$ and R^x is styryl,

anilido, or anilinocarbonyl, only one of R^5 or R^6 is alkyl;

provided that when n is 1, R^1 , R^3 , R^7 , and R^8 are hydrogen, R^2 is hydrogen, alkyl or aryl, R^4 is unsubstituted amino or amino substituted with one or more alkyl or aryl radicals, and R^5 is hydrogen, alkyl or aryl, then R^6 is other than hydroxy; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferably, R^5 and R^6 can independently be selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quaternary heteroaryl,

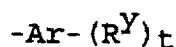
wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 ,

$P(O)R^7$, $P^+R^7R^8A^-$, or phenylene,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$.

More preferably, R^5 or R^6 has the formula:



15

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

one or more R^Y are independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$,

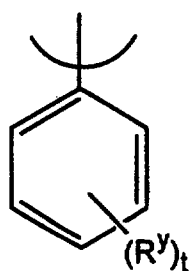
12

$\text{NR}^{13}\text{CO}_2\text{R}^{14}$, $\text{OC(O)}\text{R}^{13}$, $\text{OC(O)}\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{SOR}^{14}$,
 $\text{NR}^{13}\text{SO}_2\text{R}^{14}$, $\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{P(O)}\text{R}^{13}\text{R}^{14}$,
 $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P(OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and
 $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,

5 wherein said alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, haloalkyl, cycloalkyl, and
 heterocycle can be further substituted with one or
 more substituent groups selected from the group
 consisting of OR^7 , NR^7R^8 , SR^7 , $\text{S(O)}\text{R}^7$, SO_2R^7 , SO_3R^7 ,
 10 CO_2R^7 , CN, oxo, CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$, alkyl, alkenyl,
 alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl,
 quaternary heterocycle, quaternary heteroaryl,
 $\text{P(O)}\text{R}^7\text{R}^8$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, and $\text{P(O)}(\text{OR}^7)\text{OR}^8$, and

15 wherein said alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, haloalkyl, cycloalkyl, and
 heterocycle can optionally have one or more carbons
 replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 ,
 $\text{P(O)}\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene.

20 Still more preferably, R^5 or R^6 has the formula
 (II):

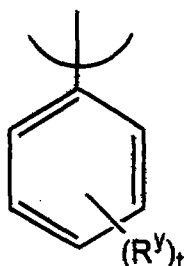


(II)

25

A first class of compounds of particular interest
 consists of those compounds of formula I wherein

q is 1 or 2;
 n is 2;
 R^1 and R^2 are each alkyl;
 R^3 is hydroxy;
 R^4 and R^6 are hydrogen;
 R^5 has the formula (II)



(II)

wherein t is an integer from 0 to 5;

one or more R^y are OR^{13} ;

R^{13} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, and quaternary heteroarylalkyl;

said R^{13} alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide;

R^{13} is optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein A^- is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

R^9 and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

5 R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be
10 OH, NH_2 , and SH; or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and

15 R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M;

R^7 and R^8 are hydrogen; and

one or more R^x are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino; or

20 a pharmaceutically acceptable salt, solvate, or prodrug thereof.

A second class of compounds of particular interest consists of those compounds of formula I
25 wherein

q is an integer from 1 to 4;

n is an integer from 0 to 2;

30 R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

35 wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and

cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and

5 $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or

10 phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl,

15 carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

20 R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

25 R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl,

30 cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

5 R^5 is aryl substituted with one or more OR^{13a} ,

wherein R^{13a} is selected from the group consisting of alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, 10 alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13a} is optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, 15 heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, 20 SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected 25 from the substituents constituting R^9 and M; and

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

30 wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and

quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl,

alkylheteroarylalkyl, alkylheterocyclalkyl,
 cycloalkyl, heterocycle, heteroaryl, quaternary
 heterocycle, quaternary heteroaryl, heterocyclalkyl,
 heteroarylalkyl, quaternary heterocyclalkyl,
 5 quaternary heteroarylalkyl, alkylammoniumalkyl, and
 carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl,
 heterocycle, and polyalkyl optionally have one or more
 carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 ,
 10 $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene,
 carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with
 one or more groups selected from the group consisting
 of hydroxy, amino, sulfo, carboxy, alkyl,
 15 carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl,
 quaternary heterocycle, quaternary heteroaryl,
 quaternary heterocyclalkyl, quaternary
 heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,
 SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen,
 20 $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$,
 $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected
 from the substituents constituting R^9 and M; or
 R^{13} and R^{14} , together with the nitrogen atom to
 25 which they are attached form a mono- or polycyclic
 heterocycle that is optionally substituted with one or
 more radicals selected from the group consisting of
 oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to
 30 which they are attached, form a cyclic ring; and
 R^{30} is selected from the group consisting of
 alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl,
 heterocycle, ammoniumalkyl, alkylammoniumalkyl,

arylalkyl, carboxyalkyl, carboxyheteroaryl,
 carboxyheterocycle, carboalkoxyalkyl,
 carboxyalkylamino, heteroarylalkyl, heterocyclalkyl,
 and alkylammoniumalkyl; and

5 R^7 and R^8 are independently selected from the
 group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from
 the group consisting of H, alkyl, alkenyl, alkynyl,
 polyalkyl, acyloxy, aryl, arylalkyl, halogen,
 10 haloalkyl, cycloalkyl, heterocycle, heteroaryl,
 polyether, quaternary heterocycle, quaternary
 heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$,
 SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 ,
 CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$,
 15 $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} ,
 $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$,
 $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and
 carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl,
 20 aryl, polyalkyl, heterocycle, acyloxy, arylalkyl,
 haloalkyl, polyether, quaternary heterocycle, and
 quaternary heteroaryl can be further substituted with
 OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 ,
 oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$,
 25 $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting
 of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle,
 heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl,
 30 heterocycle, heteroaryl, alkyl, quaternary
 heterocycle, and quaternary heteroaryl optionally are
 substituted with one or more substituents selected

from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

5 wherein in R^X , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

10 wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

 wherein quaternary heterocycle and quaternary
15 heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} ,
20 SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, or

25 a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferred compounds in this class are compounds wherein:

30 R^5 is phenyl substituted with OR^{13a} ;

R^{13a} is independently selected from the group consisting of alkylarylalkyl, alkylheteroarylalkyl,

alkylheterocyclalkyl, and
carboxyalkylaminocarbonylalkyl; and

5 R^{13a} is optionally substituted with one or more
groups selected from the group consisting of carboxy,
quaternary heterocycle, quaternary heteroaryl, and
 NR^9R^{10} .

10 More preferred compounds in this class are
compounds wherein:

R^5 is phenyl substituted with OR^{13a} ;

R^{13a} is alkylarylalkyl; and

15 R^{13a} is optionally substituted with one or more
groups selected from the group consisting of quaternary
heterocycle and quaternary heteroaryl.

Still more preferred in this class are compounds
wherein:

20 R^5 is phenyl substituted with OR^{13a} ;

R^{13a} is alkylphenylalkyl; and

R^{13a} is optionally substituted with one or more
groups selected from the group consisting of quaternary
heterocycle and quaternary heteroaryl.

25 A third class of compounds of particular interest
consists of those compounds of formula I wherein

q is an integer from 1 to 4;

n is an integer from 0 to 2;

30 R^1 and R^2 are independently selected from the
group consisting of H, alkyl, alkenyl, alkynyl,
haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,
dialkylamino, alkylthio, (polyalkyl)aryl, and
cycloalkyl,

35 wherein alkyl, alkenyl, alkynyl, haloalkyl,
alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,
dialkylamino, alkylthio, (polyalkyl)aryl, and

cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and

5 $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or

10 phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl,

15 carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

20 R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

25 R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl,

30 cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

5 R^5 is aryl substituted with one or more OR^{13b} ,

wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, 10 cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

15 R^{13b} is substituted with one or more groups selected from the group consisting of carboxyalkyl, heterocycle, heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, or guanidinyl, and

20 R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and 25 quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, 30 quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$,

$C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$,
 $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$,
 $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$,
 $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

5 wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

10 said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo , $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl,

15 $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

 wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons

20 replaced by O , NR^7 , $N^+R^7R^8A^-$, S , SO , SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl,

25 cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and

30 carboxyalkylaminocarbonylalkyl,

 wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O , NR^9 , $N^+R^9R^{10}A^-$, S , SO , SO_2 ,

$S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen,

haloalkyl, cycloalkyl, heterocycle, heteroaryl,
polyether, quaternary heterocycle, quaternary
heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$,
 SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 ,
5 CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$,
 $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} ,
 $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$,
 $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and
carbohydrate,

10 wherein alkyl, alkenyl, alkynyl, cycloalkyl,
aryl, polyalkyl, heterocycle, acyloxy, arylalkyl,
haloalkyl, polyether, quaternary heterocycle, and
quaternary heteroaryl can be further substituted with
 OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 ,
15 oxo, CO_2R^9 , CN , halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$,
 $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting
of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle,
heteroaryl, alkyl,

20 wherein acyl, arylalkoxycarbonyl, arylalkyl,
heterocycle, heteroaryl, alkyl, quaternary
heterocycle, and quaternary heteroaryl optionally are
substituted with one or more substituents selected
from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$,
25 SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen,
 $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and
 $C(O)OM$,

wherein in R^x , one or more carbons are optionally
replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$,
30 PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid,

peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more
 5 carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,
 10 alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} ,
 15 $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

20 Preferred compounds in this class are compounds wherein:

R^5 is phenyl substituted with OR^{13b} ;

R^{13b} is independently selected from the group consisting of alkyl, quaternary heteroarylalkyl, and
 25 quaternary heterocyclylalkyl; and

R^{13b} is substituted with one or more groups selected from the group consisting of heterocycle, heteroaryl, and guanidinyll.

30 A fourth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the

group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

5 wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of
 10 OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

 wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl
 15 optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

 wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

25 R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined
 30 above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

- wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or
- R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;
- R^5 is aryl substituted with one or more OR^{13b} , wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkoxyalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,
- R^{13b} is substituted with one or more groups selected from the group consisting of OR^{9a} , $NR^{9a}R^{10}$, $N^+R^{9a}R^{11}R^{12}A^-$, SR^{9a} , $S(O)R^{9a}$, SO_2R^{9a} , SO_3R^{9a} , CO_2R^{9a} , $CONR^{9a}R^{10}$, $SO_2NR^{9a}R^{10}$, $P^+R^{9a}R^{10}R^{11}A^-$, and $S^+R^{9a}R^{10}A^-$,
- wherein A^- is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, and
- wherein R^{9a} is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino and carboxyalkylaminoalkyl;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

5 wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

20 A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

 said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

30 wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and

heterocycle can optionally have one or more carbons replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 , $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkoxyalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic

heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

5 R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, 10 carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

15 one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, S(O)₂R¹³, 20 SO₃R¹³, S⁺R¹³R¹⁴A⁻, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, NR¹⁴C(O)R¹³, C(O)NR¹³R¹⁴, NR¹⁴C(O)R¹³, C(O)OM, COR¹³, OR¹⁸, S(O)_nNR¹⁸, NR¹³R¹⁸, NR¹⁸OR¹⁴, N⁺R⁹R¹¹R¹²A⁻, 25 P⁺R⁹R¹¹R¹²A⁻, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and 30 quaternary heteroaryl can be further substituted with OR⁹, NR⁹R¹⁰, N⁺R⁹R¹¹R¹²A⁻, SR⁹, S(O)R⁹, SO₂R⁹, SO₃R⁹, oxo, CO₂R⁹, CN, halogen, CONR⁹R¹⁰, SO₂OM, SO₂NR⁹R¹⁰,

$\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{C}(\text{O})\text{OM}$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

5 wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,
10 , SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_3R^9 , SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, and $\text{C}(\text{O})\text{OM}$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^{13}\text{A}^-$,
15 PR^{13} , $\text{P}(\text{O})\text{R}^{13}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more
20 carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,
25 alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} ,
30 $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferred compounds in this class are compounds wherein:

R^5 is phenyl substituted with OR^{13b} ;

R^{13b} is selected from the group consisting of alkyl and alkoxyalkyl; and

R^{13b} is substituted with one or more groups selected from the group consisting of OR^{9a} and $NR^{9a}R^{10}$; and

R^{9a} is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, and carboxyheterocycle; and

R^{10} is carboxyalkyl.

A fifth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl

optionally have one or more carbons replaced by O,
 NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or
 phenylene,

5 wherein R^9 , R^{10} , and R^W are independently
 selected from the group consisting of H, alkyl,
 alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,
 ammoniumalkyl, arylalkyl, carboxyalkyl,
 carboxyheteroaryl, carboxyheterocycle,
 carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl,
 10 heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which
 they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the
 group consisting of H, alkyl, alkenyl, alkynyl,
 15 acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , S(O)R^9 ,
 SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined
 above; or

R^3 and R^4 together form $=\text{O}$, $=\text{NOR}^{11}$, $=\text{S}$,
 $=\text{NNR}^{11}\text{R}^{12}$, $=\text{NR}^9$, or $=\text{CR}^{11}\text{R}^{12}$,

20 wherein R^{11} and R^{12} are independently selected
 from the group consisting of H, alkyl, alkenyl,
 alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl,
 heterocycle, carboxyalkyl, carboalkoxyalkyl,
 cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , S(O)R^9 ,
 25 SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $\text{CONR}^9\text{R}^{10}$,
 wherein R^9 and R^{10} are as defined above, provided that
 both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon
 atom to which they are attached form a cyclic ring;

30 R^5 is aryl substituted with one or more OR^{13b} ,
 wherein R^{13b} is selected from the group

consisting of alkyl, alkenyl, alkynyl, polyalkyl,
polyether, aryl, arylalkyl, alkylarylalkyl,
alkylheteroarylalkyl, alkylheterocyclalkyl,
cycloalkyl, heterocycle, heteroaryl, quaternary
5 heterocycle, quaternary heteroaryl, heterocyclalkyl,
heteroarylalkyl, quaternary heterocyclalkyl,
quaternary heteroarylalkyl, alkylammoniumalkyl, and
carboxyalkylaminocarbonylalkyl,

R^{13b} is substituted with one or more groups
10 selected from the group consisting of
carboxyalkylheterocycl, NR^9R^{10a} , $CONR^9R^{10a}$,
 $SO_2NR^9R^{10a}$, $P^+R^9R^{10a}R^{11}A^-$, and $S^+R^9R^{10a}A^-$,

wherein A^- is an pharmaceutically acceptable
anion and M is a pharmaceutically acceptable cation,

15 wherein R^{10a} is selected from the group
consisting of carboxyalkyl, carboalkoxyalkyl,
carboxyalkylamino, heteroarylalkyl, and
heterocyclalkyl; or

R^6 is selected from the group consisting of H,
20 alkyl, alkenyl, alkynyl, aryl, cycloalkyl,
heterocycle, quaternary heterocycle, OR^{30} , SR^9 ,
 $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl,
cycloalkyl, heterocycle, quaternary heterocycle, and
25 quaternary heteroaryl can be substituted with one or
more substituent groups independently selected from
the group consisting of alkyl, alkenyl, alkynyl,
polyalkyl, polyether, aryl, haloalkyl, cycloalkyl,
heterocycle, arylalkyl, quaternary heterocycle,
30 quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$,
 SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$,
 NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$,

$C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$,
 $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$,
 $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$,
 $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

5 wherein:

A^- is a pharmaceutically acceptable anion and M
 is a pharmaceutically acceptable cation,

 said alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, haloalkyl, cycloalkyl, and
 10 heterocycle can be further substituted with one or
 more substituent groups selected from the group
 consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 ,
 CO_2R^7 , CN , oxo , $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl,
 alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl,
 15 quaternary heterocycle, quaternary heteroaryl,
 $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and
 wherein said alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, haloalkyl, cycloalkyl, and
 heterocycle can optionally have one or more carbons
 20 replaced by O , NR^7 , $N^+R^7R^8A^-$, S , SO , SO_2 , $S^+R^7A^-$, PR^7 ,
 $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15}
 are independently selected from the group consisting
 of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, arylalkyl, alkylarylalkyl,
 25 alkylheteroarylalkyl, alkylheterocyclalkyl,
 cycloalkyl, heterocycle, heteroaryl, quaternary
 heterocycle, quaternary heteroaryl, heterocyclalkyl,
 heteroarylalkyl, quaternary heterocyclalkyl,
 quaternary heteroarylalkyl, alkylammoniumalkyl, and
 30 carboxyalkylaminocarbonylalkyl,
 wherein alkyl, alkenyl, alkynyl, arylalkyl,
 heterocycle, and polyalkyl optionally have one or more
 carbons replaced by O , NR^9 , $N^+R^9R^{10}A^-$, S , SO , SO_2 ,

$S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M ; or R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen,

- haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,
- wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,
- wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,
- wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid,

peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferred compounds in this class are compounds wherein:

R^5 is phenyl substituted with OR^{13b} ;

R^{13b} is alkyl; and

R^{13b} is substituted with $\text{NR}^9\text{R}^{10a}$; and

R^9 is hydrogen; and

R^{10} is heteroarylalkyl.

A sixth class of compounds of particular interest consists of those compounds of formula I wherein

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl,

haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

5 wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$,
10 $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O,
15 NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl,
20 carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;
25

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined
30 above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more substituent groups independently selected from the group consisting of $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, and $NR^{13}SO_2NR^{14}R^{15}$,

wherein:

R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$

, SR^9 , S(O)R^9 , SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen,
 $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO(OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$,
 $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and C(O)OM ,

wherein A^- is an pharmaceutically acceptable
 5 anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected
 from the substituents constituting R^9 and M; or
 R^{13} and R^{14} , together with the nitrogen atom to
 which they are attached form a mono- or polycyclic
 10 heterocycle that is optionally substituted with one or
 more radicals selected from the group consisting of
 oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to
 which they are attached, form a cyclic ring; and

15 R^6 is selected from the group consisting of H,
 alkyl, alkenyl, alkynyl, aryl, cycloalkyl,
 heterocycle, quaternary heterocycle, OR^{30} , SR^9 ,
 S(O)R^9 , SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl,
 20 cycloalkyl, heterocycle, quaternary heterocycle, and
 quaternary heteroaryl can be substituted with one or
 more substituent groups independently selected from
 the group consisting of alkyl, alkenyl, alkynyl,
 polyalkyl, polyether, aryl, haloalkyl, cycloalkyl,
 25 heterocycle, arylalkyl, quaternary heterocycle,
 quaternary heteroaryl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$,
 SR^{13} , S(O)R^{13} , SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$,
 NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C(O)NR}^{13}\text{R}^{14}$,
 C(O)OM , COR^{13} , $\text{NR}^{13}\text{C(O)R}^{14}$, $\text{NR}^{13}\text{C(O)NR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{CO}_2\text{R}^{14}$,
 30 OC(O)R^{13} , $\text{OC(O)NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{SOR}^{14}$, $\text{NR}^{13}\text{SO}_2\text{R}^{14}$, $\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$,
 $\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{P(O)R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P(OR}^{13})\text{OR}^{14}$,

$S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

5 said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 ,

10 CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

15 wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, 20 heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

25 wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and 30 R^{13} , R^{14} , and R^{15} are optionally substituted with

- one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroaryalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,
- wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroaryalkyl, heterocyclalkyl, and alkylammoniumalkyl; and R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$,

SO_3R^{13} , $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 ,
 CO_2R^{13} , CN , OM , SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$,
 $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , OR^{18} ,
 $\text{S}(\text{O})_n\text{NR}^{18}$, $\text{NR}^{13}\text{R}^{18}$, $\text{NR}^{18}\text{OR}^{14}$, $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,

5 $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and
 10 quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{C}(\text{O})\text{OM}$, and

15 wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are
 20 substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $\text{CONR}^9\text{R}^{10}$, SO_3R^9 , SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, and $\text{C}(\text{O})\text{OM}$,

25 wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^{13}\text{A}^-$, PR^{13} , $\text{P}(\text{O})\text{R}^{13}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

30 wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more

carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$,
 S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary
 heteroaryl are optionally substituted with one or more
 5 groups selected from the group consisting of alkyl,
 alkenyl, alkynyl, polyalkyl, polyether, aryl,
 haloalkyl, cycloalkyl, heterocycle, arylalkyl,
 halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} ,
 SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM,
 10 SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} ,
 $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$,
 and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, or

a pharmaceutically acceptable salt, solvate, or
 prodrug thereof.

15

Preferred compounds in this class are compounds
 wherein:

R^5 is aryl substituted with a radical selected
 20 from the group consisting of $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$ and $\text{NR}^{13}\text{CO}_2\text{R}^{14}$.

More preferred compounds In this class are
 compounds wherein:

R^5 is phenyl substituted with a radical selected
 25 from the group consisting of $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$ and $\text{NR}^{13}\text{CO}_2\text{R}^{14}$.

Other embodiments of the invention are further
 directed to compounds of Formula I, including each of
 the above embodiments, wherein at least one or more of
 30 the following conditions exist:

(1) R^1 and R^2 are independently selected from the
 group consisting of hydrogen and alkyl. Preferably, R^1
 and R^2 are independently selected from the group
 consisting of C_{1-6} alkyl. More preferably, R^1 and R^2 are
 35 the same C_{1-6} alkyl. Still more preferably, R^1 and R^2

are n-butyl; and/or

(2) R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 wherein R^9 is defined as set forth above. Preferably, R^3 is hydrogen and R^4 is OR^9 . Still more preferably, R^3 is hydrogen and R^4 is hydroxy; and/or

(3) R^5 is substituted aryl. Preferably, R^5 is substituted phenyl. More preferably, R^5 is phenyl substituted with a radical selected from the group consisting of OR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, and $NR^{13}SO_2NR^{14}R^{15}$ wherein R^{13} , R^{14} and R^{15} are as set forth above. Still more preferably, R^5 is phenyl substituted with OR^{13} . Still more preferably, R^5 is phenyl substituted at the para or meta position with OR^{13} wherein R^{13} comprises a quaternary heterocycle, quaternary heteroaryl or substituted amino; and/or

(4) R^6 is hydrogen; and/or

(5) R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl. Preferably, R^7 and R^8 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl. Still more preferably, R^7 and R^8 are hydrogen; and/or

(6) R^x is selected from the group consisting of OR^{13} and $NR^{13}R^{14}$. Preferably, R^x is selected from the group consisting of alkoxy, amino, alkylamino and dialkylamino. Still more preferably, R^x is selected from the group consisting of methoxy and dimethylamino.

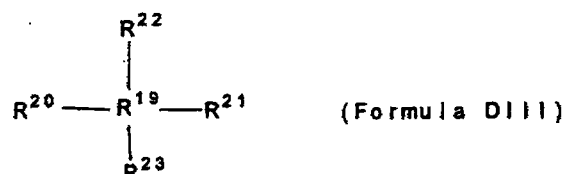
The invention is further directed to a compound selected from among:



5

and

10



wherein R^{19} is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can optionally have one or more carbon atoms replaced by O, NR^7 , $N^+R^7R^8$, S, SO, SO_2 , $S^+R^7R^8$, PR^7 , $P^+R^7R^8$, phenylene, heterocycle, quaternary heterocycle, quaternary heteroaryl, or aryl,

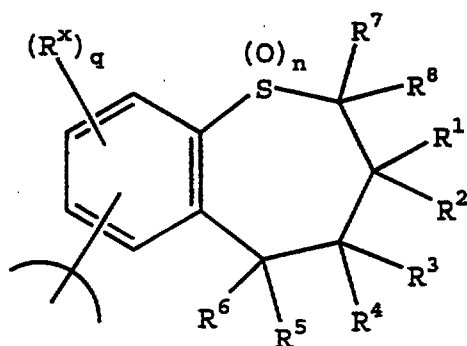
wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$,

50

$C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$,
 $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

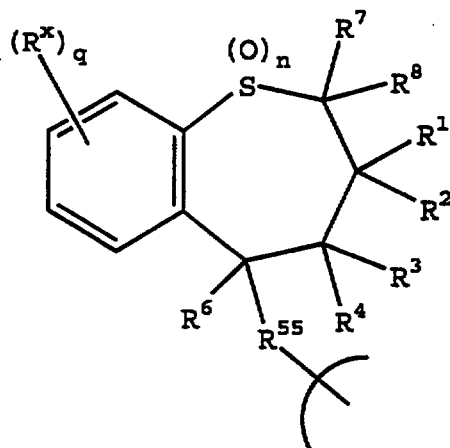
wherein R^{19} further comprises functional linkages by which R^{19} is bonded to R^{20} , R^{21} , or R^{22} in the compounds of Formulae DII and DIII, and R^{23} in the compounds of Formula DIII. Each of R^{20} , R^{21} , or R^{22} and R^{23} comprises a benzothiepine moiety as described above that is therapeutically effective in inhibiting ileal bile acid transport.

The invention is also directed to a compound selected from among Formula DI, Formula DII and Formula DIII in which each of R^{20} , R^{21} , R^{22} and R^{23} comprises a benzothiepine moiety corresponding to the Formula:



(Formula DIV)

or:



(Formula DIVA)

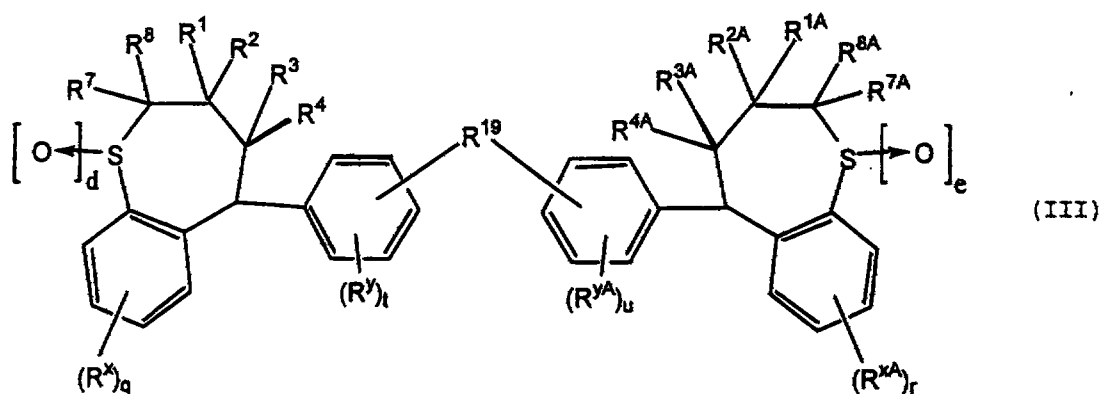
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^x , q , and n are

as defined in Formula I as described above, and R^{55} is either a covalent bond or arylene.

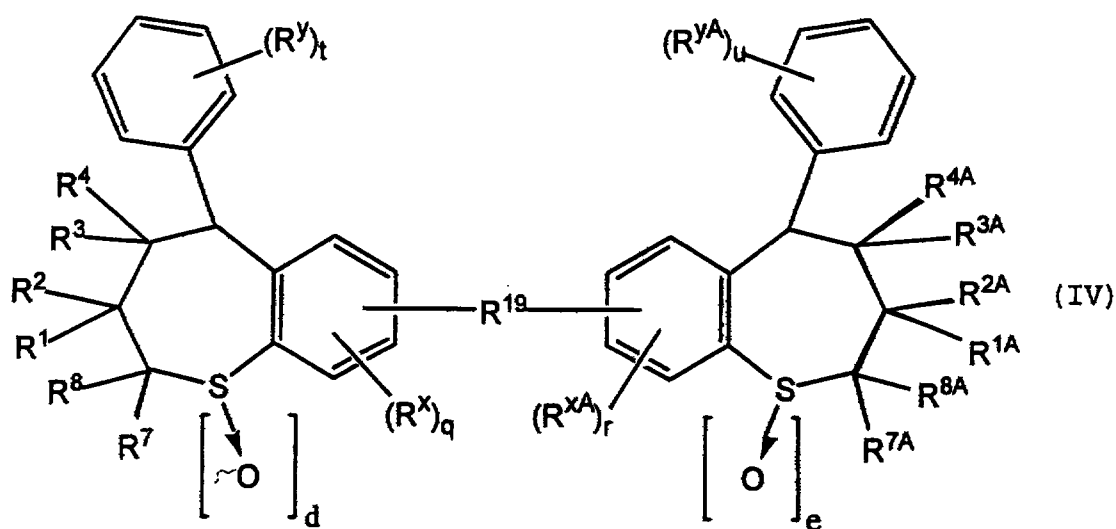
In compounds of Formula DIV, it is particularly preferred that each of R^{20} , R^{21} , and R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII, be bonded at its 7- or 8-position to R^{19} . In compounds of Formula DIVA, it is particularly preferred that R^{55} comprise a phenylene moiety bonded at a *m*- or *p*-carbon thereof to R^{19} .

Examples of Formula DI include:

10

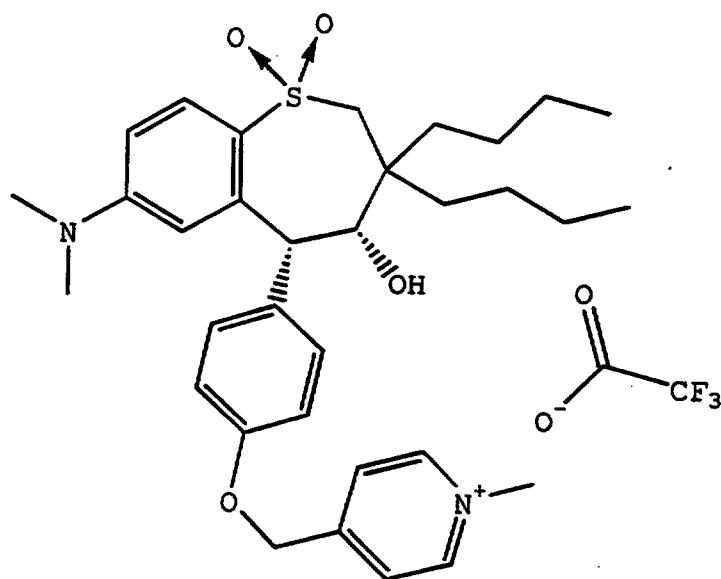
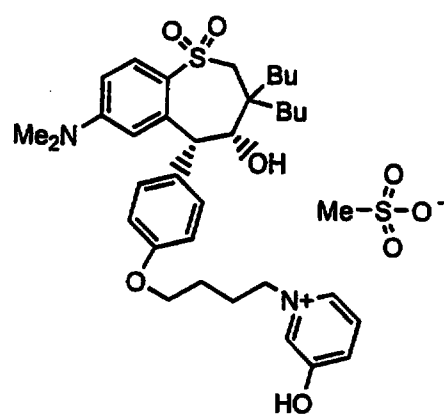


15

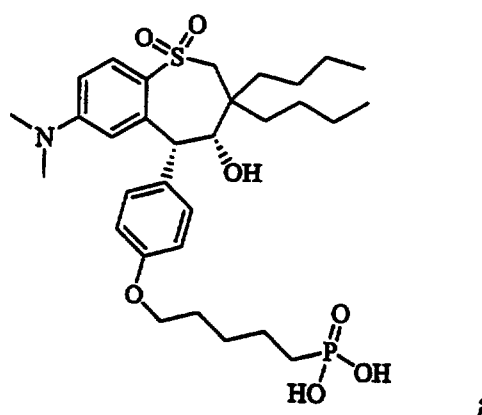


and

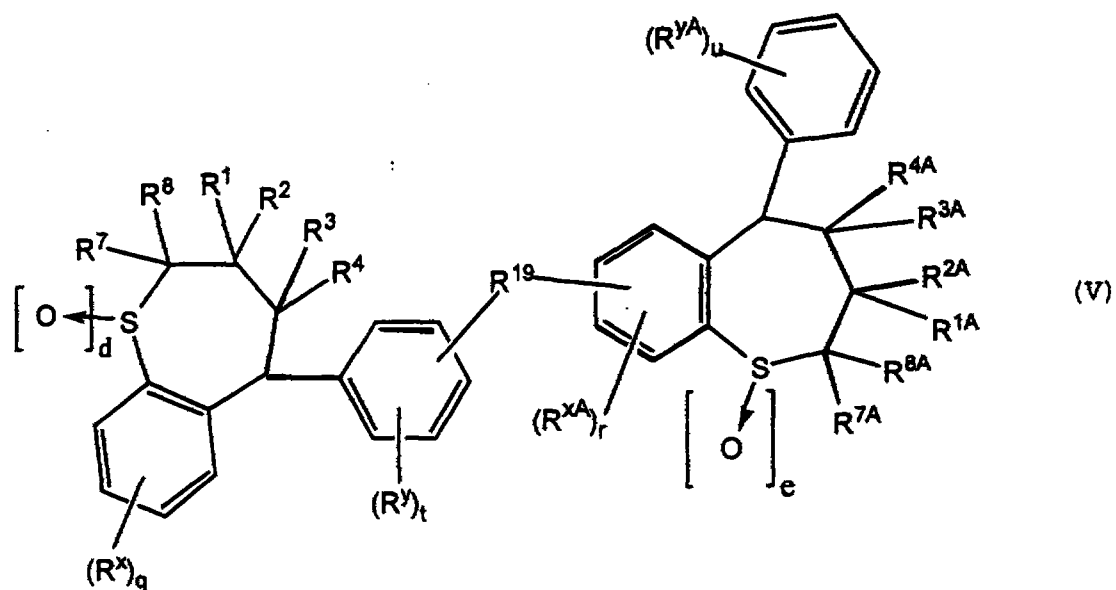
53



5



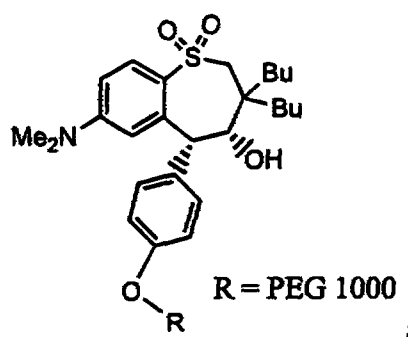
52



5 In any of the dimeric or multimeric structures discussed immediately above, benzothiepine compounds of the present invention can be used alone or in various combinations.

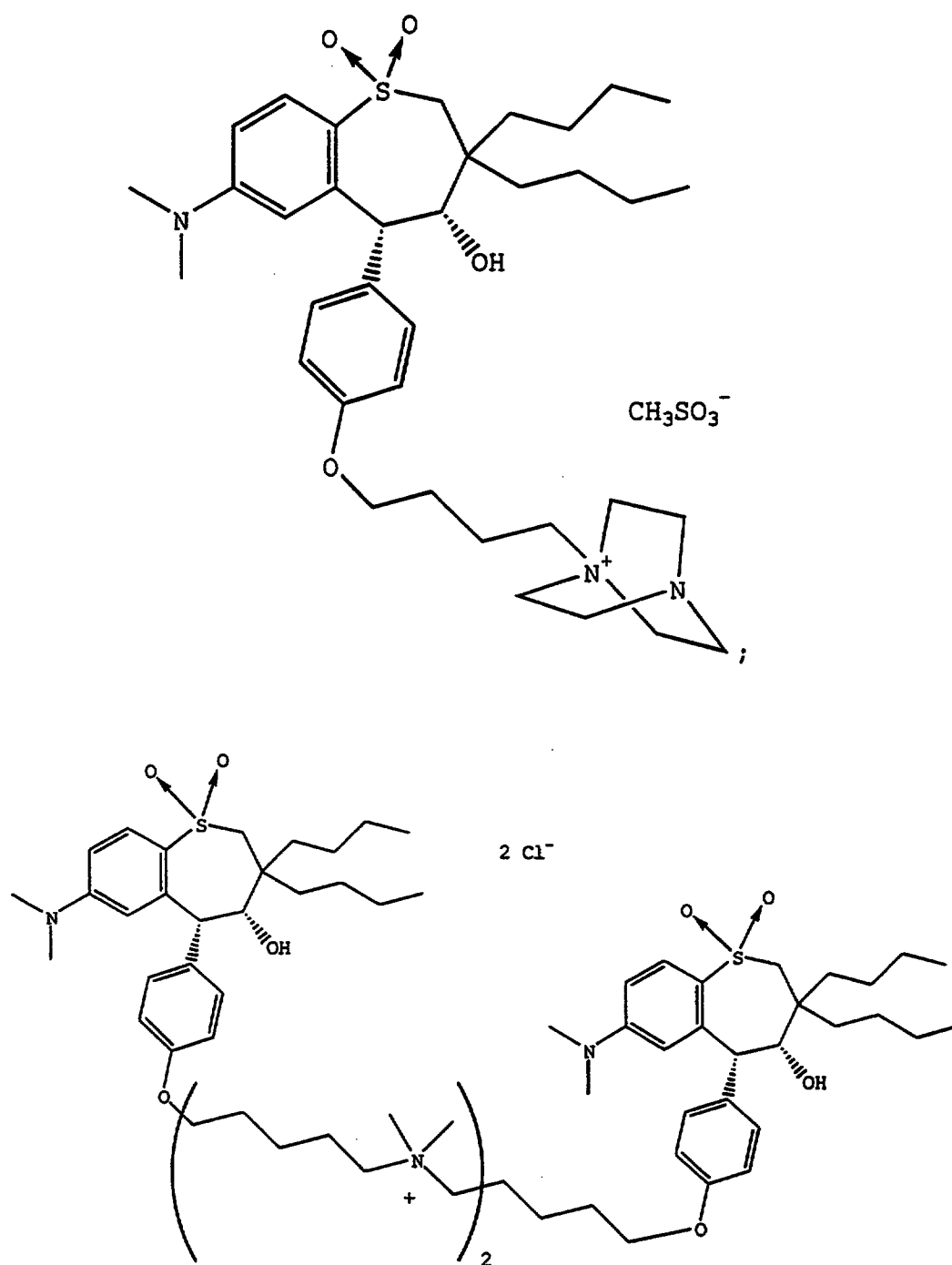
10 In any of the compounds of the present invention, R^1 and R^2 can be ethyl/butyl or butyl/butyl.

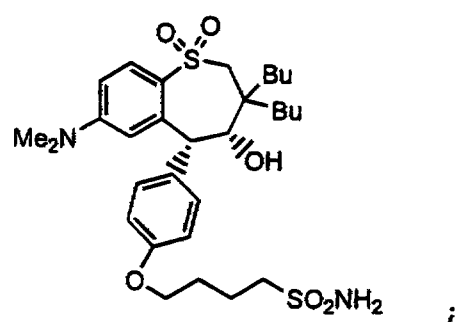
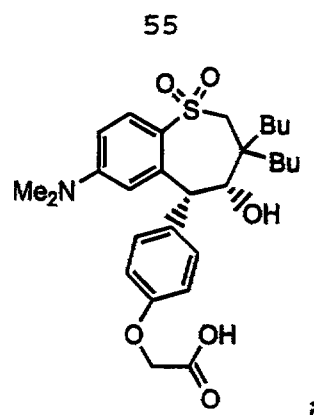
Another class of compounds of interest includes the following compounds:



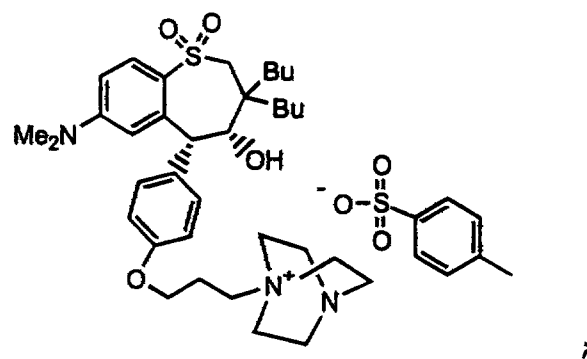
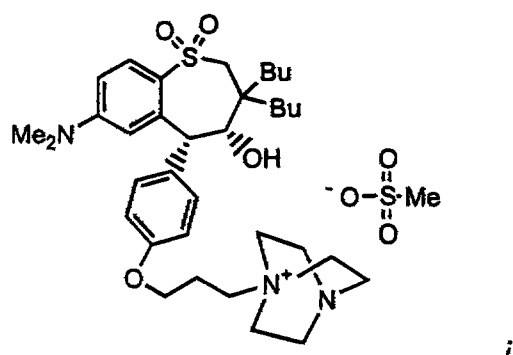
15

54



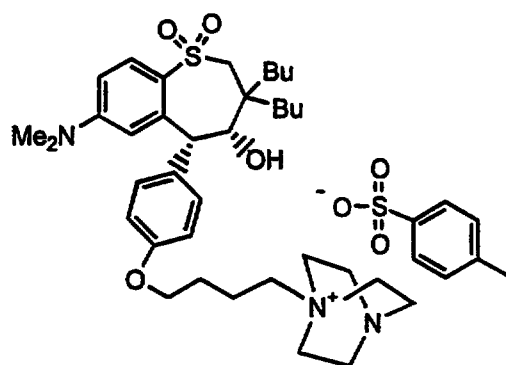


5

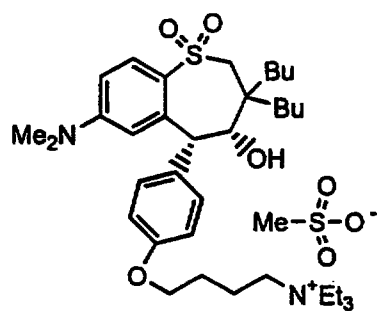


10

56

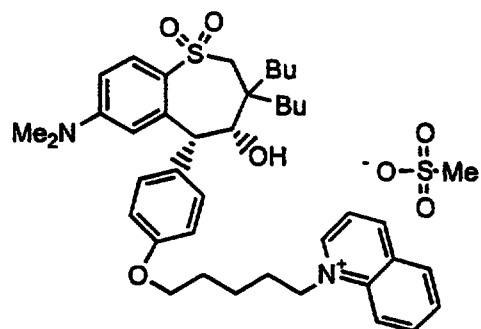


;

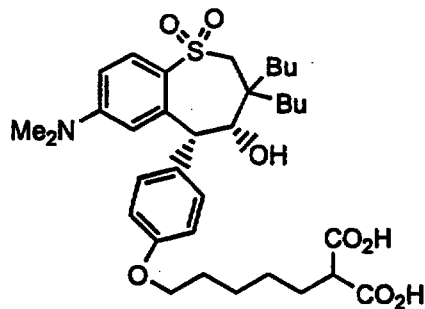


;

5



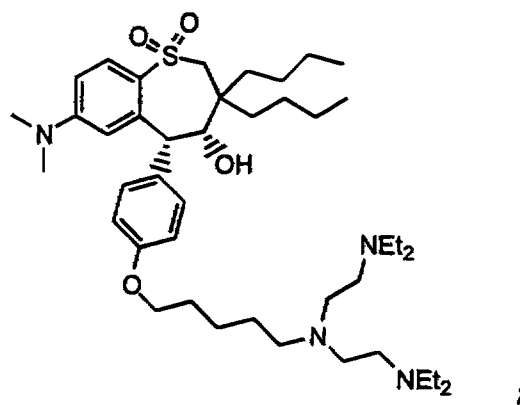
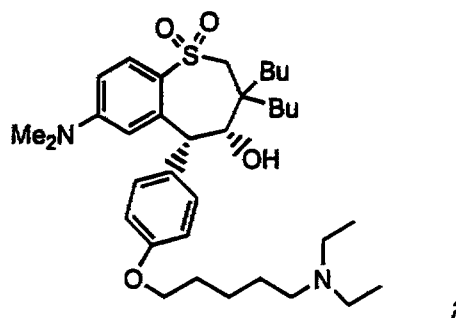
;



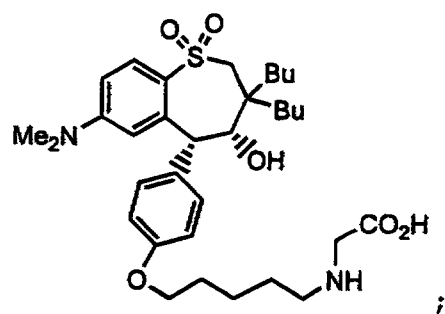
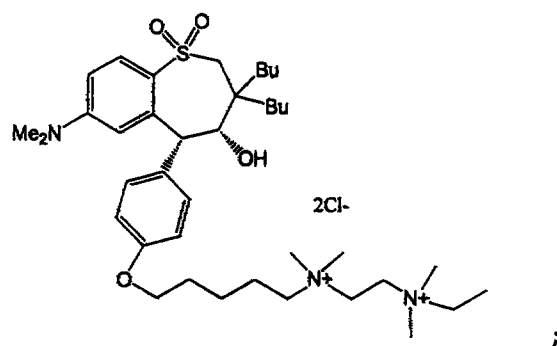
;

10

57

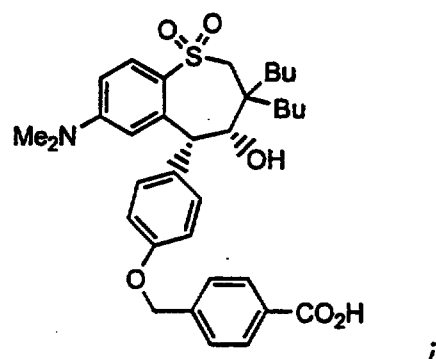


5

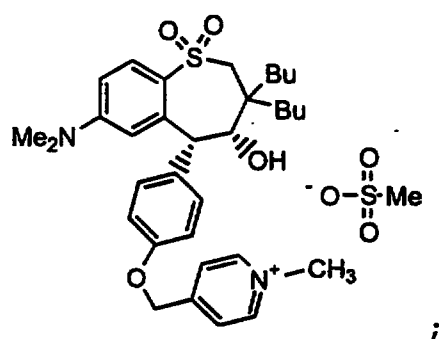


10

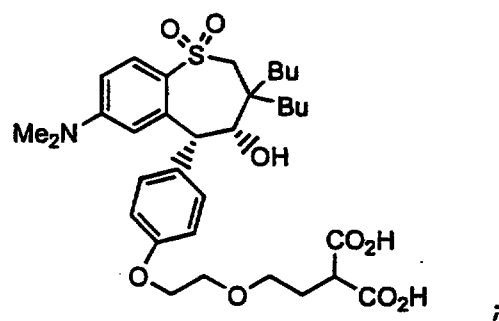
58



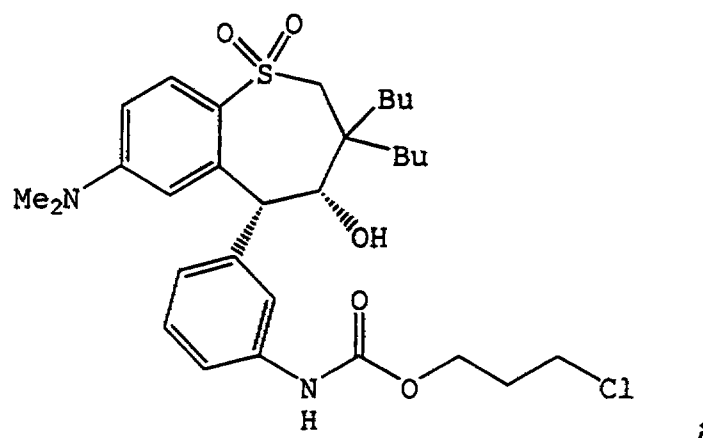
5



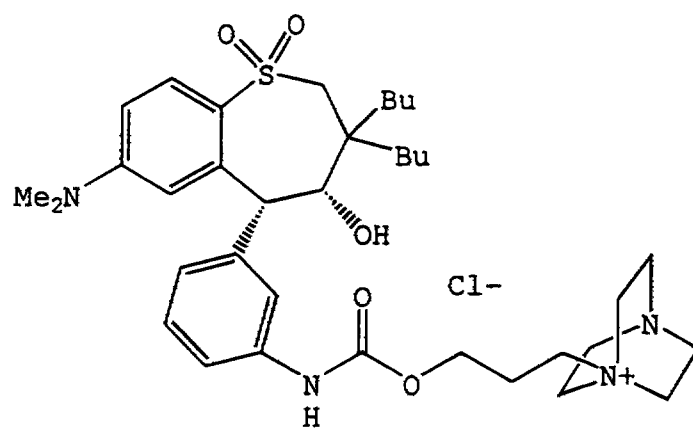
10



59

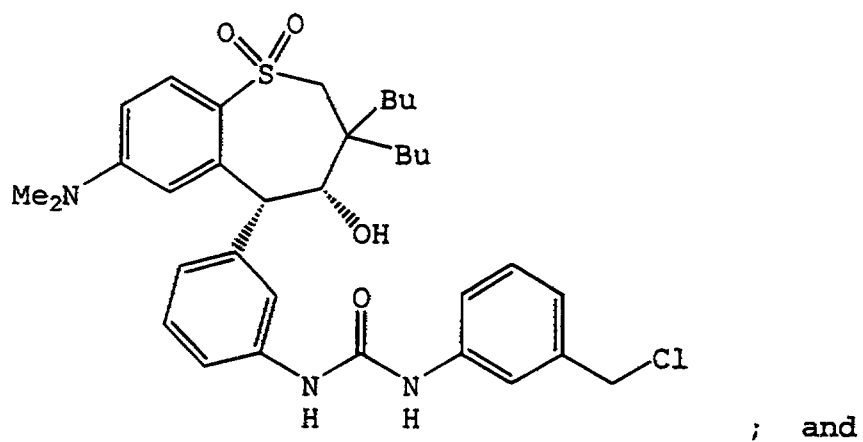


2

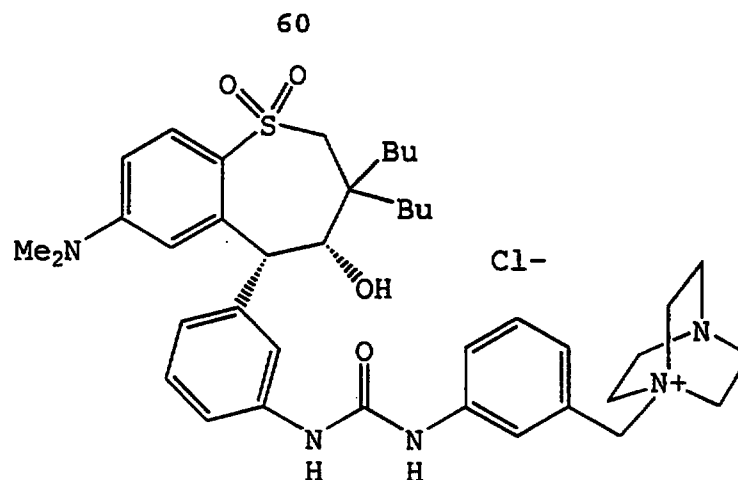


1

5



; and



5 In another aspect, the present invention provides
a pharmaceutical composition for the prophylaxis or
treatment of a disease or condition for which a bile
acid transport inhibitor is indicated, such as a
hyperlipidemic condition, for example,
10 atherosclerosis. Such compositions may comprise any
of the compounds disclosed above, alone or in
combination, in an amount effective to reduce bile
acid levels in the blood, or to reduce transport
thereof across digestive system membranes, and a
15 pharmaceutically acceptable carrier, excipient, or
diluent.

 In a further aspect, the present invention also
provides a method of treating a disease or condition
in mammals, including humans, for which a bile acid
20 transport inhibitor is indicated, comprising
administering to a patient in need any of the
compounds disclosed above, alone or in combination, in
an effective amount in unit dosage form or in divided
doses.

25 In a further aspect, the present invention also
provides the use of any of the compounds disclosed
above, alone or in combination, in the preparation of
a medicament for use in treating a disease or

61

condition in mammals, including humans, for which a bile acid transport inhibitor is indicated.

In yet a further aspect, the present invention also provides processes for the preparation of compounds of the present invention as discussed in greater detail below.

Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

Definitions

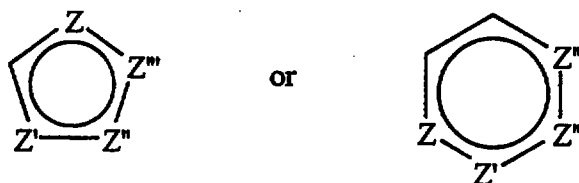
In order to aid the reader in understanding the following detailed description, the following

definitions are provided:

"Alkyl", "alkenyl," and "alkynyl" unless otherwise noted are each straight chain or branched chain hydrocarbons of from one to twenty carbons for alkyl or two to twenty carbons for alkenyl and alkynyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof.

"Aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

"Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



wherein Z, Z', Z'' or Z''' is C, S, P, O, or N, with the proviso that one of Z, Z', Z'' or Z''' is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z', Z'' or Z''' only when each is C.

The term "heteroaryl" means a fully unsaturated heterocycle.

In either "heterocycle" or "heteroaryl," the point of attachment to the molecule of interest can be

at the heteroatom or elsewhere within the ring.

The term "quaternary heterocycle" means a heterocycle in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heterocycle to the molecule of interest can be at a heteroatom or elsewhere.

The term "quaternary heteroaryl" means a heteroaryl in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heteroaryl to the molecule of interest can be at a heteroatom or elsewhere.

The term "halogen" means a fluoro, chloro, bromo or iodo group.

The term "haloalkyl" means alkyl substituted with one or more halogens.

The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

The term "diyl" means a diradical moiety wherein said moiety has two points of attachment to molecules of interest.

The term "oxo" means a doubly bonded oxygen.

The term "polyalkyl" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about

10,000, most preferably up to about 5,000.

The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

The term "cycloalkylidene" means a mono- or multi-ringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

The term "peptide" means polyamino acid containing up to about 100 amino acid units.

The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid units, most preferably from about 100 amino acid units to about 500 amino acid units.

The term "alkylammoniumalkyl" means a NH_2 group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

The term "triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and

heteroaryls.

The term "sulfo" means a sulfo group, $-SO_3H$, or its salts.

5 The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

The term "arylalkyl" means an aryl-substituted alkyl radical such as benzyl. The term "alkylarylalkyl" means an arylalkyl radical that is substituted on the aryl group with one or more alkyl groups.

10 The term "heterocyclalkyl" means an alkyl radical that is substituted with one or more heterocycle groups. Preferable heterocyclalkyl radicals are "lower heterocyclalkyl" radicals having one or more heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

15 The term "heteroarylalkyl" means an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

20 The term "quaternary heterocyclalkyl" means an alkyl radical that is substituted with one or more quaternary heterocycle groups. Preferable quaternary heterocyclalkyl radicals are "lower quaternary heterocyclalkyl" radicals having one or more quaternary heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

25 The term "quaternary heteroarylalkyl" means an alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are "lower quaternary heteroarylalkyl" radicals having one or more quaternary heteroaryl groups attached to an alkyl

30

35

radical having one to ten carbon atoms.

The term "alkylheteroarylalkyl" means a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

The term "alkoxy" an alkyl radical which is attached to the remainder of the molecule by oxygen, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and tert-butoxy.

The term "carboxy" means the carboxy group, $\text{-CO}_2\text{H}$, or its salts.

The term "carboxyalkyl" means an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.

The term "carboxyheterocycle" means a heterocycle radical that is substituted with one or more carboxy groups.

The term "carboxyheteroaryl" means a heteroaryl radical that is substituted with one or more carboxy groups.

The term "carboalkoxyalkyl" means an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.

The term "carboxyalkylamino" means an amino radical that is mono- or di-substituted with carboxyalkyl. Preferably, the carboxyalkyl

substituent is a "lower carboxyalkyl" radical wherein the carboxy group is attached to an alkyl radical having one to six carbon atoms.

5 The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

10 The term "a bile acid transport inhibitor" means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well
15 as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport
20 inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

Compounds

25 The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting
30 enantiomeric starting materials, or by separating isomers of compounds of the present invention.

Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the
35 compounds of the present invention.

The compounds of the present invention also

include tautomers.

The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

5

Compound Syntheses

The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

Generally, the compounds of the present invention can be prepared by the procedures described below.

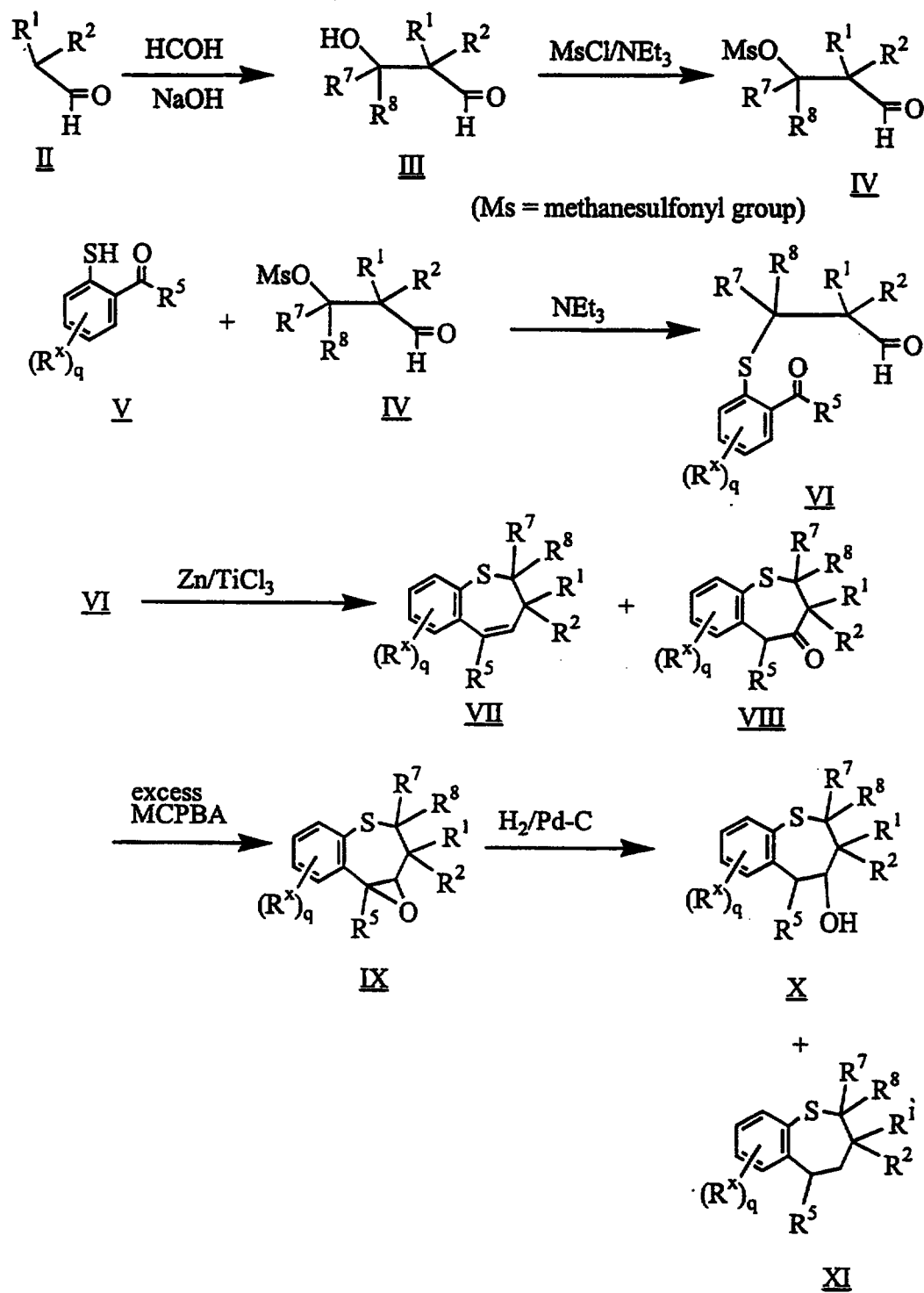
For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and triethylamine similar to the procedure described in Chem. Ber. 98, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields keto-aldehyde VI which can be cyclized with the reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-dihydrobenzothiepine VII and two racemic stereoisomers of benzothiepin-(5H)-4-one VIII when R^1 and R^2 are nonequivalent. Oxidation of VII with 3 equivalents of m-chloro-perbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two racemic stereoisomers of 2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides XI when R^1 and R^2 are nonequivalent.

35

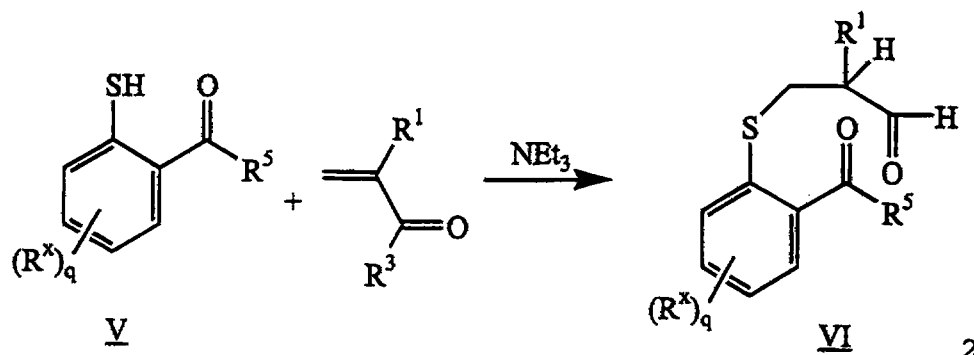
Optically active compounds of the present

invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in *J. Org. Chem.*, 39, 3904 (1974), *ibid.*, 42, 2781 (1977), and *ibid.*, 44, 4891 (1979).

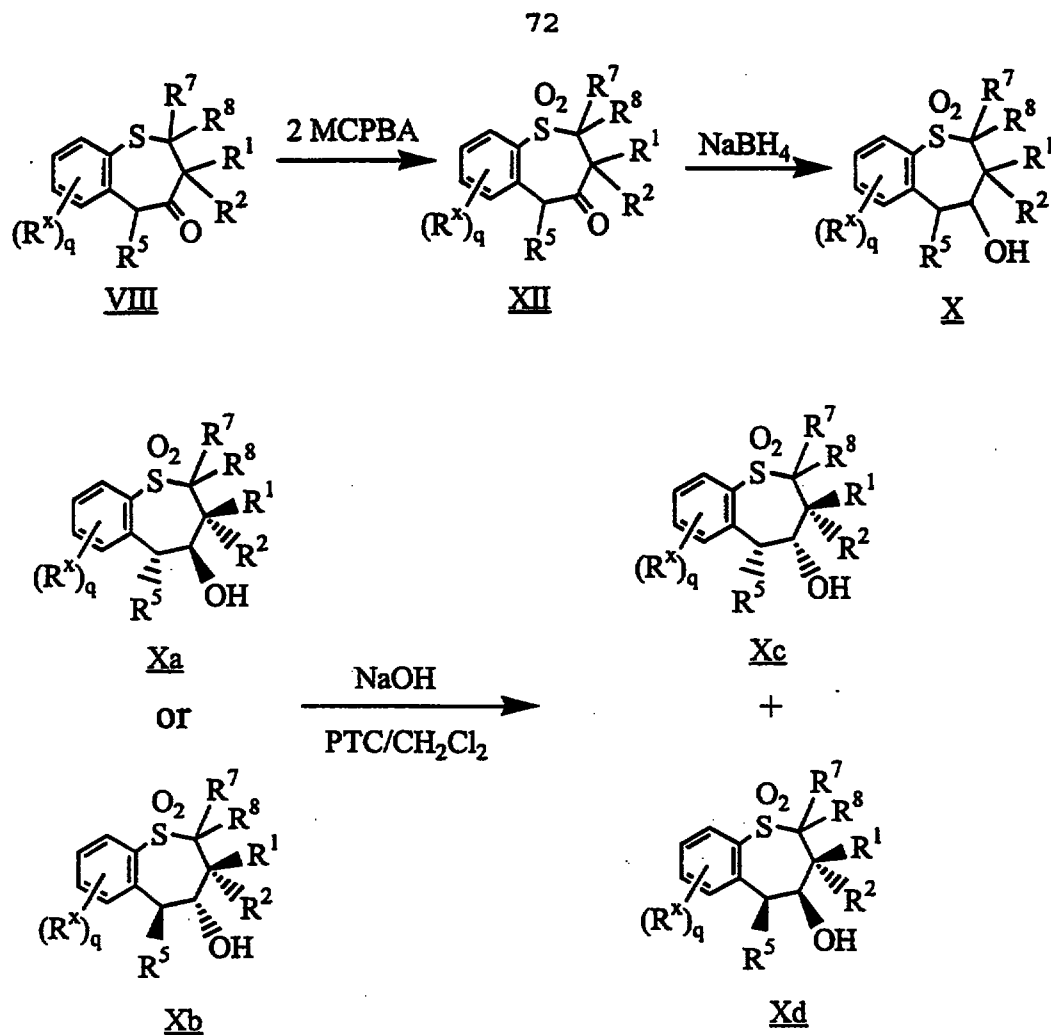
70

Scheme 1

1



Benzothiepin-(5H)-4-one VIII can be oxidized with
 MCPBA to give the benzothiepin-(5H)-4-one-1,1-dioxide
 XII which can be reduced with sodium borohydride to
 5 give four racemic stereoisomers of X. The two
 stereoisomers of X, Xa and Xb, having the OH group and
 R⁵ on the opposite sides of the benzothiepine ring can
 be converted to the other two isomers of X, Xc and Xd,
 10 having the OH group and R⁵ on the same side of the
 benzothiepine ring by reaction in methylene chloride
 with 40-50% sodium hydroxide in the presence of a
 phase transfer catalyst (PTC). The transformation can
 also be carried out with potassium t-butoxide in THF.



MCPBA = m-chloroperbenzoic acid

PTC = phase transfer catalyst

when R^1 = butyl, R^2 = ethyl, R^5 = phenyl, $\text{X} = \text{H}$, $q = 4$

6a = Xa

6b = Xb

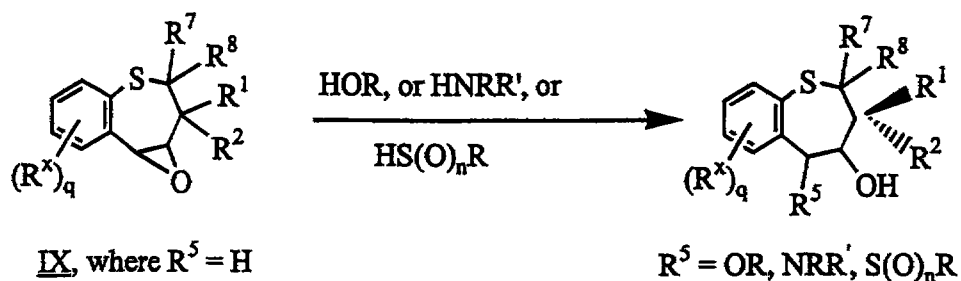
6c = Xc

6d = Xd

3

The compounds of the present invention where R^5 is OR, NRR' and $\text{S(O)}_n\text{R}$ and R^4 is hydroxy can be prepared by reaction of epoxide IX where R^5 is H with thiol, alcohol, and amine in the presence of a base.

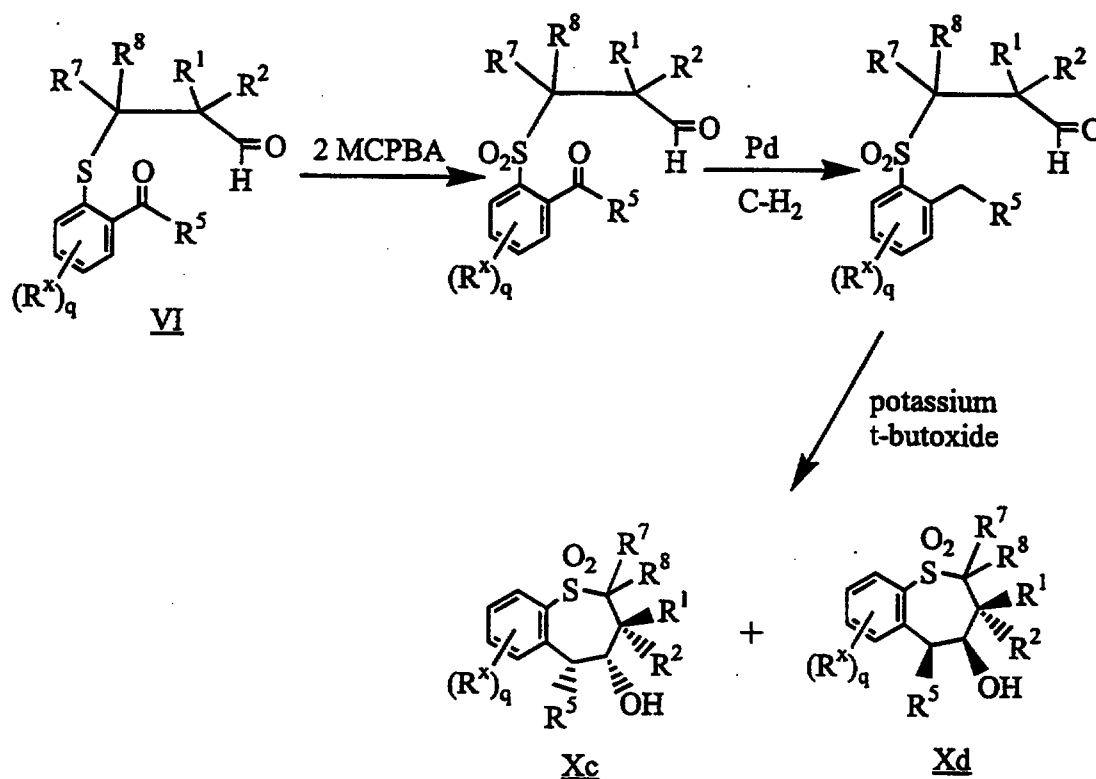
5



Another route to Xc and Xd of the present invention is shown in Scheme 2. Compound VI is oxidized to compound XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional crystallization.

The thiophenols XVIII and V used in the present invention can also be prepared according to the Scheme 3. Alkylation of phenol XV with an arylmethyl chloride in a nonpolar solvent according to the procedure in *J. Chem. Soc.*, 2431-2432 (1958) gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in *J. Org. Chem.*, 31, 3980 (1966). The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermally rearranged at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.

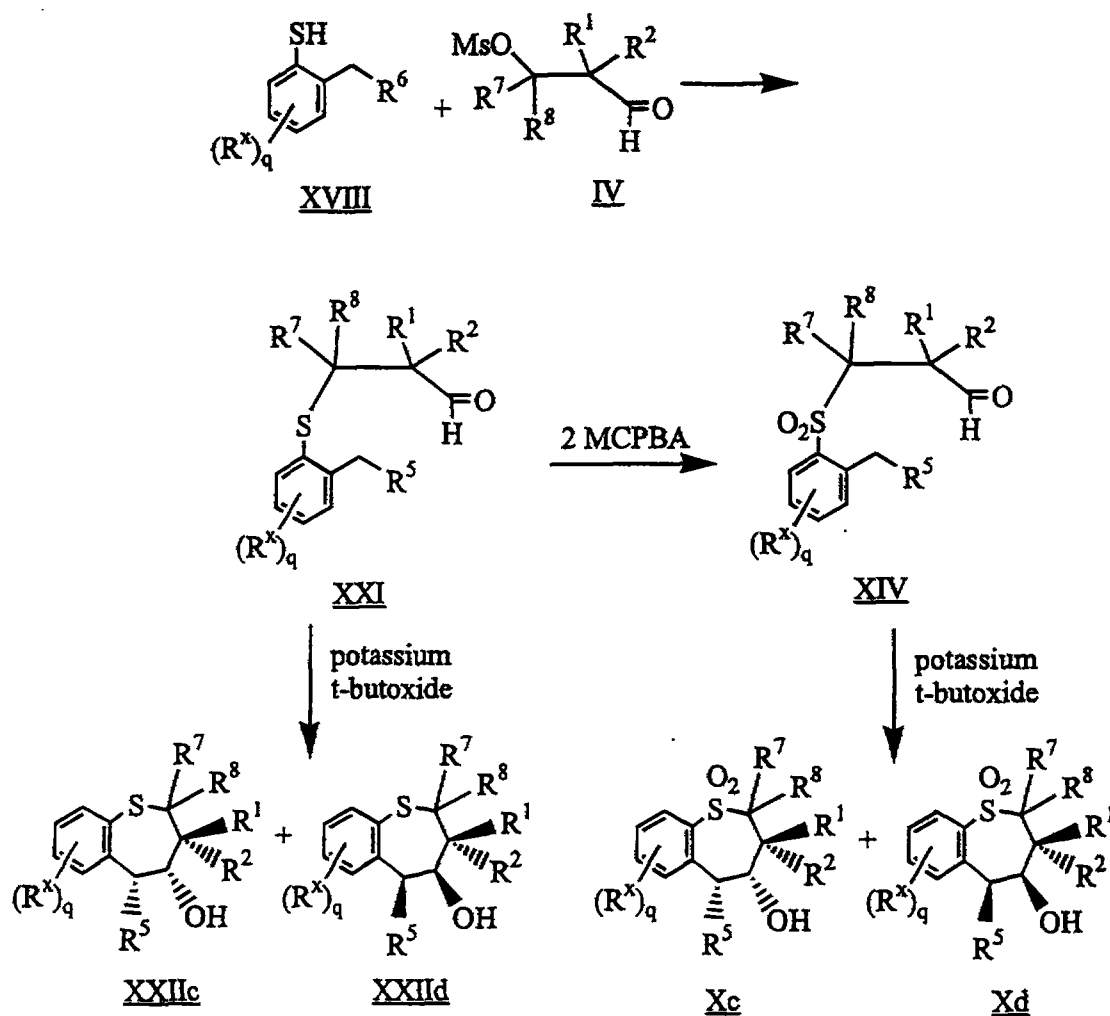
74

Scheme 2

4

5 Scheme 4 shows another route to benzothiepine-
 1,1-dioxides Xc and Xd starting from the thiophenol
 XVIII. Compound XVIII can be reacted with mesylate IV
 to give the sulfide-aldehyde XXI. Oxidation of XXI
 with two equivalents of MCPBA yields the sulfone-
 aldehyde XIV which can be cyclized with potassium t-
 10 butoxide to a mixture of Xc and Xd. Cyclyzation of
 sulfide-aldehyde with potassium t-butoxide also gives
 a mixture of benzothiepine XXII

75

Scheme 4

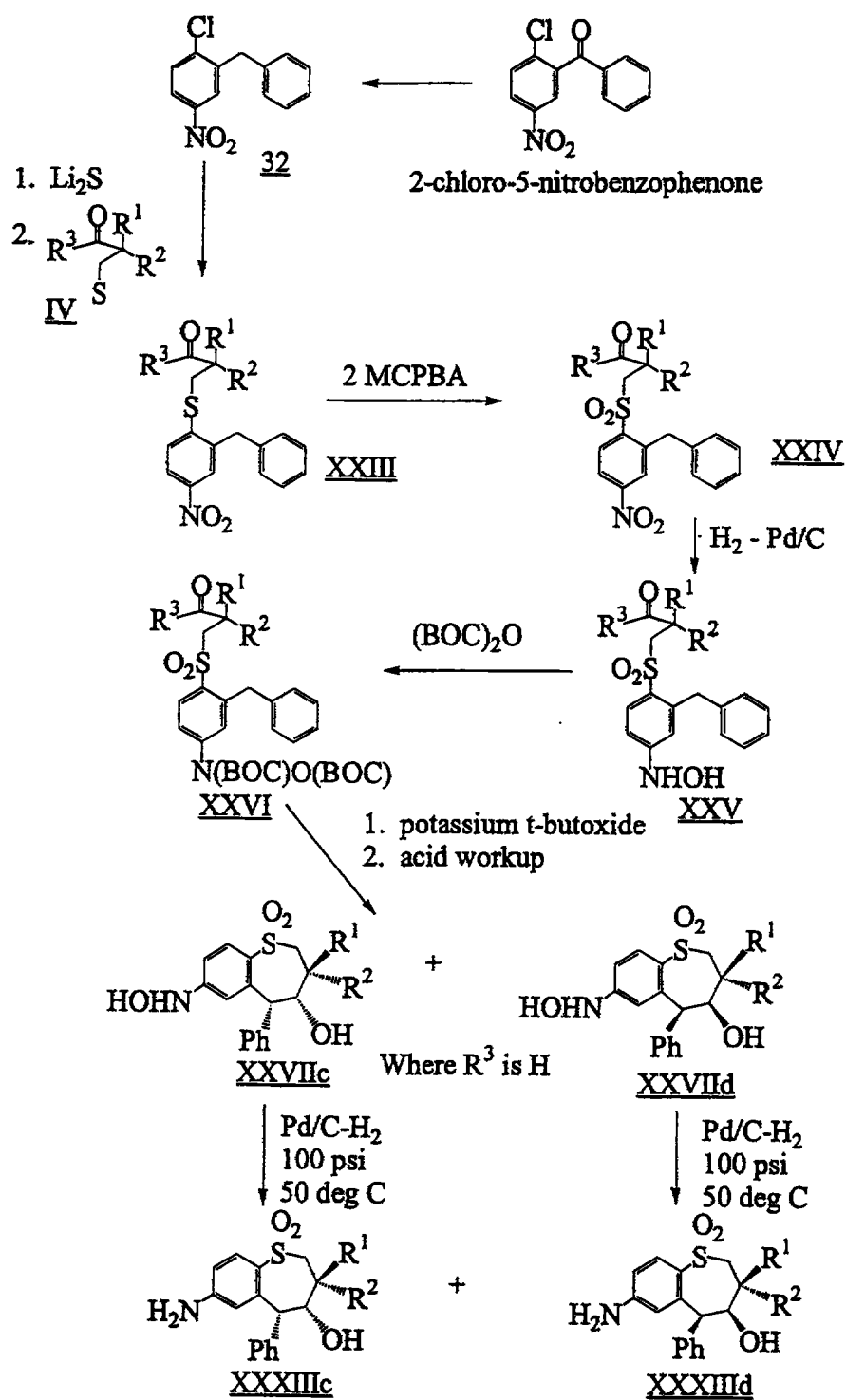
5

Examples of amine- and hydroxylamine-containing compounds of the present invention can be prepared as shown in Scheme 5 and Scheme 6. 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane **32**. Reaction of **32** with lithium sulfide followed by reacting the resulting sulfide with mesylate **IV** gives sulfide-aldehyde **XXIII**. Oxidation of **XXIII** with 2 equivalents of MCPBA yields sulfone-aldehyde **XXIV** which can be reduced by hydrogenation to the hydroxylamine **XXV**. Protecting the

hydroxylamine XXV with di-*t*-butyldicarbonate gives the *N,O*-di-(*t*-butoxycarbonyl)hydroxylamino derivative XXVI. Cyclization of XXVI with potassium *t*-butoxide and removal of the *t*-butoxycarbonyl protecting group gives a mixture of hydroxylamino derivatives XXVIIc and XXVIIId. The primary amine XXXIIId and XXXIIId derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIIId.

77

Scheme 5



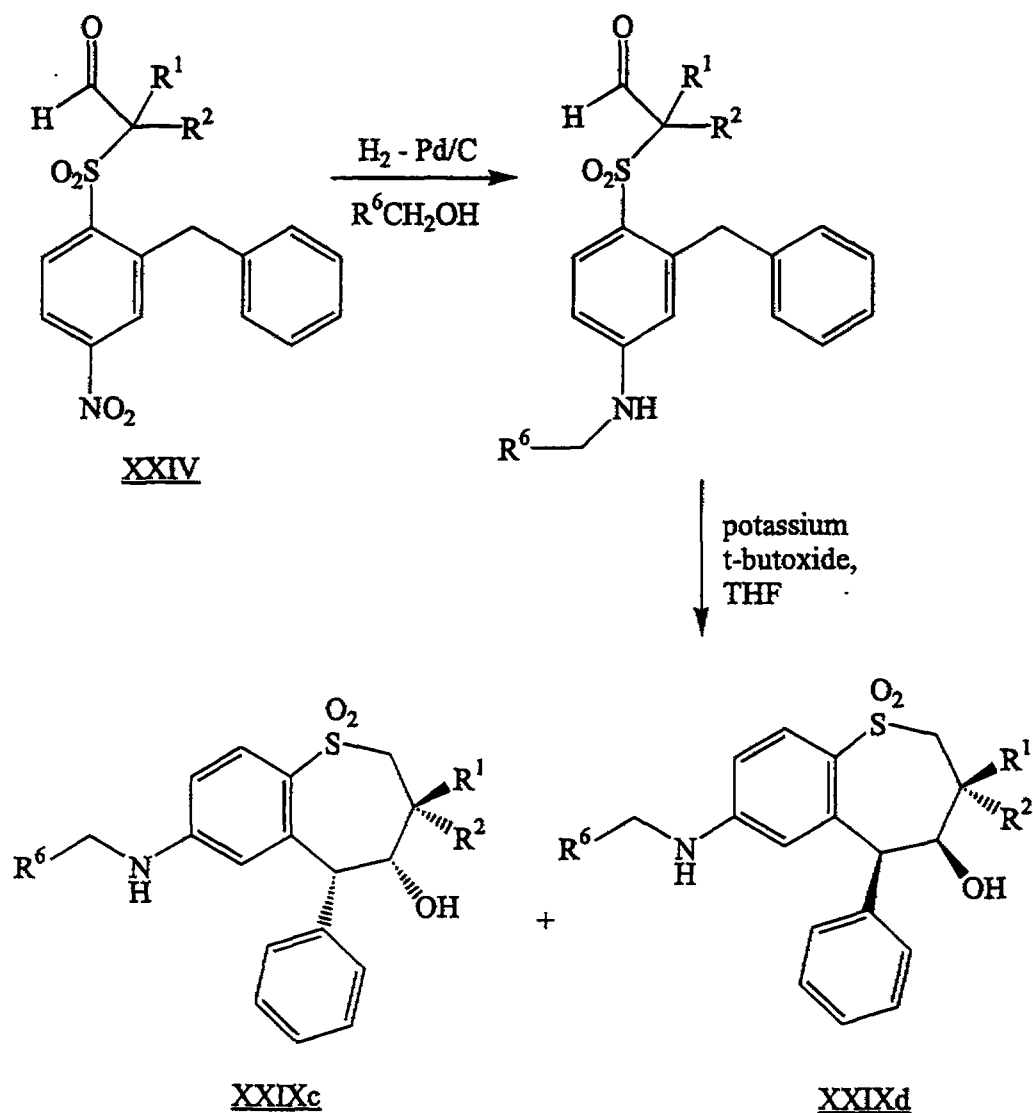
6

In Scheme 6, reduction of the sulfone-aldehyde

XXV with hydrogen followed by reductive alkylation of the resulting amino derivative with hydrogen and an aldehyde catalyzed by palladium on carbon in the same reaction vessel yields the substituted amine derivative XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd.

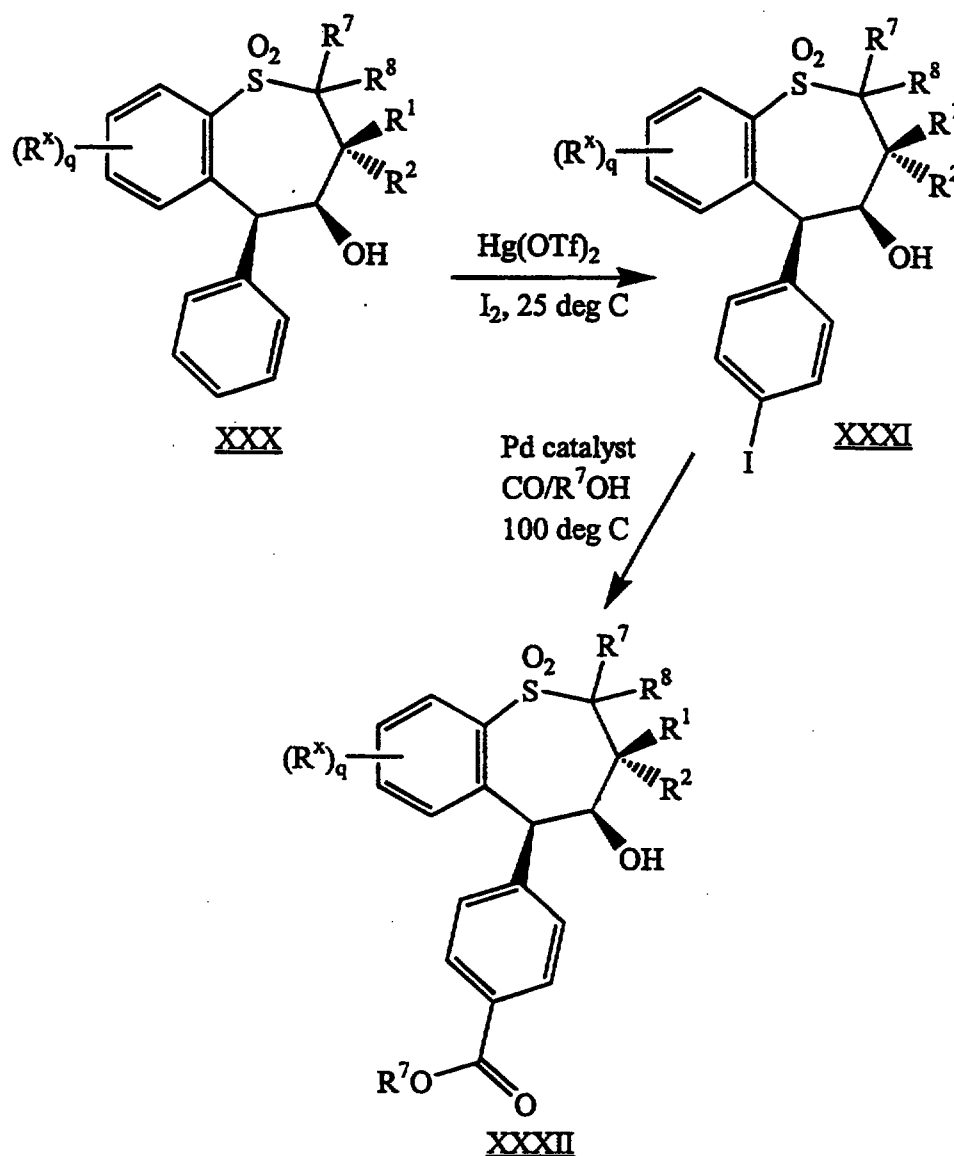
79

Scheme 6



Scheme 7 describes one of the methods of introducing a 5 substituent to the aryl ring at the 5-position of benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo derivative XXXI, which upon palladium-catalyzed carbonylation in an alcohol yields the carboxylate XXXII. Hydrolysis of the carboxylate and derivatization of the resulting acid to acid derivatives are well known in the art.

80

Scheme 7

Abbreviations used in the foregoing description have the following meanings:

5

THF---tetrahydrofuran

PTC---phase transfer catalyst

Aliquart 336---methyltricaprylammonium chloride

MCPBA---m-chloroperbenzoic acid

10

Celite--- a brand of diatomaceous earth filtering aid

	DMF---	dimethylformamide
	DME---	ethylene glycol dimethyl ether
	BOC---	t-butoxycarbonyl group
	Me---	methyl
5	Et---	ethyl
	Bu---	butyl
	EtOAc---	ethyl acetate
	Et ₂ O---	diethyl ether
	CH ₂ Cl ₂ ---	methylene chloride
10	MgSO ₄ ---	magnesium sulfate
	NaOH---	sodium hydroxide
	CH ₃ OH---	methanol
	HCl---	hydrochloric acid
	NaCl---	sodium chloride
15	NaH---	sodium hydride
	LAH---	lithium aluminum hydride
	LiOH---	lithium hydroxide
	Na ₂ SO ₃ ---	sodium sulfite
	NaHCO ₃ ---	sodium bicarbonate
20	DMSO---	dimethylsulfoxide
	KOSiMe ₃ ---	potassium trimethylsilanolate
	PEG---	polyethylene glycol
	MS---	mass spectrometry
	HRMS---	high resolution mass spectrometry
25	ES---	electrospray
	NMR---	nuclear magnetic resonance spectroscopy
	GC---	gas chromatography
	MPLC---	medium pressure liquid chromatography
	HPLC---	high pressure liquid chromatography
30	RPHPLC---	reverse phase high pressure liquid chromatography
	RT---	room temperature
	h or hr---	hour(s)
	min---	minute(s)
35	"Enantiomerically-enriched" (e.e.) means that one enantiomer or set of diastereomers preponderates over	

the complementary enantiomer or set of diastereomers.

Enantiomeric enrichment of a mixture of enantiomers is calculated by dividing the concentration of the preponderating enantiomer by the concentration of the other enantiomer, multiplying the dividend by 100, and expressing the result as a percent. Enantiomeric enrichment can be from about 1% to about 100%, preferably from about 10% to about 100%, and more preferably from about 20% to 100%.

R^1 and R^2 can be selected from among substituted and unsubstituted C_1 to C_{10} alkyl wherein the substituent(s) can be selected from among alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocycles joined to the C_1 to C_{10} alkyl through an ether linkage. Substituents at the 3-carbon can include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, $-CH_2C(=O)C_2H_5$, $-CH_2OC_2H_5$, and $-CH_2O$ -(4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R^1 and R^2 are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating optical isomerism at the 3-carbon simplifies the selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport inhibitor.

In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R^x) on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxycarbonylalkyl amine, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamoyl,

trialkylammonium (especially with a halide counterion), (N)-amido, (N)-alkylamido, -N-alkylamido, -N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-alkylsulfonamido, (N)-haloalkylsulfonamido, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamine, hydroxylamine, haloacylamine, carbohydrate, thiophene a trialkyl ammonium salt having a carboxylic acid or hydroxy substituent on one or more of the alkyl substituents, an alkylene bridge having a quaternary ammonium salt substituted thereon, $-[O(CH_2)_w]_x-X$ where x is 2 to 12, w is 2 or 3 and X is a halo or a quaternary ammonium salt, and (N)-nitrogen containing heterocycle wherein the nitrogen of said heterocycle is optionally quaternized. Among the preferred species which may constitute R^* are methyl, ethyl, isopropyl, t-butyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, hydroxylamine, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)-benzyloxycarbonyl, trimethylammonium, A^- , $-NHC(=O)CH_3$, $-NHC(=O)C_5H_{11}$, $-NHC(=O)C_6H_{13}$, carboxyethylamino, (N)-morpholinyl, (N)-azetidiny, (N)-N-methylazetidinium A^- , (N)-pyrrolidinyl, pyrrolyl, (N)-N-methylpyridinium A^- , (N)-N-methylmorpholinium A^- , and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)-N-hexylamino, thiophene, $-N^+(CH_3)_2CO_2H I^-$, $-NCH_3CH_2CO_2H$, (N)-N'-dimethylpiperazinium I^- , (N)-t-butylloxycarbonyl, (N)-methylsulfonamido, (N)N'-methylpyrrolidinium, and $-(OCH_2CH_2)_3I$, where A^- is a pharmaceutically acceptable anion. The benzo ring is can be mono-substituted at the 6, 7 or 8 position, or disubstituted at the 7- and -8 positions. Also included are the 6,7,8-trialkoxy compounds, for example the 6,7,8-trimethoxy compounds. A variety of

other substituents can be advantageously present on the 6, 7, 8, and/or 9- positions of the benzo ring, including, for example, guanidiny1, cycloalkyl, carbohydrate (e.g., a 5 or 6 carbon monosaccharide), peptide, and quaternary ammonium salts linked to the ring via poly(oxyalkylene) linkages, e.g., $-(OCH_2CH_2)_x-N^+R^{13}R^{14}R^{15}A^-$, where x is 2 to 10.

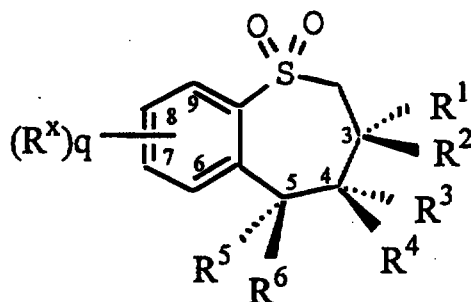
In further compounds of the present invention, R^5 and R^6 are independently selected from among hydrogen and ring-carbon substituted or unsubstituted aryl, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, pyrimidine, morpholine, N-alkylpyridinium, N-alkylpiperazinium, N-alkylmorpholinium, or furan in which the substituent(s) are selected from among halo, hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, N,N-dialkylamino, quaternary ammonium salts, a C_1 to C_4 alkylene bridge having a quaternary ammonium salt substituted thereon, alkoxycarbonyl, aryloxy carbonyl, alkylcarbonyloxy and arylcarbonyloxy, (O,O)-dioxoalkylene, $-[O(CH_2)_w]_xX$ where x is 2 to 12, w is 2 or 3 and X comprises halo or a quaternary ammonium salt, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, or furan. The aryl group of R^5 or R^6 is preferably phenyl, phenylene, or benzene triyl, i.e., may be unsubstituted, mono-substituted, or disubstituted. Among the species which may constitute the substituents on the aryl ring of R^5 or R^6 are fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, trimethylammonium (preferably with an iodide or chloride counterion), methoxycarbonyl, ethoxycarbonyl, formyl, acetyl, propanoyl, (N)-hexyldimethylammonium, hexylenetrimethylammonium, tri(oxyethylene)iodide, and tetra(oxyethylene)trimethyl-ammonium iodide, each substituted at the p-position, the m-position, or both of the aryl ring. Other substituents that can be

present on a phenylene, benzene triyl or other aromatic ring include 3,4-dioxymethylene (5-membered ring) and 3,4-dioxyethylene (6-membered ring). Among compounds which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting properties are those in which R^5 or R^6 is selected from phenyl, p-fluorophenyl, m-fluorophenyl, p-hydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, m-methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,N-dimethylaminophenyl, I^- p-(CH_3)₃-N⁺-phenyl, I^- m-(CH_3)₃-N⁺-phenyl, I^- m-(CH_3)₃-N⁺-CH₂CH₂-(OCH₂CH₂)₂-O-phenyl, I^- p-(CH_3)₃-N⁺-CH₂CH₂-(OCH₂CH₂)₂-O-phenyl, I^- m-(N,N-dimethylpiperazinium)-(N')-CH₂-(OCH₂CH₂)₂-O-phenyl, 3-methoxy-4-fluorophenyl, thienyl-2-yl, 5-cholorothienyl-2-yl, 3,4-difluorophenyl, I^- p-(N,N-dimethylpiperazinium)-(N')-CH₂-(OCH₂CH₂)₂-O-phenyl, 3-fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3-pyridinyl, N-methyl-4-pyridinium, I^- N-methyl-3-pyridinium, 3,4-dioxymethylenephenyl, 3,4-dioxyethylenephenyl, and p-methoxycarbonylphenyl. Preferred compounds include 3-ethyl-3-butyl and 3-butyl-3-butyl compounds having each of the above preferred R^5 substituents in combination with the R^x substituents shown in Table 1. It is particularly preferred that one but not both of R^5 and R^6 is hydrogen.

It is especially preferred that R^4 and R^6 be hydrogen, that R^3 and R^5 not be hydrogen, and that R^3 and R^5 be oriented in the same direction relative to the plane of the molecule, i.e., both in α - or both in β -configuration. It is further preferred that, where R^2 is butyl and R^1 is ethyl, then R^1 has the same orientation relative to the plane of the molecule as R^3 and R^5 .

Set forth in Table 1A are lists of illustrative species of R^1/R^2 , R^5/R^6 and R^x .

Table 1A: Alternative R Groups



R^1, R^2	R^3, R^4	R^5	$(R^x)_q$
Ethyl	HO-	Ph-	7-methyl
n-propyl	H-	p-F-Ph-	7-ethyl
n-butyl		m-F-Ph-	7-iso-propyl
n-pentyl		p-CH ₃ O-Ph-	7-tert-butyl
n-hexyl		p-CH ₃ O-Ph-	7-OH
iso-propyl		m-CH ₃ O-Ph-	7-OCH ₃
iso-butyl		p-(CH ₃) ₂ N-Ph-	7-O(iso-propyl)
iso-pentyl		m-(CH ₃) ₂ N-Ph-	7-SCH ₃
CH ₂ C(=O)C ₂ H ₅		I ⁻ , p-(CH ₃) ₃ -N ⁺ -Ph-	7-SOCH ₃
CH ₂ OC ₂ H ₅		I ⁻ , m-(CH ₃) ₃ -N ⁺ -Ph-	7-SO ₂ CH ₃
CH ₂ CH(OH)C ₂ H ₅		I ⁻ , p-(CH ₃) ₃ -N ⁺ -CH ₂ CH ₂ - (OCH ₂ CH ₂) ₂ -O-Ph-	7-SCH ₂ CH ₃
CH ₂ O- (4-picoline)		I ⁻ , m-(CH ₃) ₃ -N ⁺ -CH ₂ CH ₂ - (OCH ₂ CH ₂) ₂ -O-Ph-	7-NH ₂
		I ⁻ , p-(N,N-dimethylpiperazine)- (N')-CH ₂ -(OCH ₂ CH ₂) ₂ -O- Ph-	7-NHOH
		I ⁻ , m-(N,N-dimethylpiperazine)- (N')-CH ₂ -(OCH ₂ CH ₂) ₂ -O- Ph-	7-NHCH ₃
		m-F, p-CH ₃ O-Ph-	7-N(CH ₃) ₂
		3,4,dioxymethylene-Ph	7-N ⁺ (CH ₃) ₃ , I ⁻
		m-CH ₃ O-, p-F-Ph-	7-NHC(=O)CH ₃
		4-pyridine	7-N(CH ₂ CH ₃) ₂
		N-methyl-4-pyridinium, I ⁻	7-NMeCH ₂ CO ₂ H
		3-pyridine	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
		N-methyl-3-pyridinium, I ⁻	7-(N)-morpholine
		2-pyridine	7-(N)-azetidine
		p-CH ₃ O ₂ C-Ph	7-(N)-N-methylazetidinium, I ⁻
		thienyl-2-yl	7-(N)-pyrrolidine
		5-Cl-thienyl-2-yl	7-(N)-N-methyl- pyrrolidinium, I ⁻
			7-(N)-N-methyl- morpholinium, I ⁻
			7-(N)-N'-methylpiperazine
			7-(N)-N'- dimethylpiperazinium, I ⁻
			7-NH-CBZ
			7-NHC(O)C ₅ H ₁₁
			7-NHC(O)CH ₂ Br
			7-NH-C(NH)NH ₂
			7-(2)-thiophene

continued next page...

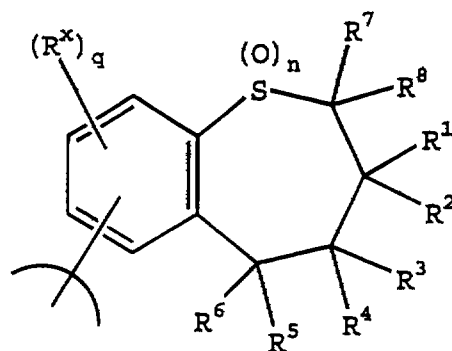
8-methyl
8-ethyl
8-iso-propyl
8-tert-butyl
8-OH
8-OCH₃
8-O(iso-propyl)
8-SCH₃
8-SOCH₃
8-SO₂CH₃
8-SCH₂CH₃
8-NH₂
8-NHOH
8-NHCH₃
8-N(CH₃)₂
8-N⁺(CH₃)₃, I⁻
8-NHC(=O)CH₃
8-N(CH₂CH₃)₂
8-NMeCH₂CO₂H
8-N⁺(Me)₂CH₂CO₂H, I⁻
8-(N)-morpholine
8-(N)-azetidine
8-(N)-N-methylazetidinium,
I⁻
8-(N)-pyrrolidine
8-(N)-N-methyl-
pyrrolidinium, I⁻
8-(N)-N-methyl-
morpholinium, I⁻
8-(N)-N'-methylpiperazine
8-(N)-N'-
dimethylpiperazinium,
I⁻
8-NH-CBZ
8-NHC(O)C₅H₁₁
8-NHC(O)CH₂Br
8-NH-C(NH)NH₂
8-(2)-thiophene

continued next page...

9-methyl
9-ethyl
9-iso-propyl
9-tert-butyl
9-OH
9-OCH₃
9-O(iso-propyl)
9-SCH₃
9-SOCH₃
9-SO₂CH₃
9-SCH₂CH₃
9-NH₂
9-NHOH
9-NHCH₃
9-N(CH₃)₂
9-N⁺(CH₃)₃, I⁻
9-NHC(=O)CH₃
9-N(CH₂CH₃)₂
9-NMeCH₂CO₂H
9-N⁺(Me)₂CH₂CO₂H, I⁻
9-(N)-morpholine
9-(N)-azetidine
9-(N)-N-methylazetidinium,
I⁻
9-(N)-pyrrolidine
9-(N)-N-methyl-
pyrrolidinium, I⁻
9-(N)-N-methyl-
morpholinium, I⁻
9-(N)-N'-methylpiperazine
9-(N)-N'-
dimethylpiperazinium,
I⁻
9-NH-CBZ
9-NHC(O)C₅H₁₁
9-NHC(O)CH₂Br
9-NH-C(NH)NH₂
9-(2)-thiophene

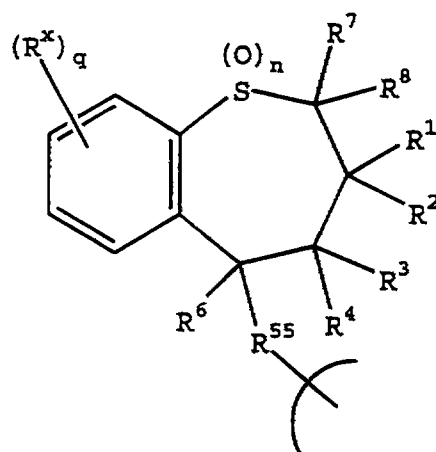
7-OCH₃, 8-OCH₃
7-SCH₃, 8-OCH₃
7-SCH₃, 8-SCH₃
6-OCH₃, 7-OCH₃, 8-OCH₃

Further preferred compounds of the present invention comprise a core structure having two or more pharmaceutically active benzothiepine structures as described above, covalently bonded to the core moiety via functional linkages. Such active benzothiepine structures preferably comprise:



(Formula DIV)

10 or:



(Formula DIVA)

where R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , X , q and n are as defined above, and R^{55} is either a covalent bond or arylene.

The core moiety can comprise alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy

diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{R}^8$, PR^7 , $\text{P}^+\text{R}^7\text{R}^8$, phenylene, heterocycle, quaternary heterocycle, quaternary heteroaryl, or aryl,

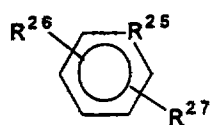
wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$;

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $\text{S}(\text{O})\text{R}^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $\text{P}(\text{O})\text{R}^7\text{R}^8$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, and $\text{P}(\text{O})(\text{OR}^7)\text{OR}^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 , $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene.

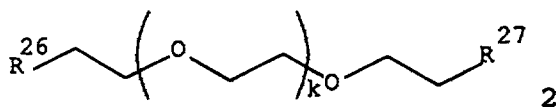
Exemplary core moieties include:

91

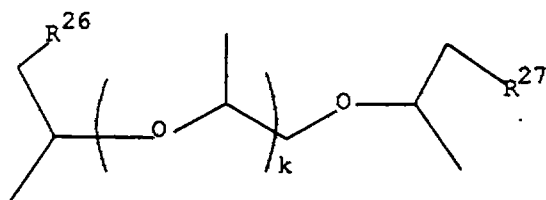


1

5

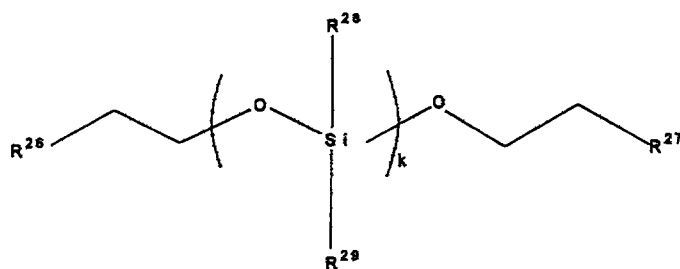


2



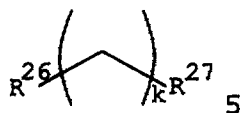
3

10



4

20



5

25

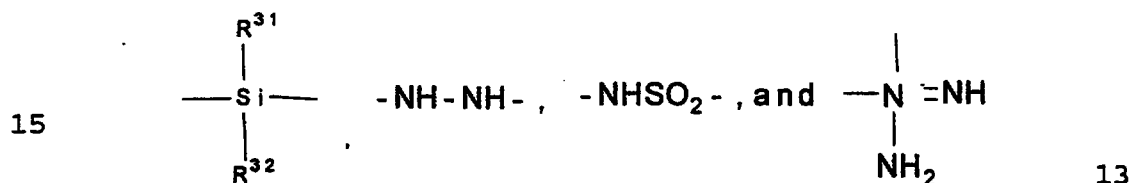
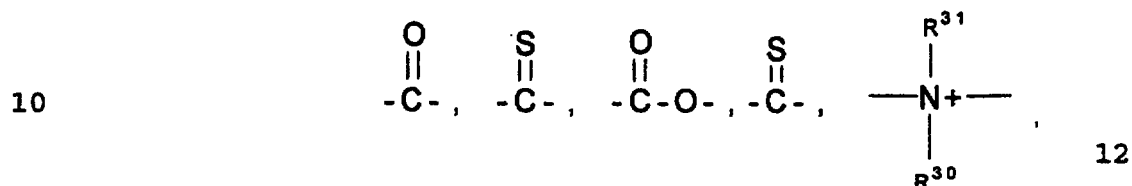
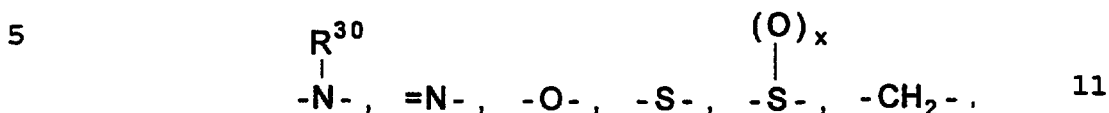
10

wherein:

R^{25} is selected from the group consisting of C and

N, and

R^{26} and R^{27} are independently selected from the group consisting of:



20 wherein R^{26} , R^{29} , R^{30} and R^{31} are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

25 A^- is a pharmaceutically acceptable anion, and $k = 1$ to 10.

In compounds of Formula DIV, R^{20} , R^{21} , R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R^{19} . In compounds of Formula DIVA, it is preferred
30 that R^{55} comprises a phenylene moiety bonded at a m- or p-position thereof to R^{19} .

In another embodiment, a core moiety backbone, R^{19} , as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant
35 active benzothiepine units, i.e., R^{20} , R^{21} , R^{22} , and R^{23} as discussed above, through multiple functional groups

within the core moiety backbone. The core moiety backbone unit, R^{19} , can comprise a single core moiety unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, i.e., alone or in combination. The number of individual core moiety backbone units can range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. The number of points of attachment of similar or different pendant active benzothiepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. Such points of attachment can include bonds to C, S, O, N, or P within any of the groups encompassed by the definition of R^{19} .

The more preferred benzothiepine moieties comprising R^{20} , R^{21} , R^{22} and/or R^{23} conform to the preferred structures as outlined above for Formula I.

The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^* can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(oxyalkylene), especially poly- or oligo(exyethylene) or poly- or oligo(oxypropylene).

Dosages, Formulations, and Routes of Administration

The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of

action in the body, for example in the ileum of a mammal, e.g., a human.

For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound *per se*.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, and alkaline earth salts such as magnesium and calcium salts.

The anions of the definition of A⁻ in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from the above list.

The compounds of the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably

formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

These compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

The amount of compound which is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of administration, and the clinical condition of the recipient.

In general, a daily dose can be in the range of from about 0.3 to about 100 mg/kg bodyweight/day, preferably from about 1 mg to about 50 mg/kg bodyweight/day, more preferably from about 3 to about 10 mg/kg bodyweight/day. This total daily dose can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

Orally administrable unit dose formulations, such as tablets or capsules, can contain, for example, from about 0.1 to about 100 mg of benzothiepine compound, preferably about 1 to about 75 mg of compound, more preferably from about 10 to about 50 mg of compound. In the case of pharmaceutically acceptable salts, the

weights indicated above refer to the weight of the benzothiepine ion derived from the salt.

Oral delivery of an ileal bile acid transport inhibitor of the present invention can include
5 formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH
10 of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active
15 drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release
20 formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic
25 acid methyl ester.

When administered intravenously, the dose can, for example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg
30 body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this
35 purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg

per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

5 Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although
10 the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

15 Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or
20 granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the
25 active compound(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and
30 then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine,
35 the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant,

inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

5 Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in
10 an inert base such as gelatin and glycerin or sucrose and acacia.

 Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of the
15 present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations can conveniently be prepared by admixing
20 the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound disclosed herein.

25 Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa
30 butter, and then shaping the resulting mixture.

 Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline,
35 lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active

compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible.

5 Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the
10 present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the
15 compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

20 In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

25 The solid dosage forms for oral administration including capsules, tablets, pills, powders, and granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice,
30 additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

35 Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions,

solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Pharmaceutically acceptable carriers encompass all the foregoing and the like.

Treatment Regimen

The dosage regimen to prevent, give relief from, or ameliorate a disease condition having hyperlipemia as an element of the disease, e.g., atherosclerosis, or to protect against or treat further high cholesterol plasma or blood levels with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological

considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

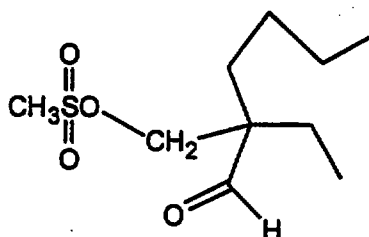
Initial treatment of a patient suffering from a hyperlipidemic condition can begin with the dosages indicated above. Treatment should generally be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic disease condition has been controlled or eliminated. Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored by, for example, measuring serum cholesterol levels by any of the methods well known in the art, to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of ileal bile acid transport inhibitor of the present invention which exhibits satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.

The following non-limiting examples serve to illustrate various aspects of the present invention.

35

EXAMPLES OF SYNTHETIC PROCEDURES

102

Preparation 1**2-Ethyl-2-(mesyloxymethyl)hexanal (1)**

1

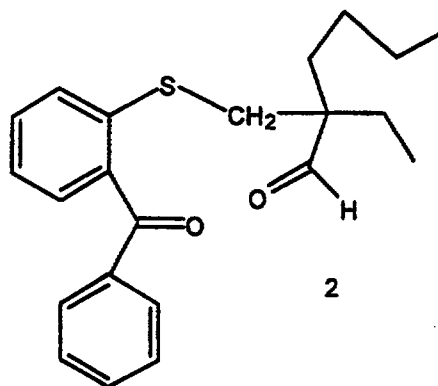
5

To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of triethylamine was added dropwise 15.8 g of 2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in Chem. Ber. 98, 728-734 (1965), while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with dilute HCl and extracted with methylene chloride. The methylene chloride extract was dried over MgSO₄ and concentrated in vacuo to give 24.4 g of brown oil.

15

Preparation 2**2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)**

20

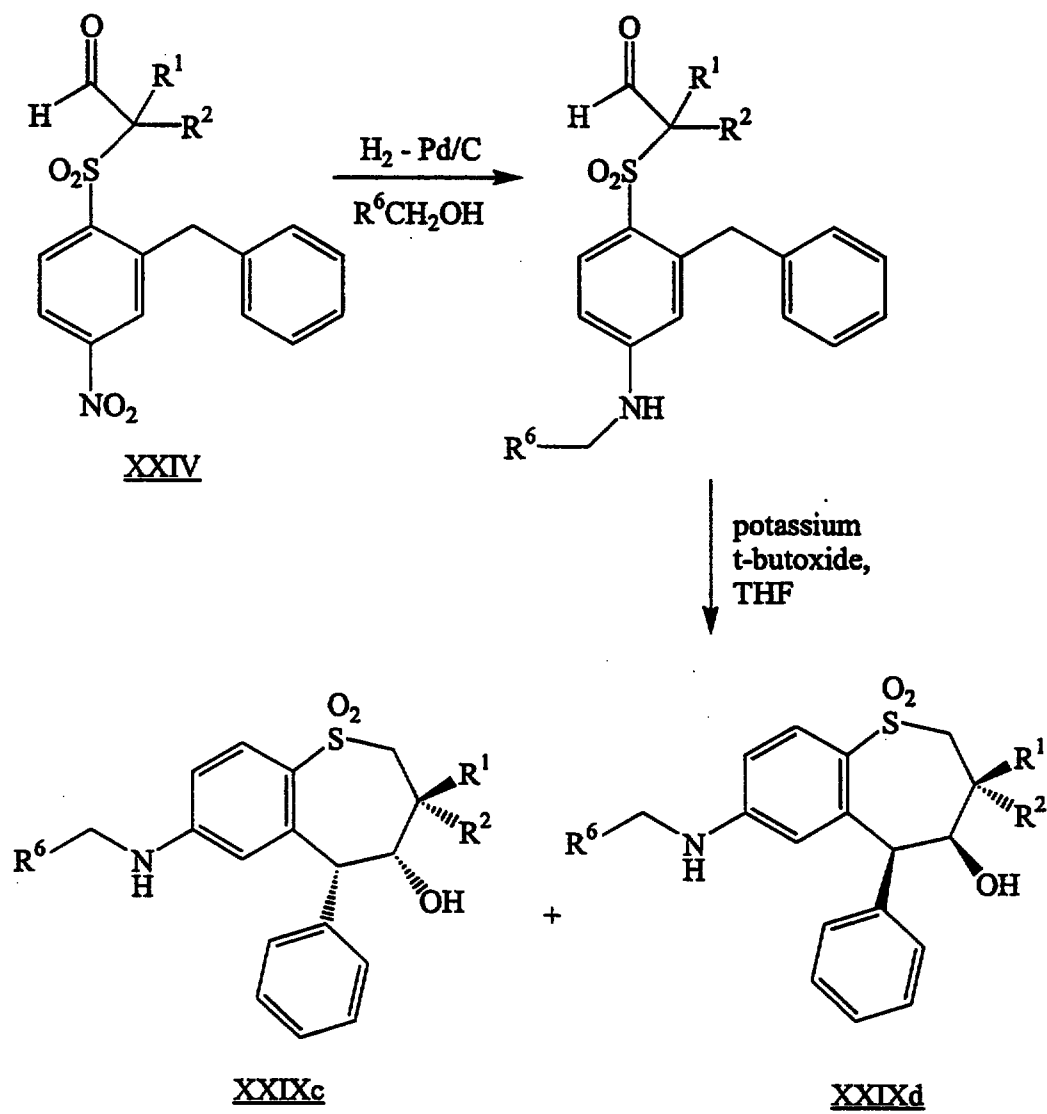


2

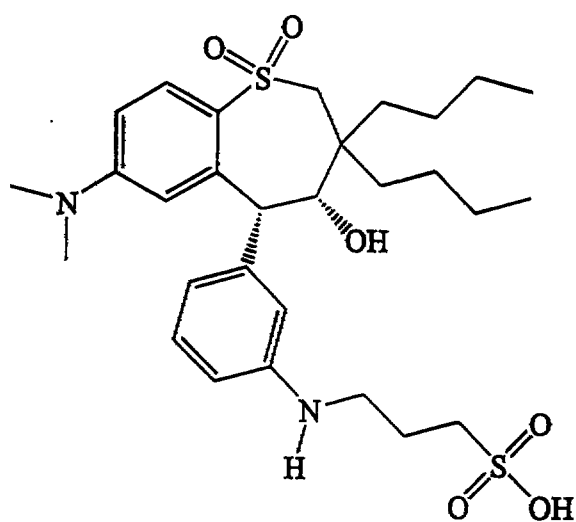
A mixture of 31 g (0.144 mol) of 2-

mercaptobenzophenone, prepared according to the procedure described in WO 93/16055, 24.4 g (0.1 mole) of 2-ethyl-2-(methoxymethyl)-hexanal (1), 14.8 g (0.146 mole) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The reaction mixture was poured into 3N HCl and extracted with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH, dried over MgSO₄, and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC (10% EtOAc-hexane) to give 20.5 g (58%) of 2 as an oil.

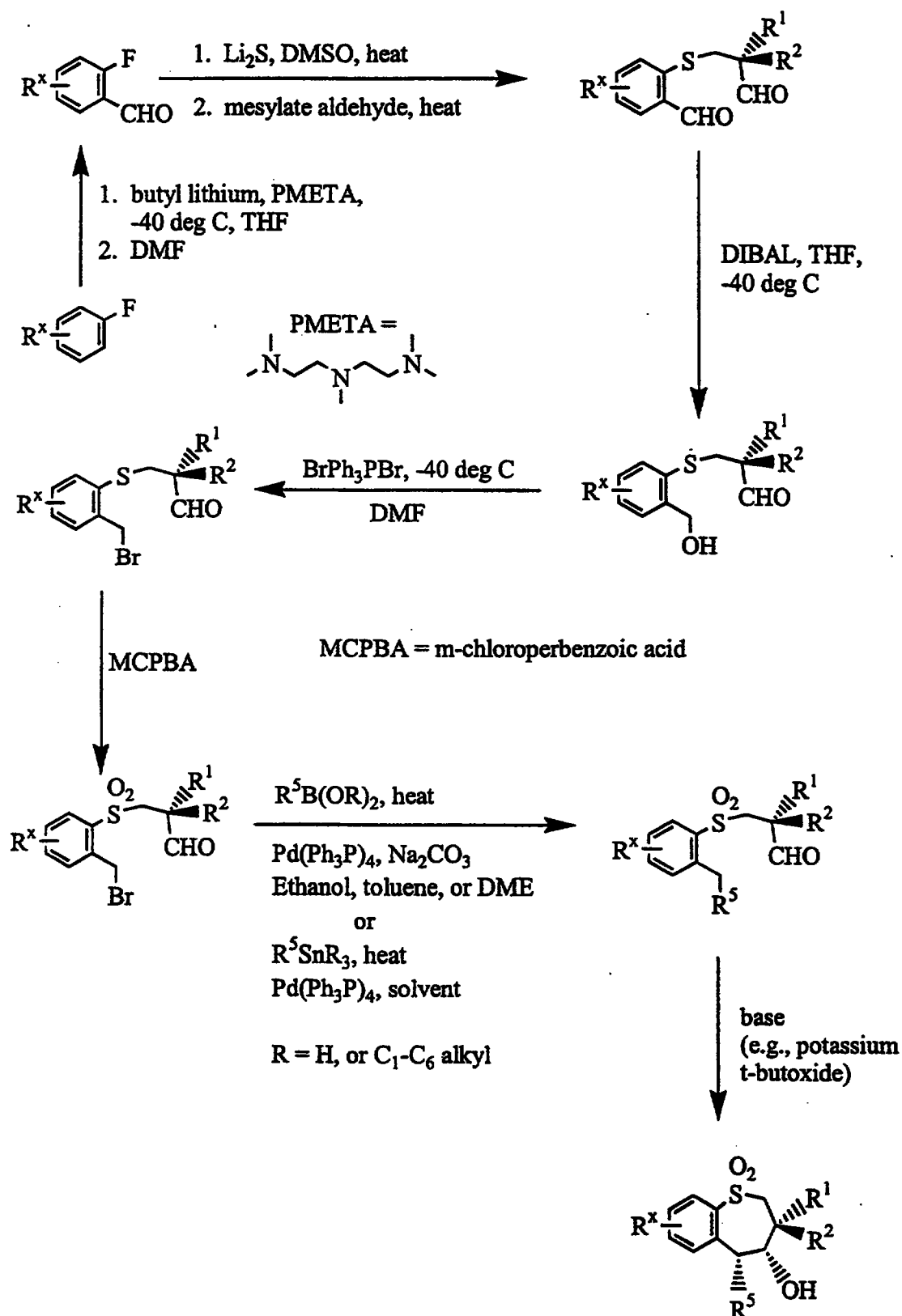
Scheme 6



105



Generic Scheme X



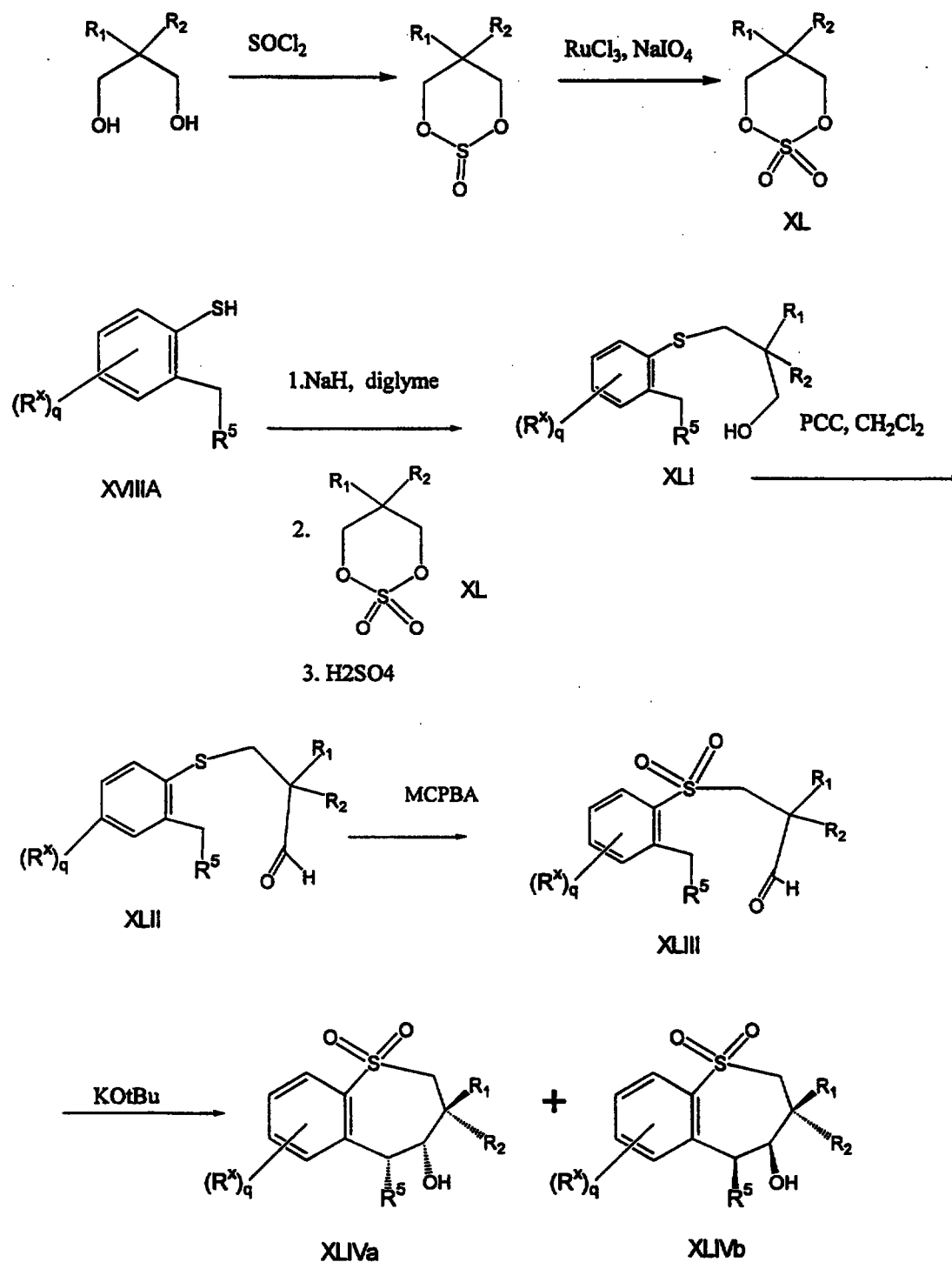
Generic Scheme X: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with lithium sulfide or other nucleophilic sulfide anion in polar solvent (such as DMF, DMA, DMSO, etc.), followed by the addition of dialkyl mesylate aldehyde (X), provided a dialkyl benzene dialdehyde Y. DIBAL reduction of the dialdehyde at low temperature yielded benzyl alcohol monoaldehyde Z. Conversion of benzyl alcohol to benzyl bromide, followed by oxidation of sulfide to sulfone yielded the key intermediate W.

The compounds of this invention can also be synthesized using cyclic sulfate (XL, below) as the reagent as shown in the following schemes XI and XII.

The following examples describe a procedure for using the cyclic sulfate as the reagent.

108

SCHEME XI.

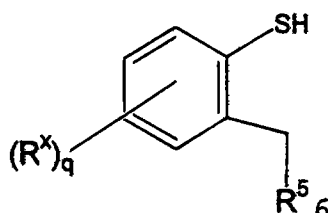


Scheme XI illustrates yet another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl

analogous, starting from the thiophenol XVIIIA.

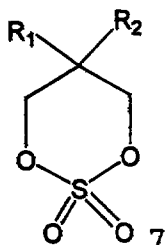
Thiophenol XVIIIA can be reacted with cyclic sulfate XL to give the alcohol XLI which can be oxidized to yield the aldehyde XLII. Aldehyde XLII itself can be further oxidized to give the sulfone XLIII which can be cyclized to give a stereoisomeric mixture of benzothiepine XLIVa and XLIVb.

Thiophenol XVIIIA can be prepared according to Scheme 3 as previously discussed and has the following formula:



XVIII A

wherein R^5 , R^x and q are as previously defined for the compounds of formula I. Cyclic sulfate XL can be prepared according to synthetic procedures known in the art and has the following formula:



XL

wherein R^1 and R^2 are as previously defined for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XI, thiophenol XVIIIA is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction

conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at about room temperature for about two hours. The reaction preferably employs an
5 approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield can be improved by using about 1.01 to 1.3 equivalents of cyclic sulfate XL for each equivalent of thiophenol
10 XVIIIIA present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIIA present.

In the process of the invention, thiophenol XVIIIIA also is treated with an abstracting agent. The
15 abstracting agent can be added to the solvent containing thiophenol XVIIIIA prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the hydrogen
20 atom from the mercaptan group attached to the benzene ring of thiophenol XVIIIIA. The resulting sulfur anion of the thiophenol then reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the thiophenol then bonds with a terminal carbon atom of
25 the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group.

The abstracting agent generally is a base having a pH greater than about 10. Preferably, the base is
30 an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; more preferably, the base is sodium hydride. A slight excess of abstracting agent is preferred relative to thiophenol XVIIIIA. Reaction time and yield is improved by using
35 about 1.0 to about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIIA

present. More preferably, this ratio is about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present.

5 The sulfate group of the intermediate product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield alcohol XLI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid.

10 The several reactions involving thiophenol XVIIIA, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need for isolation of any of the intermediates produced.

15 Alcohol XLI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to aldehyde XLII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate.

The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

25 Aldehyde XLII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde XLIII. Preferably, the oxidizing agent is metachloroperbenzoic acid.

30 Sulfone-aldehyde XLIII likewise is isolated by conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The cyclizing agent preferably is a base having a pH between about 8 and about 9. More preferably, the base is an alkoxide base, and still more preferably, the base is potassium tert-butoxide.

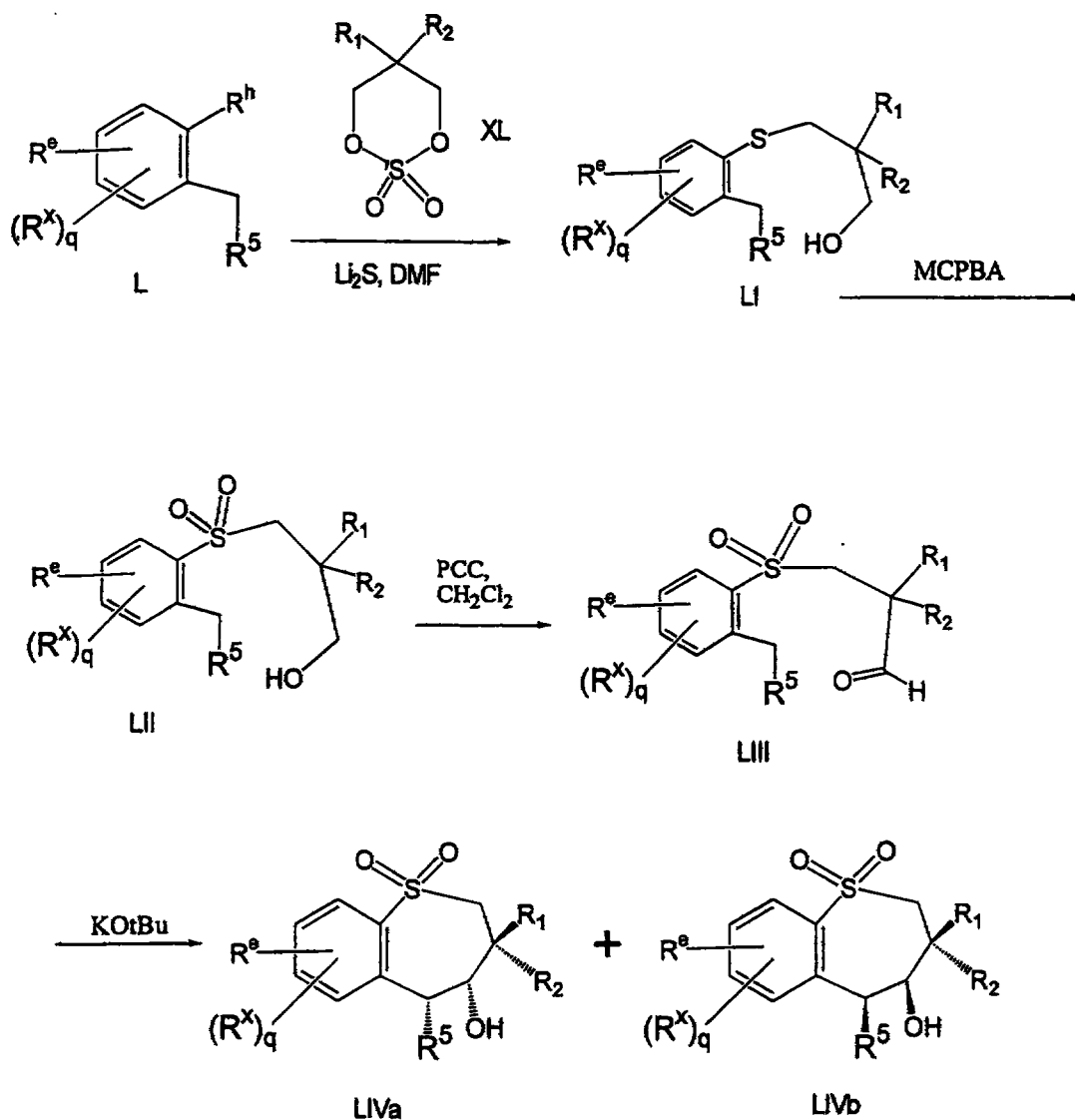
35 The two oxidation steps of Scheme XI can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield

112

a sulfone-alcohol which is then oxidized to yield a sulfone-aldehyde.

113

Scheme XII



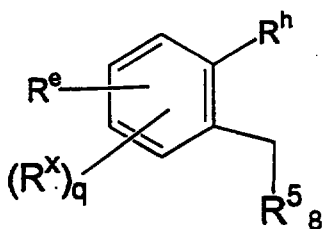
5

Scheme XII illustrates still another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the halobenzene **L**. Halobenzene **L** can be reacted with cyclic sulfate **XL** disclosed above to give the alcohol **LI** which can be oxidized to yield the sulfone-alcohol **LII**. Sulfone-alcohol **LII** itself can be further oxidized to give the sulfone-aldehyde **LIII** which can be cyclized to give a stereoisomeric mixture of benzothiepine **LIVa** and **LIVb**.

10

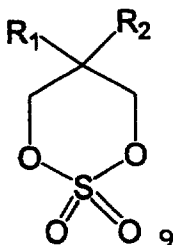
114

Halobenzene L (which is commercially available or can be synthesized from commercially available halobenzenes by one skilled in the art) has the following formula:



L

wherein R^5 , R^X , and q are as previously defined for the compounds of formula I; R^h is a halogen such as chloro, bromo, fluoro or iodo; and R^e is an electron withdrawing group at the ortho or para position of the halobenzene, and is preferably a p-nitro or o-nitro group. Cyclic sulfate XL can be prepared as set forth in Scheme XI and can have the following formula:



XL

wherein R^1 and R^2 are as previously defined for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XII, halobenzene L is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as dimethyl formamide or N:N-dimethylacetamide, and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature and time

are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C for about 8 to 12 hours. More preferably, the reaction temperature is maintained at about 80°C. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield is improved by using about 1.1 to 1.3 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present.

In the process of the invention, halobenzene L also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing halobenzene L prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the halogen atom attached to the benzene ring of halobenzene L and replaces that atom with a divalent sulfur atom. The resulting sulfur anion reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the halobenzene then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group. The abstracting agent generally is a dialkali metal sulfide, and preferably it is dilithium sulfide. A slight excess of the abstracting agent is preferred relative to halobenzene L. Reaction time and yield is improved by using about 1.01 to 1.3 equivalents of abstracting agent for each equivalent of halobenzene L present. More preferably, this ratio is about 1.05 equivalents of abstracting agent for each equivalent of halobenzene L present.

The sulfate group of the product of the reaction

of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield a mixture of an ester and alcohol LI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid. The ester is then converted to alcohol LI by treatment with an alkali metal hydroxide, preferably sodium hydroxide.

The several reactions involving halobenzene L, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need to isolate any of the intermediates produced.

Alcohol LI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to sulfone-alcohol LII. Preferably, the oxidizing agent is metachloroperbenzoic acid. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

Sulfone-alcohol LII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde LIII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

Sulfone-aldehyde XLIII is then converted to the desired benzothiepine-1,1-dioxides according to the procedure previously set forth in Scheme XI.

The two oxidation steps can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield an aldehyde which is then oxidized to yield a sulfone-aldehyde.

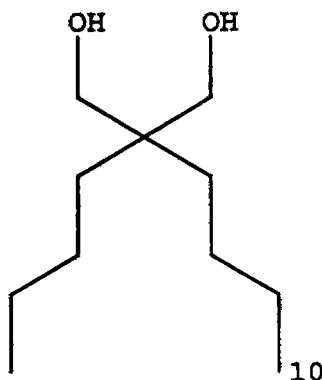
Use of the cyclic sulfate reagent instead of a mesylate reagent in Schemes XI and XII improves the overall yield and avoids many of the purification

difficulties encountered relative to those reaction schemes proceeding through a mesylate intermediate. Overall yields are significantly improved when a cyclic sulfate is used instead of a mesylate reagent.

- 5 In addition, chromatographic separation of the intermediate product of the cyclic sulfate coupling step of the reaction is not necessary. For example, in Schemes XI and XII the intermediate is a water soluble alkali metal salt and the impurities can be removed by extraction with ether. The intermediate is then hydrolyzed to the desired alcohol.
- 10

Example Corresponding to Scheme XI:

- 15 Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:

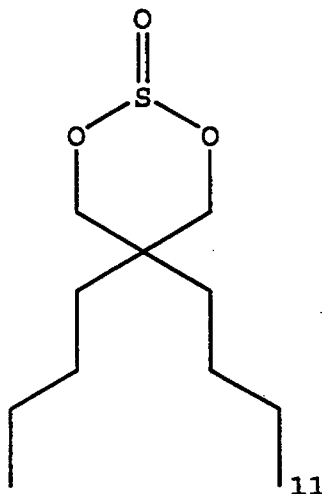


- Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%)
- 20
- 25

118

of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 2: Dibutyl-cyclic-sulfite:



5

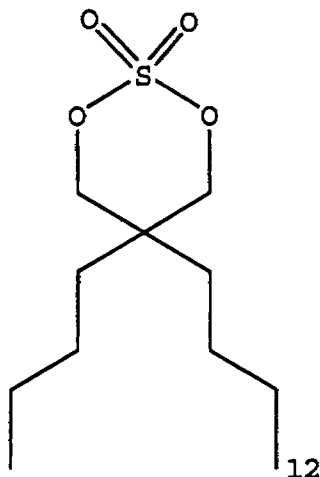
A solution of the dibutyl-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice water twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibutyl-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

10

15

20

119

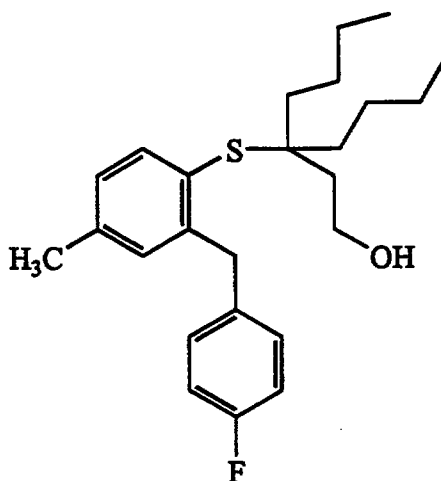
Step 3: Dibutyl-cyclic sulfate:

To a solution of the dibutyl-cyclic-sulfite of
step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and
5 500 ml of water cooled in an ice bath under nitrogen
was added ruthenium(III) chloride (1 g) and sodium
periodate (233 g, 1.08 mol). The reaction was stirred
overnight and the color of the solution turned black.

Gas chromatography confirmed there was no starting
10 material left. The mixture was extracted once with
300 ml of ether and three times with brine. The
organic phase was dried over magnesium sulphate and
passed through celite. The filtrate was concentrated
under vacuum and gave 133 g (yield 97.8%) of the
15 dibutyl-cyclic-sulfate as an oil. Proton NMR, carbon
NMR and MS confirmed the product.

120

Step 4: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)methyl]-2-butylhexanol:



5 A 60% oil dispersion of sodium hydride (0.27 g, 6.68 mmole) was washed with hexane. The hexane was decanted and 20 ml of methoxyethyl ether was added to the washed sodium hydride and cooled in an ice bath. A mixture of diphenylmethane thiophenol (1.55 g, 6.68 mmole) in 10 ml of methoxyethyl ether was added dropwise over a period of 15 minutes. A mixture of the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 mmole) in 10 ml of methoxyethyl ether was then added.

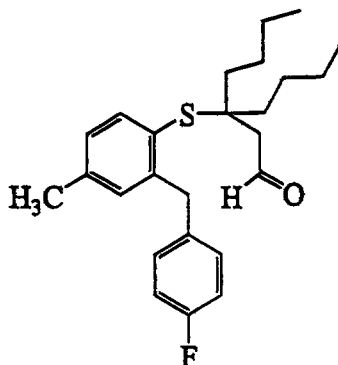
The resulting mixture was stirred for 30 minutes at 0°C and 1 hour at room temperature under nitrogen. Gas chromatography confirmed there was no thiol left.

15 The solvent was evaporated and washed with water and ether two times. The water layer was separated and 20 ml of 10% NaOH was added. This aqueous mixture was boiled for 30 minutes, cooled, acidified with 6N HCl, and boiled for 10 minutes. The mixture was cooled and extracted with ether. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum to give 2.47 g (yield 92.5%) of the hexanol as an oil.

25 Proton NMR, C13-NMR and MS confirmed the product.

121

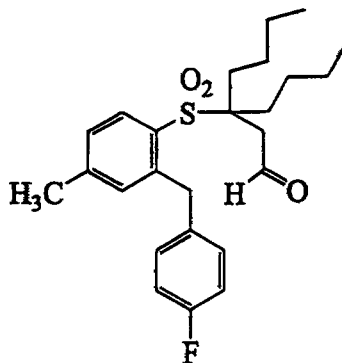
Step 5: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)methyl]-2-butylhexanal:



14

To a solution of the hexanol of step 4 (2 g, 4.9 mmole) in 40 ml of methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmole). The reaction mixture was stirred for 3 hours and filtered through silica gel. The filtrate was concentrated under vacuum to give 1.39 g (yield 70%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 6: 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl)methyl]-2-butylhexanal



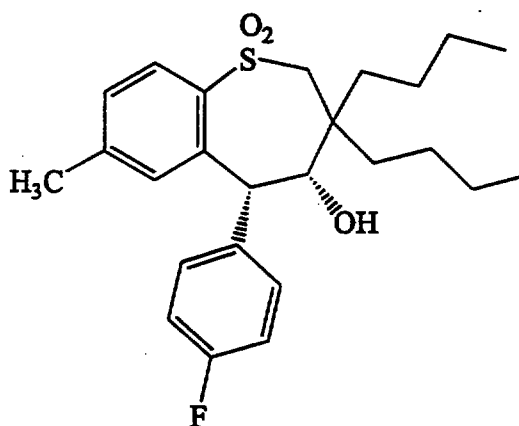
15

To a solution of the hexanal of step 5 (0.44 g, 1.1 mmole) in 20 ml of methylene chloride cooled by an ice bath under nitrogen was added 70 % metachloroperbenzoic acid (0.54 g, 2.2 mmole). The reaction mixture was stirred for 18 hours and

122

filtered. The filtrate was washed successively with 10% NaOH(3X), water, and brine, dried over magnesium sulphate, and concentrated under vacuum to give 0.42 g (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 7: Cis-3,3-dibutyl-7-methyl-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide:

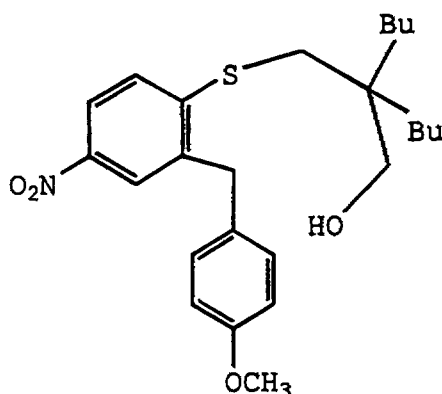


A mixture of the hexanal of step 6 (0.37 g, 0.85 mmole) in 30 ml of anhydrous THF was stirred in an ice bath at a temperature of about 0° C. Potassium-tert-butoxide (102 mg, 0.85 mmole) was then added. After 3 hours thin layer chromatography confirmed the presence of the product and a small amount of the starting material. The crude reaction mixture was acidified with 10% HCl, extracted with ether, washed successively with water and brine, dried with MgSO₄, and concentrated under vacuum. This concentrate was purified by HPLC (10% EtOAc-Hexane). The first fraction came as 0.1 g of the starting material in the form of an oil. The second fraction yielded 0.27 g (75% yield) of the desired benzothiepine as a white solid. Proton NMR, carbon NMR and MS confirmed the product. (M+H=433).

123

Example Corresponding to Scheme XII

Step 1: 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanol:



5 Chlorodiphenylmethane (10g) was dissolved in 25 ml of DMF and lithium sulfide [1.75 g, 1.05 equivalents] was added. The solution color changed to red. The reaction mixture was heated at 80°C

10 overnight. The solution was cooled to 0°C and dibutyl-cyclic-sulfate (9.9g; prepared as set forth in Step 3 of the Scheme XI examples) in 10 ml of DMF was added and stirred at room temperature overnight. The solvent was evaporated and washed successively with

15 water and ether (three times). The water layer was separated and 40 ml of concentrated sulfuric acid was added and the reaction mixture boiled overnight. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water

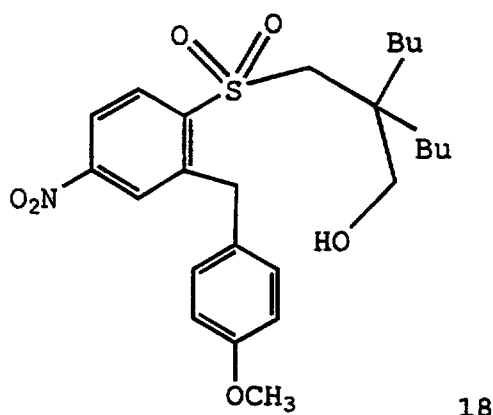
20 and brine, dried over magnesium sulphate, and concentrated under vacuum. The product was boiled with 3M of NaOH for 1 hour. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried

25 over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under

124

vacuum to give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

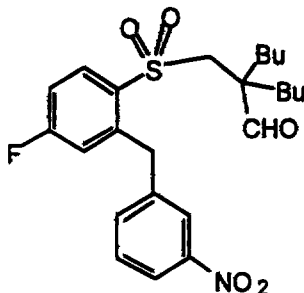
5 Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanal:



To a solution of the hexanol of step 1 (6 g, 13 mmole) in 50 ml methylene chloride cooled in ice bath under nitrogen was added 70% MCPBA (8.261 g, 33 mmole). The reaction was stirred for 18 hours at room temperature and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, C13-NMR and MS confirmed the product.

Example 1398

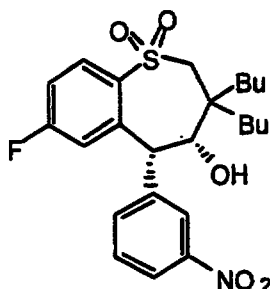
Step 1. Preparation of 2



- 5 To a solution of 6.0 g of dibutyl 4-fluorobenzene
dialdehyde of Example 1395 (14.3 mmol) in 72 mL of
toluene and 54 mL of ethanol was added 4.7 g 3-
nitrobenzeneboronic acid (28.6 mmol), 0.8 g of
tetrakis (triphenylphosphine) palladium(0) (0.7 mmol)
10 and 45 mL of a 2 M solution of sodium carbonate in
water. This heterogeneous mixture was refluxed for
three hours, then cooled to ambient temperature and
partitioned between ethyl acetate and water. The
organic layer was dried over MgSO₄ and concentrated in
15 vacuo. Purification by silica gel chromatography
(Waters Prep-2000) using ethyl acetate/hexanes (25/75)
gave 4.8 g (73%) of the title compound as a yellow
solid. ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.45 Hz, 6H),
0.99-1.38 (m, 8H), 1.62-1.75 (m, 2H), 1.85-2.00 (m,
20 2H), 3.20 (s, 2H), 4.59 (s, 2H), 6.93 (dd, J = 10.5
and 2.4 Hz, 1H), 7.15 (dt, J = 8.4 and 2.85 Hz, 1H),
7.46-7.59 (m, 2H), 8.05-8.16 (m, 3H), 9.40 (s, 1H).

126

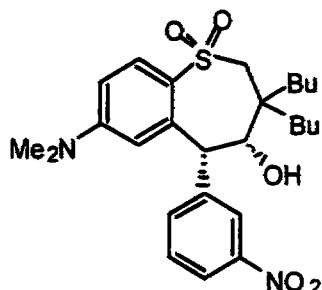
Step 3. Preparation of 3



5 A solution of 4.8 g (10.4 mmol) of 2 in 500 mL THF was cooled to 0 °C in an ice bath. 20 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirring was continued for 30 minutes, then the reaction was quenched with 100 mL
10 of saturated ammonium chloride. The mixture was partitioned between ethyl acetate and water; the organic layer was washed with brine, then dried (MgSO₄) and concentrated in vacuo. Purification by silica gel chromatography through a 100 ml plug using CH₂Cl₂ as
15 eluent yielded 4.3 g (90%) of 3 as a pale yellow foam. ¹H NMR (CDCl₃) δ 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 (q_{AB}, J_{AB} = 15.0 Hz, ΔV = 33.2 Hz, 2H), 4.17 (d, J = 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz, 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H).
20 MS(FABH⁺) m/e (relative intensity) 464.5 (100), 446.6 (65). HRMS calculated for M+H 464.1907. Found
25 464.1905.

127

Step 4. Preparation of 4

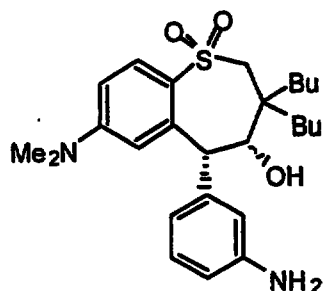


5 To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of
3 in 30 ml THF contained in a stainless steel reaction
vessel was added 8.2 g dimethyl amine (182 mmol). The
vessel was sealed and heated to 110 °C for 16 hours.
The reaction vessel was cooled to ambient temperature
10 and the contents concentrated in vacuo. Purification
by silica gel chromatography (Waters Prep-2000) using
an ethyl acetate/hexanes gradient (10-40% ethyl
acetate) gave 4.0 g (88%) of 4 as a yellow solid. ¹H
NMR (CDCl₃) δ 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H),
15 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H),
3.09 (q_{AB}, J_{AB} = 15.0 Hz, DV= 45.6 Hz, 2H), 4.90 (d, J
= 9.0 Hz, 1H), 5.65 (s, 1H), 5.75 (d, J = 2.1 Hz, 1H),
6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4
Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0
20 Hz, 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (s,
1H). MS(FABH⁺) m/e (relative intensity) 489.6 (100),
471.5 (25). HRMS calculated for M+H 489.2423. Found
489.2456.

25

128

Step 5. Preparation of 5



5

To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml ethanol in a stainless steel Parr reactor was added 1 g 10% palladium on carbon. The reaction vessel was sealed, purged twice with H₂, then charged with H₂ (100 psi) and heated to 45 °C for six hours. The reaction vessel was cooled to ambient temperature and the contents filtered to remove the catalyst. The filtrate was concentrated in vacuo to give 0.9 g (96%) of 5. ¹H NMR (CDCl₃) δ 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J = 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H). MS(FABH⁺) m/e (relative intensity) 459.7 (100). HRMS calculated for M+H 459.2681. Found 459.2670.

129

Step 6. Preparation of 6

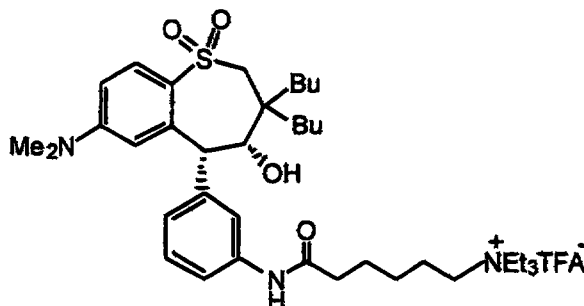
To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride.

5 Next was added 4 g (39.6 mmol) TEA. The reaction was stirred 10 minutes, then partitioned between ethyl acetate and brine. The organic layer was dried (MgSO_4) and concentrated in vacuo. Purification by silica gel chromatography through a 70 ml MPLC column using a gradient of ethyl acetate(20-50%) in hexane as eluent yielded 0.9 g (73%) of 6 as a pale yellow oil.

10 ^1H NMR (CDCl_3) δ 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, $J = 6.9$ Hz, 2H), 2.80 (s, 6H), 3.07 (q_{AB}, $J_{AB} = 15.6$ Hz, DV = 40.4 Hz, 2H), 3.43 (t, $J =$
15 6.9 Hz, 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 9.3$ and 2.7 Hz, 1H), 7.28 (s, 1H), 7.32-7.41 (m, 2H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 9.0$ Hz, 1H).

20

Step 7. Preparation of 7



25

To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo.

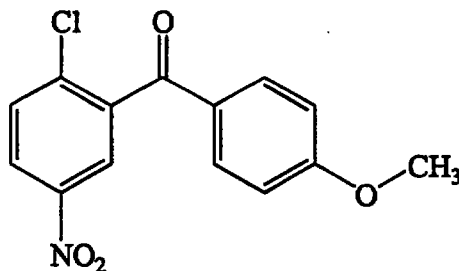
30 Purification by reverse-phase silica gel

130

chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of 7 as a white foam. ¹H NMR (CDCl₃) δ 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 9.3 and 2.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.74 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

Example 1398a

Step 1



C₁₄H₁₀ClNO₄ fw=291.69

20

In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N₂ inlet adapter and suba seal. Remove from inert atmosphere and begin N₂ purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl₅ via syringe and begin stirring with magnetic stir bar.

Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N₂ purge. Stir at

131

room temperature overnight. After stirring at room temperature for ~20hrs, place in oil bath and heat at 50C for 1hr. Remove chlorobenzene by high vacuum.

5 Wash residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.

In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.

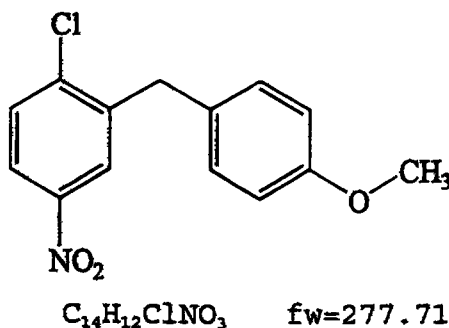
10 Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Fit reaction flask with addition funnel and a N₂ inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N₂ purge.

15 Slowly add AlCl₃ to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .

20 Quench reaction by pouring into a solution of 300 mls 1N HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with 2% NaOH, then twice with deionized H₂O. Dry with MgSO₄, filter and rotovap to dryness. Remove anisole by high vacuum. Crystallize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms.

25 Yield 41%. Obtain NMR and mass spec (m/z=292).

Step 2



30

Dissolve 38.10gms (0.131 moles) of the

132

benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N₂ inlet, addition funnel and stopper. Stir with magnetic stir bar. Chill solution with ice bath.

5 Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

10 Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

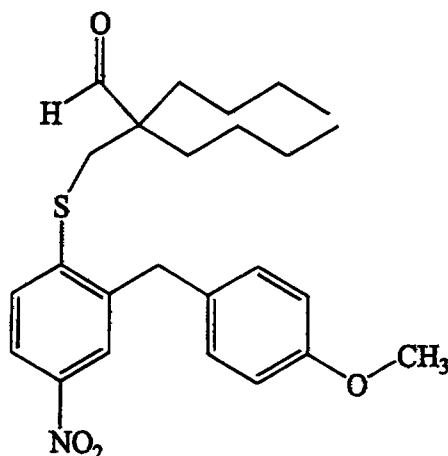
15 Prepare a second solution of 39.32 gms trifluoromethane sulfonic acid and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

20 Prepare a second solution of 22.85 gms triethyl silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. After all additions are made allow to slowly warm to room temperature overnight. Stir under N₂ overnight.

25 Prepare 1300 mls saturated NaHCO₃ in a 4 liter beaker. Chill with ice bath. While stirring vigorously, slowly add reaction mixture. Stir at chilled temperature for 30 min. Pour into a
30 separatory funnel and allow separation. Remove organic layer and extract aqueous layer 2 times with methylene chloride. Dry organic layers with MgSO₄. Crystallize from ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm by NMR and mass spec (m/z=278).

133

Step 3

 $C_{25}H_{33}NO_4S$ fw=443.61

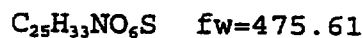
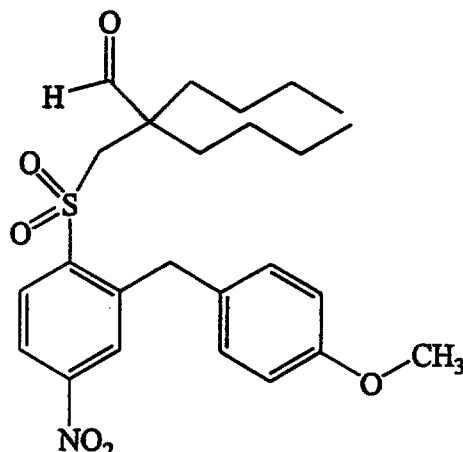
5

Dissolve 10.12 gms (0.036 moles) of product 2 with 200 mls anhydrous DMSO. Place in a 500 ml round bottom flask with magnetic stir bar. Fit flask with water condenser, N₂ inlet, and stopper. Add 1.84 gms
10 Li₂S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N₂ overnight then cool to room temperature.

Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to
15 reaction solution. Purge well with N₂, heat overnight at 80°C.

Cool to room temperature. Prepare 500 mls of 5% acetic acid in a 2 liter beaker. While stirring, slowly add reaction mixture. Stir 30 min. Extract
20 with ether 3 times. Combine organic layers and extract with water and sat'd NaCl. Dry organic layer with MgSO₄, filter and rotovap to dryness. Dry oil on vacuum line. Obtain pure product by column chromatography using 95% hexane and 5% ethyl acetate as the mobile
25 phase. Dry wt=7.8 gms. Obtain NMR and mass spec (m/z=444).

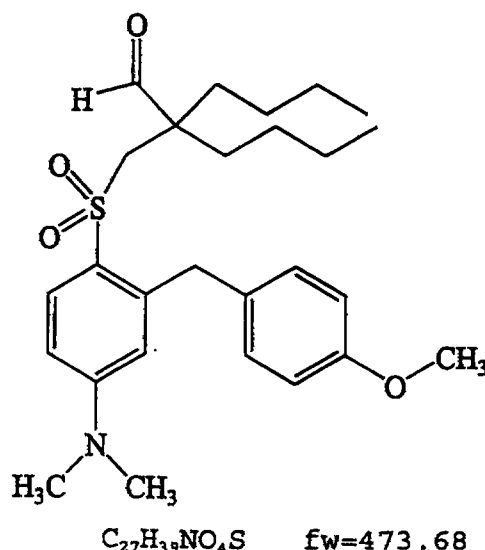
Step 4



Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice bath under N_2 purge. Slowly add 11.54 gms 3-chloroperbenzoic acid (0.0435 moles, Fluka 25800, ~65%). After addition is complete warm to room temperature and monitor reaction by TLC. Reaction goes quickly to the sulfoxide intermediate but takes 8 hrs to convert to the sulfone. Chill solution over night in freezer. Filter solid from reaction, extract filtrate with 10% K_2CO_3 . Extract aqueous layer twice with methylene chloride. Combine organic layers and dry with MgSO_4 . Filter and rotovap to dryness. Obtain pure product by crystallizing from ethanol or isolating by column chromatography. Obtain NMR and mass spec ($m/z=476$).

135

Step 5



5 Reaction is done in a 300 ml stainless steel Parr stirred mini reactor. Place 9.68 gms (0.0204 moles) of product 4 in reactor base. Add 160 mls ethanol. For safety reasons next two compounds are added in a N_2 atmosphere glove bag. In glove bag, add 15.3 mls
10 formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H_2 . Heat to $55^\circ C$
15 under H_2 . Run reaction at 200 psig H_2 , $55^\circ C$, and a stir rate of 250 rpm. Run overnight under these conditions.

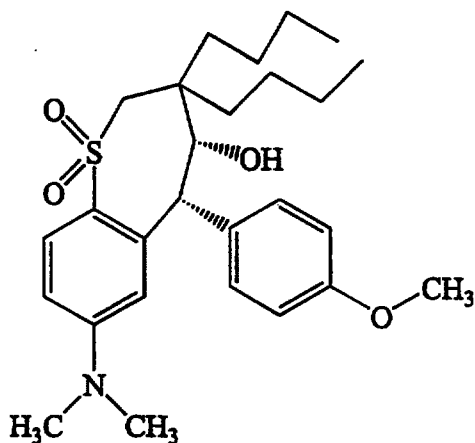
 Cool reactor and vent H_2 . Purge with N_2 . Check progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction
20 mixture over a bed of celite washing well with ether. Rotovap and redissolve with ether. Extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line.

 Charge reactor again with same amounts, seal
25 reactor and run overnight under same conditions. After second run all of the material has been converted to the desired product. Cool and vent H_2

136

pressure. Purge with N₂. Filter over a bed of celite, washing well with ether. Rotovap to dryness. Dissolve with ether and extract with water. Dry organic layer with MgSO₄, filter and rotovap to dryness. Dry on vacuum line. Obtain NMR and mass spec (m/z=474).

Step 6

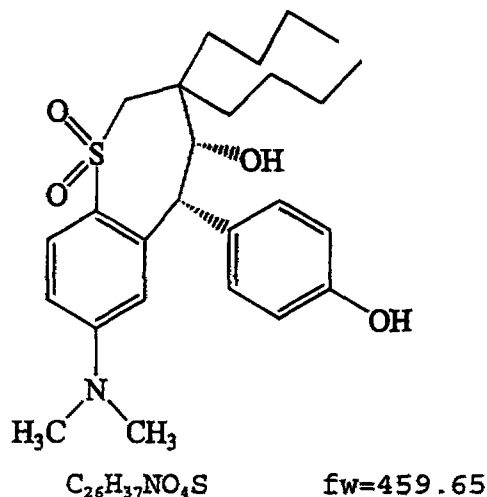


C₂₇H₃₉NO₄S fw=473.68

Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N₂ inlet and stopper. Chill solution with ice/salt bath under N₂ purge. Slowly add 2.55 gms potassium t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at -10°C monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with ether. Dry organic layer with MgSO₄, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec (m/z=474).

137

Step 7



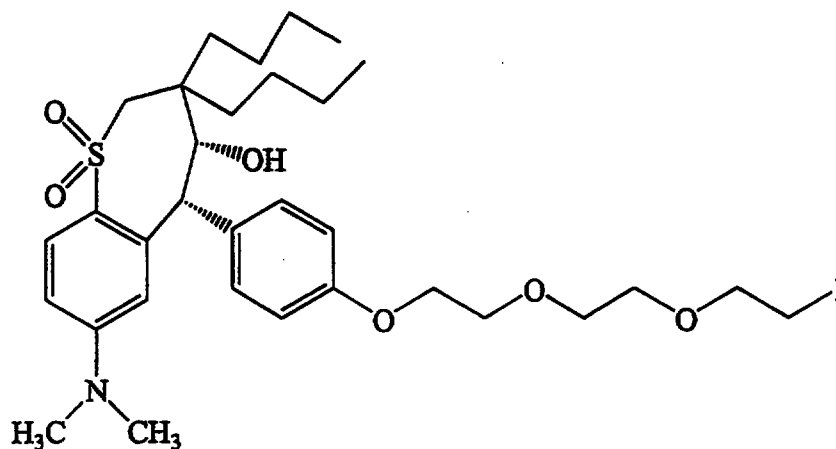
5

Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N_2 purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

Chill solution with ice bath. Quench with 100 mls 10% K_2CO_3 while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl , once H_2O , and once with saturated NaCl solution. Dry organic layer with MgSO_4 , filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec ($m/z=460$).

138

Step 8

 $\text{C}_{32}\text{H}_{46}\text{NO}_6\text{SI}$ fw=701.71

5 Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill NaH with ice bath and begin N_2 purge.

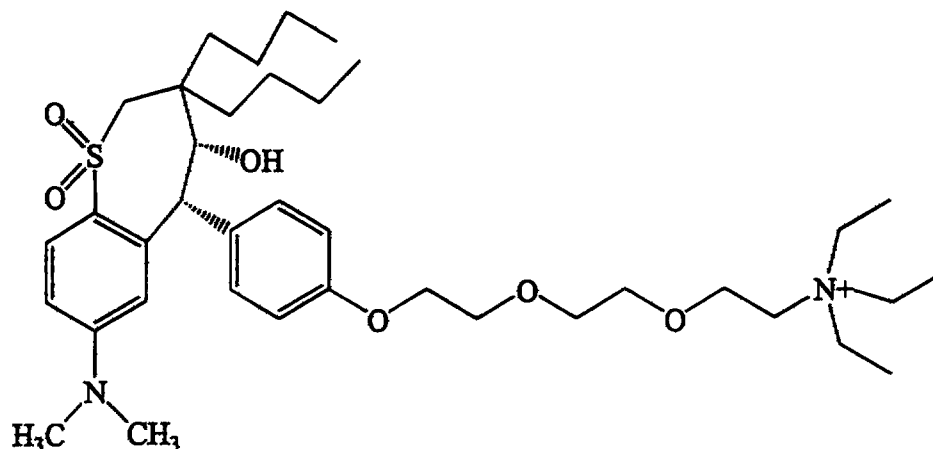
10 Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMF. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K_2CO_3 (9.57 mmoles Fisher P-208).

15 Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N_2 .

20 Cleanup by diluting with ether and extracting sequentially with 5% NaOH, H_2O , and saturated NaCl. Dry organic layer with MgSO_4 , filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec ($m/z=702$).

139

Step 9

 $\text{C}_{38}\text{H}_{63}\text{N}_2\text{O}_6\text{SI}$ fw=802.90

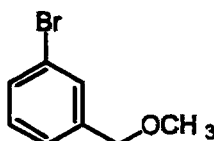
5 Dissolve 1.0 gms (1.43 mmoles) of product 8 with
10 mls anhydrous acetonitrile. Place in a 3 ounce
Fischer-Porter pressure reaction vessel with magnetic
stir bar. Add 2.9 gms triethyl amine (28.6 mmoles
Aldrich 23,962-3) dissolved in 10 mls anhydrous
10 acetonitrile. Purge well with N_2 then close system .
Heat at 45°C . Monitor reaction by TLC. Reaction is
usually complete in 48 hrs.

15 Perform cleanup by removing acetonitrile under
vacuum. Redissolve with anhydrous chloroform and
precipitate quaternary ammonium salt with ether.
Repeat several times. Dry to obtain crystalline
product. Obtain NMR and mass spec ($m/z=675$).

20

Example 1399

Step 1. Preparation of 1

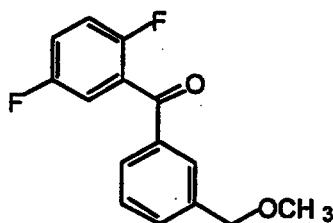


25 To a solution of 144 g of KOH (2560 mmol) in 1.1 L of

140

DMSO was added 120 g of 2-bromobenzyl alcohol (641 mmol) slowly via addition funnel. Then was added 182 g of methyl iodide (80 mL, 1282 mmol) via addition funnel. Stirred at ambient temperature for fifteen minutes. Poured reaction contents into 1.0 L of water and extracted three times with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated in vacuo. Purified by silica-gel chromatography through a 200 mL plug using hexanes (100%) as elutant yielded 103.2 g (80%) of 1 as a clear colorless liquid. ^1H NMR (CDCl_3) d 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, $J = 7.45$, 1H), 7.50 (s, 1H).

Step 2. Preparation of 2

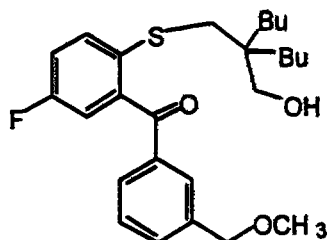


To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of 95 g (472 mmol) of 1 in 1.5 L THF was added 240 mL of 2.5 M n-butyl lithium (576 mmol). The mixture was stirred for one hour, and then to it was added 180 g of zinc iodide (566 mmol) dissolved in 500 mL THF. The mixture was stirred thirty minutes, allowed to warm to $5\text{ }^{\circ}\text{C}$, cooled to $-10\text{ }^{\circ}\text{C}$ and to it was added 6 g of $\text{Pd}(\text{PPh}_3)_4$ (5.2 mmol) and 125 g 2,5-difluorobenzoyl chloride (708 mmol). The mixture was stirred at ambient temperature for 18 hours and then cooled to $10\text{ }^{\circ}\text{C}$, quenched with water, partitioned between ethyl acetate and water, and washed organic layer with 1N HCL and with 1N NaOH. The organic layer was dried over MgSO_4 and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 5% ethyl acetate/hexanes as elutant gave 53.6 g (43 %) of 2 as an orange oil. ^1H

141

NMR (CDCl₃) δ 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

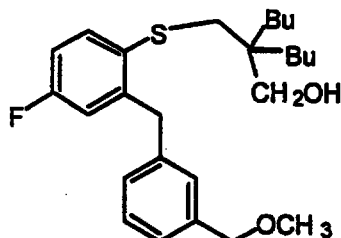
5 Step 3. Preparation of 3



A solution of 53 g (202.3 mmol) of 2 and 11.2 g Li₂S (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18 hours. The reaction was cooled (0 °C) and 60.7 g of X' (the cyclic sulfate compound of example 1397) (242.8 mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and refluxed 2 days. Cooled to ambient temperature and extracted with methylene chloride, dried organic layer over MgSO₄ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate / hexanes as elutant gave 42.9 g (48 %) of 3 as a yellow oil. ¹H NMR (CDCl₃) δ 0.86 (t, J = 7.25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = 8.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).

142

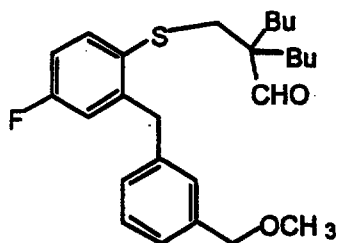
Step 4. Preparation of 4



To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of 3 in 200 mL of methylene chloride was added 21.6 g trifluoromethane sulfonic acid (12.8 mL, 144 mmol) followed by the addition of 22.4 g triethyl silane (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, quenched with water and warmed to ambient temperature.

Partitioned between methylene chloride and water, dried the organic layer over MgSO₄ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%) of 4 as a oil. ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32 (m, 2H), 7.42 (m, 1H).

Step 5. Preparation of 5

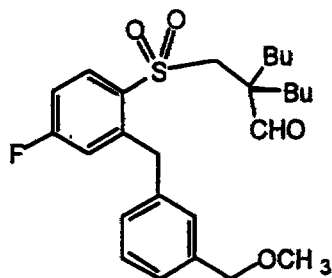


To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water and extracted three times with ethyl acetate. Washed

143

organics with 5% HCl (300 mL) and then with brine (300 mL), dried organics over MgSO₄ and condensed in vacuo to give 23.1 g (96 %) of 5 as a light brown oil. ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

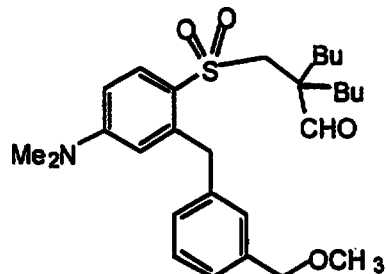
Step 6. Preparation of 6



To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of 5 in 200 mL methylene chloride was added 28.6 g meta chloroperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na₂SO₃, partitioned between water and methylene chloride. Dried organic layer over MgSO₄ and condensed in vacuo to give 24.5 g (98%) of 6 as a light yellow oil. ¹H NMR (CDCl₃) δ 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

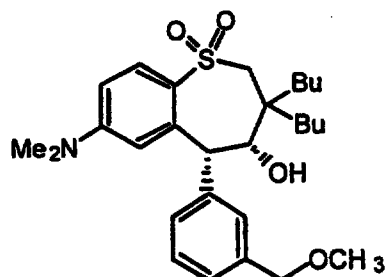
144

Step 7. Preparation of 7



To a solution of 24.5 g (52.9 mmol) of 6 in 20 mL of THF contained in a stainless steel reaction vessel was added 100 mL of a 2.0 M solution of dimethyl amine and 20 mL of neat dimethyl amine. The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl acetate/hexanes gave 21.8 g (84 %) of 7 as a clear colorless oil. ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.25 Hz, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 - 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H), 9.36 (s, 1H).

Step 8. Preparation of 8

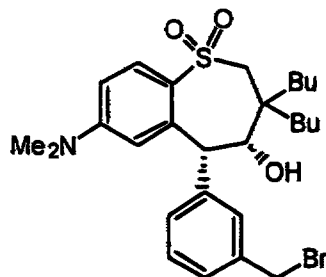


A solution of 21.8 g (44.8 mmol) of 7 in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the

145

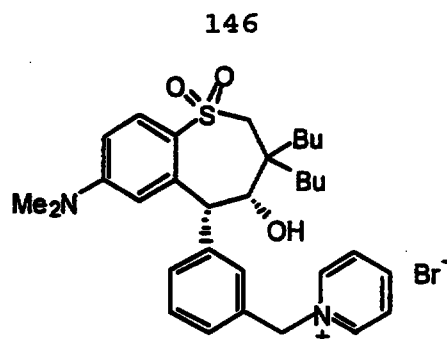
temperature at $<5^{\circ}\text{C}$. Stirred for 30 minutes, then quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO_4 and concentrated in vacuo. Purification by recrystallization from ~10% ethyl acetate/hexanes gave 15.1 g of 8 as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of 8 as a white solid. MS (FABLi^+) m/e 494.6. HRMS (EI^+) calculated for $\text{M}+\text{H}$ 487.2756. Found 487.2746.

Step 9. Preparation of 9



A solution of 2.0 g (4.1 mmol) of 8 in 20 mL of methylene chloride was cooled to -60°C . 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to -10°C and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over MgSO_4 and concentrated in vacuo. Purification by recrystallization from 50% ethyl acetate/methylene chloride gave 1.95 g (89%) of 9 as a white solid. MS (FABH^+) m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

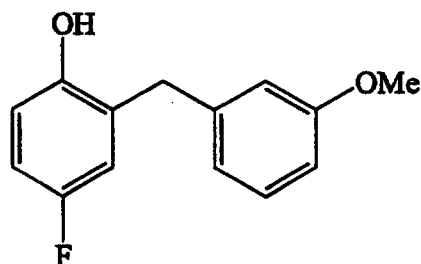
Step 10. Preparation of 10



A solution of 1.09 g (2.0 mmol) of 9 and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of 10 as an off white solid. MS (FAB⁺) m/e 535.5.

Example 1400

Step 1



$C_{14}H_{13}O_2F$ fw=232.25

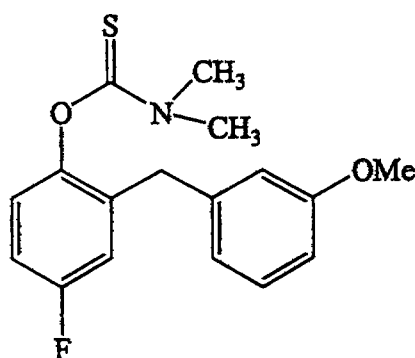
A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h.

A solution of 3-methoxybenzyl chloride

147

(783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aq. KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H NMR and MS [(M + H)⁺ = 233] confirmed desired structure.

Step 2



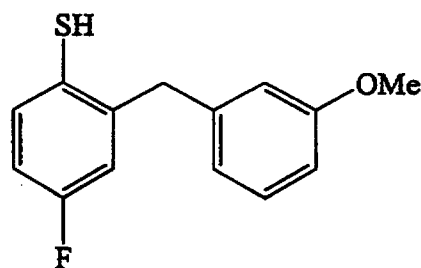
C₁₇H₁₈NO₂FS fw=319.39

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N₂ gas adaptor. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added.

148

The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H₂O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H₂O and saturated aqueous NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ¹H NMR and MS [(M+H)⁺ = 320] confirm desired structure.

Step 3



C₁₄H₁₃OFS fw=248.32

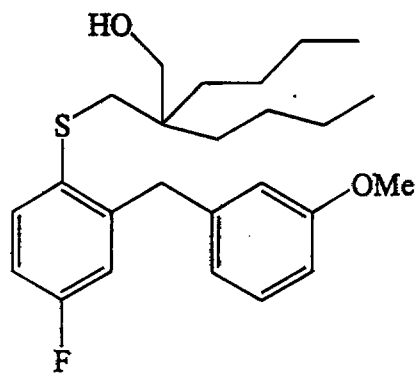
A 12-liter, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with

149

H₂O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether.

The ether extracts were dried (MgSO₄), filtered, and concentrated in vacuo to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

Step 4



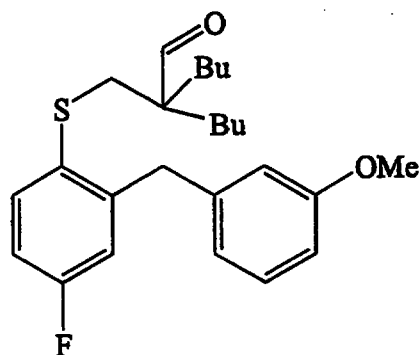
C₂₅H₃₅O₂FS fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H₂O. The aqueous solution was washed with ethyl ether, and concentrated H₂SO₄ was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried (MgSO₄), filtered, and conc'd in vacuo to give an amber oil (143.94g/85% yield). ¹H

150

NMR and MS $[(M + H)^+ = 419]$ confirm the desired structure.

Step 5



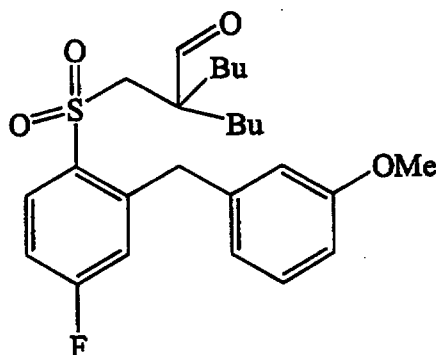
$C_{25}H_{33}O_2FS$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2 . The corresponding alcohol (143.94g/343.8mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was concentrated in vacuo to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS $[(M + H)^+ = 417]$ confirm the desired structure.

10

15

20 Step 6

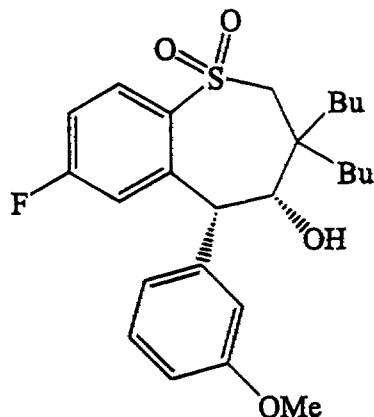


151

 $C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2 . The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3 . An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

Step 7

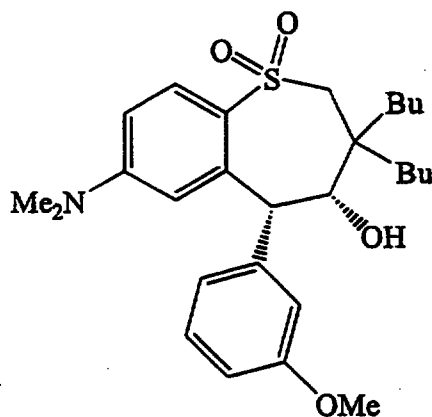
 $C_{25}H_{33}O_4FS$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2 . The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L)

152

were added, and the mixture was cooled to 0 C.
Potassium tert-butoxide (23.35g/208.1mmol) was added
via addition funnel. After 1h, 10% aq/ HCl (1.0 L)
was added. After 1 h, the mixture was extracted three
5 times with ethyl ether, dried (MgSO₄), filtered, and
concentrated in vacuo. The crude product was purified
by recryst. from 80/20 hexane/ethyl acetate to give a
white solid (32.18 g). The mother liquor was
concentrated in vacuo and recrystelized from 95/5
10 toluene/ethyl acetate to give a white solid (33.60g/
combined yield: 71%). ¹H NMR confirmed the desired
product.

Step 8



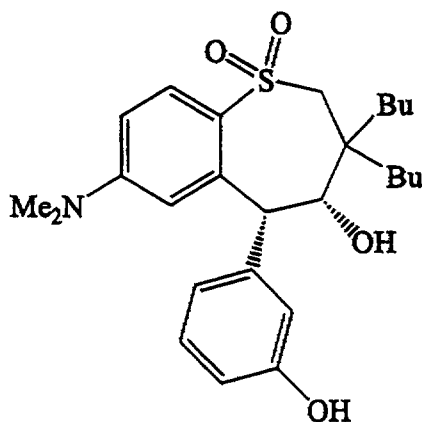
C₂₇H₃₉O₄NS fw=473.67

A Fisher porter bottle was fitted with N₂ line and
magnetic stirrer. The system was purged with N₂. The
20 corresponding fluoro-compound (28.1g/62.6mmol) was
added, and the vessel was sealed and cooled to -78 C.
Dimethylamine (17.1g/379mmol) was condensed via a
CO₂/acetone bath and added to the reaction vessel.
The mixture was allowed to warm to room temperature
25 and was heated to 60 C. After 20 h, the reaction
mixture was allowed to cool and was dissolved in ethyl
ether. The ether solution was washed with H₂O,

153

saturated aqueous NaCl, dried (MgSO_4), filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

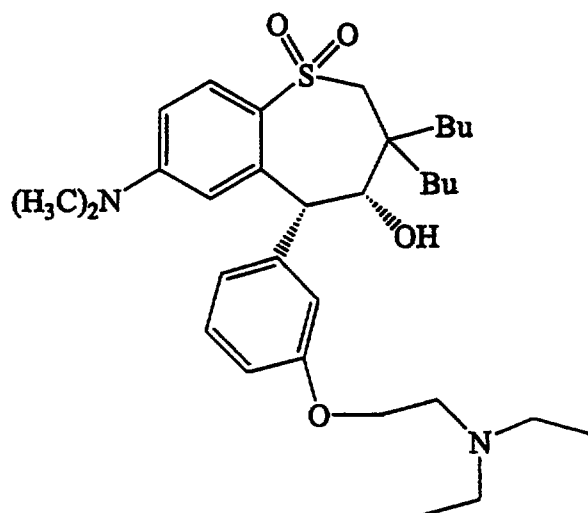
5 Step 9

 $\text{C}_{26}\text{H}_{37}\text{O}_4\text{NS}$ fw=459.64

10 A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2 . The corresponding methoxy-compound (6.62g/14.0mmol) and CHCl_3 (150 mL) were added. The reaction mixture was cooled to -78°C , and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature. After 4 h, 15 the reaction mixture was cooled to 0°C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The CHCl_3 and 20 ether extracts were combined, washed with saturated aqueous NaCl, dried (MgSO_4), filtered, and concentrated in vacuo to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

154

Step 10

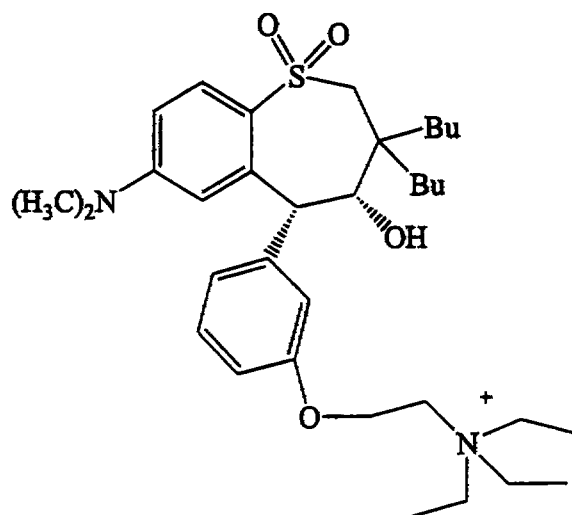


5 In a 250 ml single neck round bottom Flask with stir
bar place 2- diethylaminoethyl chloride hydrochloride
(fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol, 4.12g),
34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15
10 minutes and then separate by ether extraction and dry
over anhydrous potassium carbonate.

In a separate 2-necked 250 ml round bottom flask with
stir bar add sodium hydride (60% dispersion in mineral
oil, 100 mg , 2.6 mmol) and 34 ml of DMF. Cool to ice
15 temperature. Next add phenol product(previous step)
1.1 g (2.4 mmoles in 5 ml DMF and the ether solution
prepared above. Heat to 40C for 3 days. The product
which contained no starting material by TLC was
diluted with ether and extracted with 1 portion of 5%
20 NaOH, followed by water and then brine. The ether
layer was dried over magnesium sulfate and isolated by
removing ether by rotary evaporation (1.3 gms).The
product may be further purified by chromatography
(SiO₂ 99% ethyl acetate/1% NH₄OH at 5ml/min.).
25 Isolated yield: 0.78 g (mass spec , and H1 NMR)

155

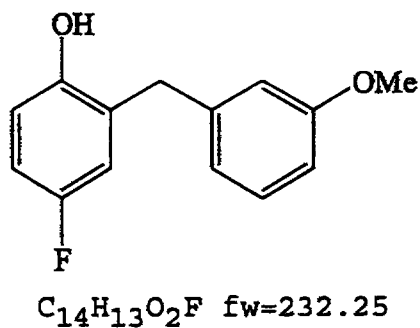
Step 11



5 The product from step 10 (0.57gms, 1.02 millimole fw
558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was
placed in 5 ml acetonitrile in a fischer-porter bottle
and heated to 45 C for 3 days. The solution was
evaporated to dryness and redissolved in 5 mls of
10 chloroform. Next ether was added to the chloroform
solution and the resulting mixture was chilled. The
desired product is isolated as a precipitate 0.7272
gms. (Mass spec M-I = 587.9, H NMR).

15 Example 1401

Step 1



20

A 12-liter, 4-neck round-bottom flask was equipped

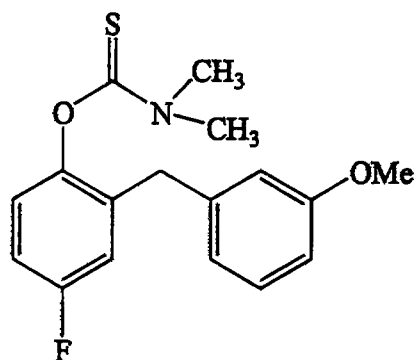
156

with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h.

A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aqueous KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H NMR and MS [(M + H)⁺ = 233] confirmed desired structure.

157

Step 2

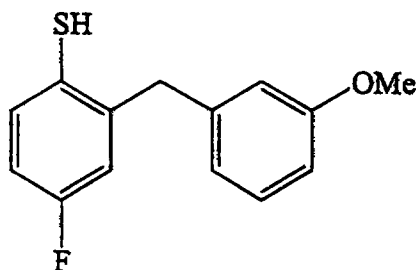
 $C_{17}H_{18}NO_2FS$ fw=319.39

5

A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ^1H NMR and MS [$(M+H)^+ = 320$] confirm desired structure.

20

Step 3

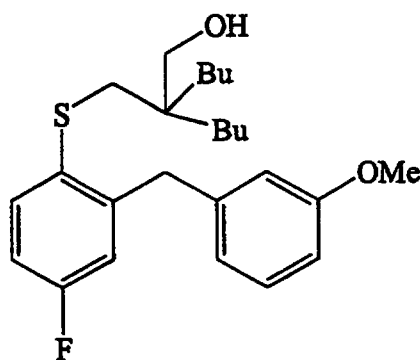


158

 $C_{14}H_{13}OFS$ fw=248.32

A 12-liter, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and reflux
5 condenser. The system was purged with N_2 . 4-Fluoro-
2-(3-methoxybenzyl)-phenyldimethylthiocarbamate
(605.3g/1.895mol) and phenyl ether (2.0kg) were added,
and the solution was heated to reflux for 2 h. The
mixture was stirred for 64 h. at room temperature and
10 then heated to reflux for 2 h. After cooling to room
temperature, MeOH (2.0 L) and THF (2.0 L) were added,
and the solution was stirred for 15 h. Potassium
hydroxide (425.9g/7.590mol) was added, and the mixture
was heated to reflux for 4 h. After cooling to room
15 temperature, the mixture was concentrated by rotavap,
dissolved in ethyl ether (1.0 L), and extracted with
 H_2O . The aqueous extracts were combined, acidified
with conc. HCl, and extracted with ethyl ether. The
ether extracts were dried ($MgSO_4$), filtered, and
20 concentrated in vacuo to give an amber oil (463.0g,
98% yield). ^1H NMR confirmed desired structure.

Step 4

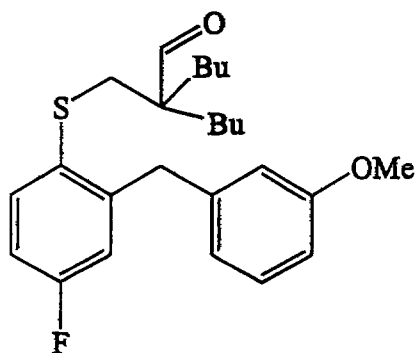
 $C_{25}H_{35}O_2FS$ fw=418.61

A 5-liter, 3-neck, round-bottom flask was
equipped with N_2 gas adaptor and mechanical stirrer.

159

The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature. 2,2-Dibutylpropylene sulfide (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H₂O. The aqueous solution was washed with ethyl ether, and conc. H₂SO₄ was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried (MgSO₄), filtered, and concentrated in vacuo to give an amber oil (143.94g/85% yield). ¹H NMR and MS [(M + H)⁺ = 419] confirm the desired structure.

Step 5



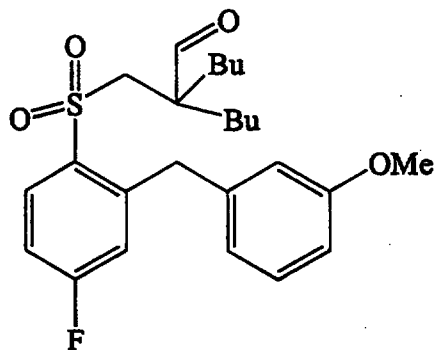
C₂₅H₃₃O₂FS fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, and mechanical stirrer. The system was purged with N₂. The corresponding alcohol (143.94 g/343.8 mmol) and CH₂Cl₂ (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate

160

(140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(\text{M} + \text{H})^+ = 417$] confirm the desired structure.

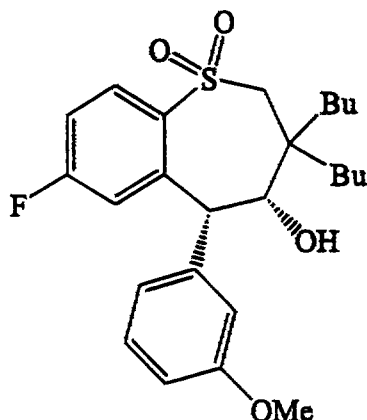
Step 6

 $\text{C}_{25}\text{H}_{33}\text{O}_4\text{FS}$ fw=448.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2 . The corresponding sulfide (110.6g/265.5mmol) and CH_2Cl_2 (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K_2CO_3 . An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried (MgSO_4), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ^1H NMR confirmed the desired structure.

161

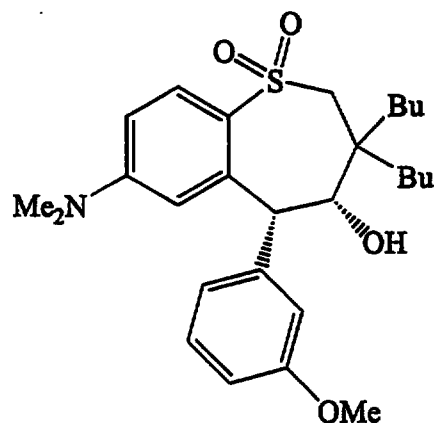
Step 7

 $C_{25}H_{33}O_4FS$ fw=448.59

- 5 A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2 . The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to
- 10 0 C. Potassium tert-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was
- 15 purified by recrystallized from 80/20 hexane/ethyl acetate to give a white solid (32.18g). The mother liquor was concentrated in vacuo and recrystallized from 95/5 toluene/ethyl acetate to give a white solid (33.60g, combined yield: 71%). ^1H NMR confirmed the
- 20 desired product.

162

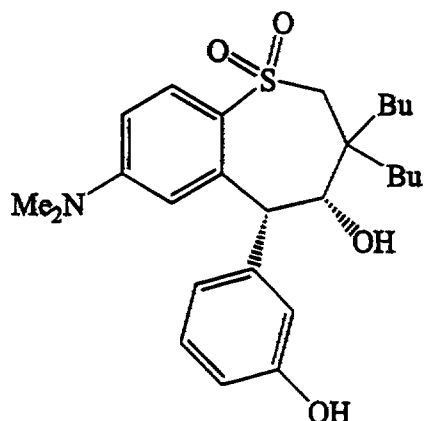
Step 8

 $C_{27}H_{39}O_4NS$ fw=473.67

- 5 A Fisher porter bottle was fitted with N₂ line and magnetic stirrer. The system was purged with N₂. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a
- 10 CO₂/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H₂O,
- 15 saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). ¹H NMR confirmed the desired structure.

163

Step 9

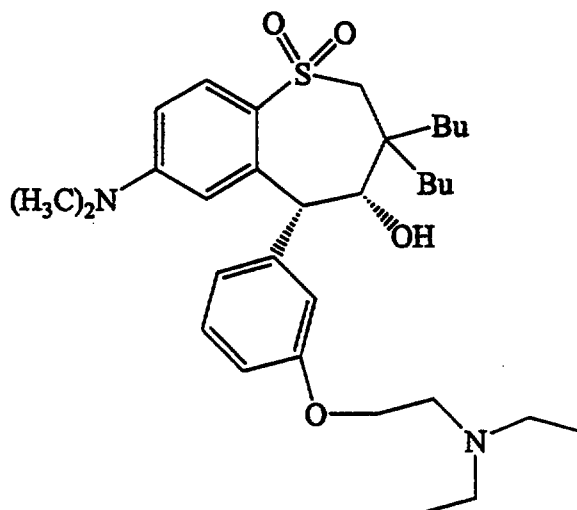
 $\text{C}_{26}\text{H}_{37}\text{O}_4\text{NS}$ fw=459.64

5 A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2 . The corresponding methoxy-
10 compound (6.62g/14.0mmol) and CHCl_3 (150 mL) were added. The reaction mixture was cooled to -78°C , and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature. After 4 h, the reaction mixture was cooled to 0°C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was
15 extracted two times with ethyl ether. The CHCl_3 and ether extracts were combined, washed with saturated aqueous NaCl , dried over MgSO_4 , filtered, and concentrated in vacuo to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

20

164

Step 10

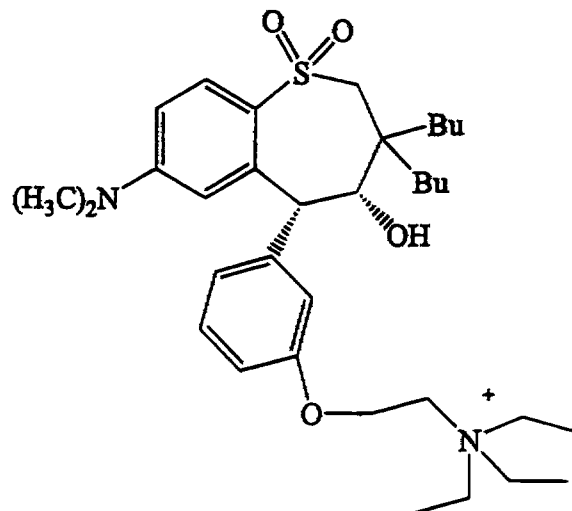


5 In a 250 ml single neck round bottom flask with
stir bar place 2- diethylaminoethyl chloride
hydrochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4
millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N
KOH (aqueous). Stir 15 minutes and then separate by
10 ether extraction and dry over anhydrous potassium
carbonate.

 In a separate 2-necked 250 ml round bottom flask
with stir bar add sodium hydride (60% dispersion in
15 mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool
to ice temperature. Next add phenol product (previous
step) 1.1 g (2.4 mmol in 5 ml DMF and the ether
solution prepared above. Heat to 40C for 3 days. The
product which contained no starting material by TLC
20 was diluted with ether and extracted with 1 portion of
5% NaOH, followed by water and then brine. The ether
layer was dried over Magnesium sulfate and isolated by
removing ether by rotary evaporation (1.3 gms). The
product may be further purified by chromatography
25 (silica 99% ethyl acetate/1% NH4OH at 5ml/min.).
Isolated yield: 0.78 g (mass spec , and H1 NMR)

165

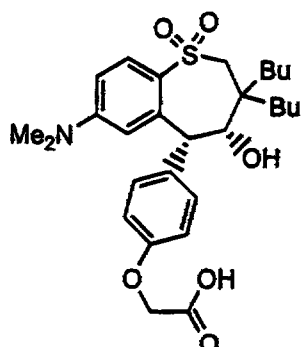
Step 11



5

The product from step 10 (0.57gms, 1.02 millimole
fw 558.83 g/mole) and iodoethane (1.6 gms (10.02
mmilimoles) was placed in 5 ml acetonitrile in a
Fischer-Porter bottle and heated to 45 C for 3 days.
The solution was evaporated to dryness and redissolved
in 5 mls of chloroform. Next ether was added to the
chloroform solution and the resulting mixture was
chilled. The desired product is isolated as a
precipitate 0.7272 gms. Mass spec M-I = 587.9, ¹H
NMR).

15

Example 1402

(4R-cis)-5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]pentyl]thio]-1H-tetrazole-1-
acetic acid

Step 1. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol

To a stirred solution of 23.66 g of 95% sodium
hydride (0.94 mol) in 600 mL of dry toluene was added
100.0 g of 4-fluorophenol (0.89 mol) at 0°C. The
mixture was stirred at 90°C for 1 hour until gas
evolution stopped. The mixture was cooled down to room
temperature and a solution of 139.71 g of 3-
methoxybenzyl chloride (0.89 mol) in 400 mL of dry
toluene was added. After refluxing for 24 hours, the
mixture was cooled to room temperature and quenched
with 500 mL of water. The organic layer was separated,
dried over MgSO₄, and concentrated under high vacuum.
The remaining starting materials were removed by
distillation. The crude dark red oil was filtered
through a layer of 1 L of silica gel with neat hexane
to yield 53.00 g (25.6%) of the product as a pink
solid: ¹H NMR (CDCl₃) δ 3.79 (s, 3H), 3.90 (s, 2H), 4.58
(s, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11-
7.16 (m, 2H).

Step 2. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

Step 2a. Preparation of thiocarbamate

To a stirred solution of 50.00 g (215.30 mmol) of
4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL
of dry DMF was added 11.20 g of 60% sodium hydride
dispersion in mineral oil (279.90 mmol) at 2°C. The
mixture was allowed to warm to room temperature and
26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol)

167

was added. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 100 mL of water in an ice bath. The solution was extracted with 500 mL of diethyl ether. The ether solution was washed with 500 mL of water and 500 mL of brine. The ether solution was dried over MgSO_4 and stripped to dryness. The crude product was filtered through a plug of 500 mL silica gel using 5% ethyl acetate/hexane to yield 48.00 g (69.8%) of the product as a pale white solid: ^1H NMR (CDCl_3) δ 3.21 (s, 3H), 3.46 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.78-6.86 (m, 3H), 6.90-7.00 (m, 2H), 7.09 (d, $J = 8.7$ Hz, 2H).

Step 2b. Rearrangement and hydrolysis of thiocarbamate to 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

A stirred solution of 48.00 g (150.29 mmol) of thiocarbamate (obtained from Step 2a) in 200 mL of diphenyl ether was refluxed at 270°C overnight. The solution was cooled down to room temperature and filtered through 1 L of silica gel with 2 L of hexane to remove phenyl ether. The rearrangement product was washed with 5% ethyl acetate/hexane to give 46.00 g (95.8%) of the product as a pale yellow solid: ^1H NMR (CDCl_3) δ 3.02 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), 4.07 (s, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, $J = 8.4$ Hz, 2.7 Hz, 1H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.49 (dd, $J = 6.0$ Hz, 8.7 Hz, 1H).

To a solution of 46.00 g (144.02 mmol) of the rearrangement product (above) in 200 mL of methanol and 200 mL of THF was added 17.28 g of NaOH (432.06 mmol). The mixture was refluxed under nitrogen overnight. The solvents were evaporated off and 200 mL of water was added. The aqueous solution was washed with 200 mL of diethyl ether twice and placed in an ice bath. The aqueous mixture was acidified to pH 6 with concentrated HCl solution. The solution was extracted with 300 mL of

diethyl ether twice. The ether layers were combined, dried over MgSO_4 and stripped to dryness to afford 27.00 g (75.5%) of the product as a brown oil: ^1H NMR (CDCl_3) δ 3.24 (s, 1H), 3.80 (s, 3H), 3.99 (s, 2H), 5 6.81-6.87 (m, 4H), 7.09 (d, $J = 8.7$ Hz, 2H), 7.27-7.33 (m, 1H).

Step 3. Preparation of dibutyl cyclic sulfate

Step 3a. Preparation of 2,2-dibutyl-1,3-propanediol.

10 To a stirred solution of di-butyl-diethylmalonate (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an acetone/dry ice bath was added LAH (1 M THF) 662 ml (1.2 eq., 0.66 mol) dropwise maintaining the temperature between -20 to 0°C . The reaction was 15 stirred at RT overnight. The reaction was cooled to -20°C and 40 ml of water, and 80 mL of 10% NaOH and 80 ml of water were added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated in vacuo to give diol 20 98.4 g (yield 95%) as an oil. MS spectra and proton and carbon NMR spectra were consistent with the product.

Step 3b. Preparation of dibutyl cyclic sulfite

25 A solution of 2,2-dibutyl-1,3-propanediol (103 g, 0.548 mol, obtained from Step 3a) and triethylamine (221 g, 2.19 mol) in anhydrous methylene chloride (500 ml) was stirred at 0°C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise 30 and within 5 min the solution turned yellow and then black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. at 0°C . GC showed that there was no starting material left. The mixture was washed with ice water twice then 35 with brine twice. The organic phase was dried over magnesium sulfate and concentrated under vacuum to give

169

128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

5 Step 3c. Oxidation of dibutyl cyclic sulfite to dibutyl cyclic sulfate

10 To a solution of the dibutyl cyclic sulfite (127.5 g, 0.54 mol, obtained from Step 3b) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium (III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. GC showed that there was no starting material left. The mixture was extracted with 300 ml of ether and the ether extract was washed three times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The filtrate was concentrated under vacuum and to give 133 g (97.8%) of the dibutyl cyclic sulfate as an oil. Proton and carbon NMR and MS were consistent with the product.

20 Step 4. Preparation of aryl-3-hydroxypropylsulfide

25 To a stirred solution of 27.00 g (108.73 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)thiophenol (obtained from Step 2) in 270 mL of diglyme was added 4.35 g of 60% sodium hydride dispersion in mineral oil (108.73 mmol) at 0°C. After gas evolution ceased, 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (obtained from Step 3c) was added at 0°C and stirred for 10 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated and 200 mL of water was added. The solution was washed with 200 mL of diethyl ether and added 25 mL of concentrated sulfuric acid to make a 2.0 M solution that was refluxed overnight. The solution was extracted with ethyl acetate and the organic solution was dried over MgSO₄ and concentrated in

170

vacuo. The crude aryl-3-hydroxypropylsulfide was purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) of the product as a light brown oil: ^1H NMR (CDCl_3) δ 0.90 (t, $J = 7.1$ Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77-6.92 (m, 4H), 7.09 (d, $J = 8.7$ Hz, 2H), 7.41 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H).

10 Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

To a stirred solution of 20.00 g (47.78 mmol) of aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 L of methylene chloride was added 31.50 g of 96% (1R)-(-)-(8,8-dichloro-10-camphor-sulfonyl)oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the oxaziridine dissolved the mixture was placed into a -30°C freezer for 72 hours. The solvent was evaporated and the crude solid was washed with 1 L of hexane. The white solid was filtered off and the hexane solution was concentrated in vacuo. The crude oil was purified on a silica gel column (Waters Prep 500) using 15% ethyl acetate/hexane to afford 19.00 g (95%) of the enantiomerically-enriched aryl-3-hydroxypropylsulfoxide as a colorless oil: ^1H NMR (CDCl_3) δ 0.82-0.98 (m, 6H), 1.16-1.32 (m, 12H), 2.29 (d, $J = 13.8$ Hz, 1H), 2.77 (d, $J = 13.5$ Hz, 1H), 3.45 (d, $J = 12.3$ Hz, 1H), 3.69 (d, $J = 12.3$ Hz, 1H), 3.79 (s, 3H), 4.02 (q, $J = 15.6$ Hz, 1H), 6.83-6.93 (m, 3H), 7.00 (d, $J = 8.1$ Hz, 2H), 7.18-7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess was determined by chiral HPLC on a (R,R)-Whelk-O column using 5% ethanol/hexane as the eluent. It showed to be 78% e.e. with the first eluting peak as the major product.

35

Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

To a stirred solution of 13.27 g of triethylamine (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide were added 19.00 g (43.72 mmol) of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide (obtained from Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 mmol, Aldrich) at room temperature. After the mixture was stirred at room temperature for 48 hours, 500 mL of water was added to the mixture and stirred vigorously.

The mixture was then extracted with 500 mL of ethyl acetate twice. The ethyl acetate layer was separated, dried over MgSO_4 , and concentrated in vacuo. The crude oil was filtered through 500 mL of silica gel using 15% ethyl acetate/hexane to give 17.30 g (91%) of the enantiomerically-enriched aryl-3-propanalsulfoxide as a light orange oil: ^1H NMR (CDCl_3) δ 0.85-0.95 (m, 6H), 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.57 (d, $J = 14.1$ Hz, 1H), 2.91 (d, $J = 13.8$ Hz, 1H), 3.79 (s, 3H), 3.97 (d, $J = 15.9$ Hz, 1H), 4.12 (d, $J = 15.9$ Hz, 1H), 6.84-6.89 (m, 3H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.19 (dt, $J = 8.4$ Hz, 2.4 Hz, 1H), 8.02 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H), 9.49 (s, 1H).

Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R)

To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium t-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C . The THF layer was separated, dried over MgSO_4 , and concentrated in vacuo.

The enantiomerically-enriched tetrahydrobenzothiepine-

172

1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: ^1H NMR (CDCl_3) δ 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, $J = 13.0$ Hz, 1H), 3.00 (d, $J = 13.0$ Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, $J = 9.9$ Hz, 2.4 Hz, 1H), 6.94 (d, $J = 9$ Hz, 2H), 7.13 (dt, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.82 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H).

Step 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a stirred solution of 13.44 g (31.07 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (obtained from Step 7) in 150 mL of methylene chloride was added 9.46 g of 68% *m*-chloroperoxybenzoic acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 °C for 2 hours, the mixture was allowed to warm up to room temperature and stirred for 4 hours. 50 mL of saturated Na_2SO_3 was added into the mixture and stirred for 30 minutes. The solution was then neutralized with 50 mL of saturated NaHCO_3 solution. The methylene chloride layer was separated, dried over MgSO_4 , and concentrated in vacuo to give 13.00 g (97.5%) of the enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a light yellow solid: ^1H NMR (CDCl_3) δ 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 1H), 3.14 (q, $J = 15.6$ Hz, 1H), 3.87 (s, 3H), 4.18 (s, 1H), 5.48 (s, 1H), 6.54 (dd, $J = 10.2$ Hz, 2.4 Hz, 1H), 6.96-7.07 (m, 3H), 7.40 (d, $J = 8.1$ Hz, 2H), 8.11 (dd, $J = 8.6$ Hz, 5.9 Hz, 1H).

Step 9. Preparation of enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

173

To a solution of 13.00 g (28.98 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 8) in 73 mL of dimethylamine (2.0 M in THF, 146 mmol) in a Parr
5 Reactor was added about 20 mL of neat dimethylamine. The mixture was sealed and stirred at 110°C overnight, and cooled to ambient temperature. The excess dimethylamine was evaporated. The crude oil was dissolved in 200 mL of ethyl acetate and washed with
10 100 mL of water, dried over MgSO₄ and concentrated in vacuo. Purification on a silica gel column (Waters Prep 500) using 20% ethyl acetate/hexane gave 12.43 g (90.5%) of the enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
15 (4R,5R) as a colorless solid: ¹H NMR (CDCl₃) δ 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, J = 15.3 Hz, 1H), 3.15 (d, J = 15.3 Hz, 1H), 3.84 (s, 3H), 4.11 (d, J = 7.5 Hz, 1H), 5.49 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J =
20 8.7 Hz, 2.4 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). The product was determined to have 78% e.e. by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from ethyl
25 acetate/hexane gave 1.70 g of the racemic product. The remaining solution was concentrated and recrystallized to give 9.8 g of colorless solid. Enantiomeric excess of this solid was determined by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the
30 eluent. It showed to have 96% e.e with the first eluting peak as the major product.

Step 10: Demethylation of 5-(4'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
35 (4R,5R)

174

To a solution of 47 g (99 mmol) of enantiomeric-enriched (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 9) in 500 mL of methylene chloride at -10 °C was added dropwise a solution of boron tribromide (297 mL, 1M in methylene chloride, 297 mmol), and the resulting solution was stirred cold (-5 °C to 0 °C) for 1 hour or until the reaction was complete. The reaction was cooled in an acetone-dry ice bath at -10 °C, and slowly quenched with 300 mL of water. The mixture was warmed to 10 °C, and further diluted with 300 mL of saturated sodium bicarbonate solution to neutralize the mixture. The aqueous layer was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with 200 mL of water, brine, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in 500 mL of ethyl acetate and stirred with 50 mL of glacial acetic acid for 30 minutes at ambient temperature. The mixture was washed twice with 200 mL of water, 200 mL of brine, dried over MgSO₄ and concentrated in vacuo to give the crude 4-hydroxyphenyl intermediate. The solid residue was recrystallized from methylene chloride to give 37.5 g (82%) of the desired 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide as a white solid: ¹H NMR (CDCl₃) δ 0.84-0.97 (m, 6H), 1.1-1.5 (m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83 (s, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8,7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H).

Alternatively, enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the intermediate just described, can be prepared via non-

175

enantioselective synthesis followed by chiral chromatography separation. Oxidation of aryl-3-hydroxypropylsulfide (obtained from Step 4) with m-chloroperbenzoic acid (under the similar conditions as in Step 8, but with 2.2 equivalent of m-CPBA) gave the racemic sulfone intermediate. The sulfone was carried through the synthetic sequences (under the same conditions as in Step 7 and Step 9) to give the racemic 5-(4'-hydroxyphenyl)-7-

(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide. The two enantiomers were further separated into the desired enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide by appropriate chiral chromatographic purification.

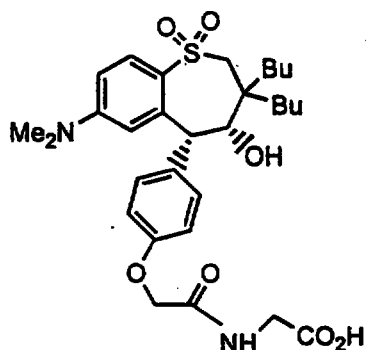
Step 11: Preparation of ester intermediate

To a solution of 1.0 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 10) in 10 mL dimethylformamide was added 60 mg (2.38 mmol) of 95% sodium hydride and stirred for 15 minutes. To the reaction mixture was added 400 μ L (2.52 mmol) of benzyl 2-bromoacetate and stirred for two hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 1.30g (98%) of the ester intermediate: ^1H NMR (CDCl_3) δ 0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.24 (m, 1H), 2.81 (s, 6H), 3.00 (d, J = 15.1 Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (s, 1H), 5.26 (s, 2H), 5.49 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 7.37 (s, 5H), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H).

176

Step 12: Preparation of acid

A solution of 1.30 g (2.14 mmol) of ester intermediate (obtained from Step 1) in 40 mL ethanol with 10% palladium on carbon was placed under an atmosphere of hydrogen gas (40 psi) for three hours. The reaction mixture was filtered through celite and the solvent was evaporated to afford the desired title compound as a white solid: mp 119 - 123 °C; ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (s, 1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for C₂₈H₄₀NO₆S: 518.2576. Found: 518.2599.

Example 1403

(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

Step 1: Preparation of glycine ester intermediate

To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100

177

ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 48.9$ Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H).

Step 2: Preparation of acid

A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g $\text{LiOH}\cdot\text{H}_2\text{O}$ (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 hours. This was then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound as a white crystalline solid: mp 149-150 °C; ^1H NMR (CD_3OD) δ 0.88-0.98 (m, 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 21.6$ Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, $J = 9.0$ Hz, 1H), 7.08 (d, $J = 7.8$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.76 (d, $J = 9.0$ Hz, 1H), 8.42 (m, 1H). HRMS (ES+)

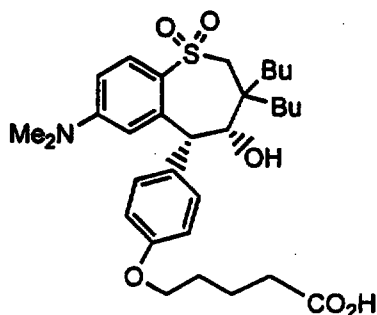
178

Calc'd for $C_{30}H_{42}N_2O_7S$: 575.2712. Found: 575.2790. Anal.

Calc'd for: $C_{30}H_{42}N_2O_7S$ C, 62.69; H, 7.37; N, 4.87.

Found: C, 62.87; H, 7.56; N, 4.87.

5 Example 1404



10 (4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentanoic acid

Step 1: Preparation of ester intermediate

15 A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.0 g, 2.2 mmol, obtained from Example 1402, Step 10) in acetone (10 mL) at 25 °C under N_2 was treated with powdered K_2CO_3 (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5-bromovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a
20 catalytic amount of tetra-n-butylammonium iodide (2 mg), and the resulting solution was stirred at 65 °C for 24 hours. The pale amber slurry was cooled to 25 °C and was concentrated in vacuo to provide a yellow residue. Purification by flash chromatography (2.4 x
25 30 cm silica, 20-40% EtOAc/hexane) afforded the ester intermediate (1.2 g, 86%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, J = 15.1 Hz, J = 47.7 Hz, 2H), 4.10 (d, J = 7.9 Hz, 1H), 5.13 (s, 2H), 5.47 (s, 1H), 6.00 (d, J
30

179

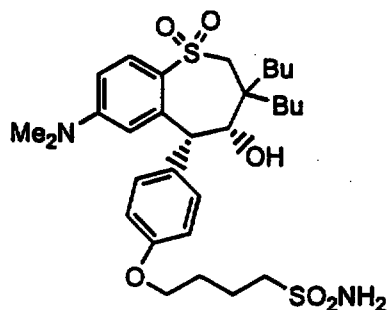
= 2.5 Hz, 1H), 6.50 (dd, $J = 8.9$, 2.5 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.36 (m, 5H), 7.40 (d, $J = 8.5$ Hz, 2H), 7.86 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $C_{30}H_{51}NO_6S$: 650.3515. Found: 650.3473.

5

Step 2: Preparation of acid

A solution of the ester intermediate (0.99 g, 1.5 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25 °C was treated with 5% palladium on carbon (0.15 g, 10 wt %) then stirred under an atmosphere (1 atm) of H_2 via hydrogen balloon. Every 10 min, hydrogen gas was bubbled through the slurry for 1 min, for a total reaction time of 4 hours. The slurry was placed under an atmosphere of N_2 and nitrogen was bubbled through the reaction mixture for 10 min. The mixture was filtered through a plug of Celite® (10 g) and concentrated in vacuo to give a white foam. Purification by flash chromatography (2.6 x 25 cm silica, 1.5% EtOH/ CH_2Cl_2) afforded the desired title compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; ^1H NMR ($CDCl_3$) δ 0.90 (m, 6H), 1.10-1.46 (br m, 10H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, $J = 15.1$ Hz, $J = 49.7$ Hz, 2H), 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.48 (dd, $J = 8.9$, 2.4 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.39 (m, 5H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.84 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $C_{31}H_{49}NO_6S$: 560.3046. Found: 560.3043.

180

Example 1405

5 (4R-cis) -4- [4- [3,3-Dibutyl-7- (dimethylamino) -2,3,4,5-
tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-
yl]phenoxy-1-butanesulfonamide

10 Step 1: Preparation of sulfonic acid intermediate

A solution of 7.4 g (16.1 mmol) of 5-(4'-
hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-
thiepine-1,1-dioxide (obtained from Example 1402, Step
10) in acetone (35 mL) at 25 °C under N₂ was treated
15 with powdered potassium carbonate (3.3 g, 24.1 mmol,
1.5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol,
1.5 equiv.) and stirred and heated at 65 °C for 64 h.

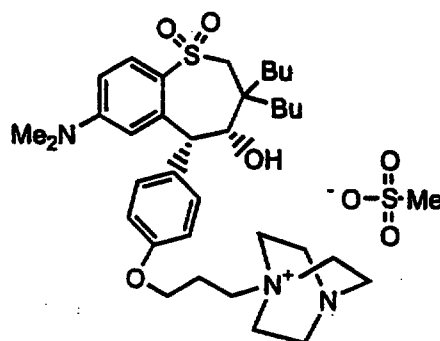
The solution was allowed to cool to 25 °C and
quenched by the addition of water (50 mL), until a
20 homogeneous mixture was obtained. The clear and
colorless solution was added dropwise to a 4 N HCl
solution cooled to 0 °C over a 30 min period. The
mixture was vigorously stirred for 4 h then allowed to
warm to ambient temperature and stirred for an
25 additional 16 h. The resultant white precipitate was
filtered and washed with water and dried in vacuo to
provide 8.8 g (92%) of the desired sulfonic acid as a
white solid. A portion of the white solid was
recrystallized from CH₃CN/hexane to give the desired
30 sulfonic acid as colorless needles: mp 229-236 °C

181

(decomposed); ^1H NMR ($\text{DMSO}-d_6$) δ 0.82 (m, 6H), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86 (s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.92 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.60 (d, $J = 8.9$ Hz, 1H); Anal. Calc'd for $\text{C}_{30}\text{H}_{45}\text{NO}_7\text{S}_2$: C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

10 Step 2: Preparation of 7-(dimethylamino)-benzothiepin-5-yl]phenoxy-1-butanefulfonamide

To a solution of 1.12 g (1.88 mmol) of the sulfonic acid (obtained from Step 1) in 10 mL CH_2Cl_2 was added 785 mg (3.77 mmol) PCl_5 and stirred for 1 hour. Water was added and the mixture was extracted and washed with brine. Dried with MgSO_4 , filtered and solvent evaporated. To the residue was added 30 mL of 0.5M NH_3 in dioxane and stirred 16 hours. The precipitate was filtered and the solvent evaporated. The residue was purified by MPLC (33% EtOAc in hexane) to afford the desired title compound as a beige solid (125 mg, 11%): mp 108-110 °C; ^1H NMR (CDCl_3) δ 0.85-0.93 (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, $J = 15.3$ Hz, 1H), 3.15 (t, $J = 15.3$ Hz, 1H), 3.23 (t, $J = 7.7$ Hz, 2H), 4.03 (t, $J = 5.8$ Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s, 2H), 5.47 (s, 1H), 6.02 (d, $J = 2.4$ Hz, 1H), 6.52 (dd, $J = 8.9, 2.6$ Hz, 1H), 6.91 (d, $J = 8.9$ Hz, 2H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 1H). HRMS. Calc'd for $\text{C}_{30}\text{H}_{47}\text{N}_2\text{O}_6\text{S}_2$: 595.2876. Found: 595.2874.

Example 1406

5

(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-
10 azoniabicyclo[2.2.2]octane, methanesulfonate (salt)

Step 1: Preparation of dimesylate intermediate

To a cooled (-20 °C) solution of 5.0 g (65.7 mmol)
of 1,3-propanediol in 50 mL of triethylamine and 200 mL
15 of methylene chloride was added 15.8 g (137.9 mmol) of
methanesulfonyl chloride. The mixture was stirred for
30 minutes, then warmed to ambient temperature and
partitioned between ethyl acetate and 1N HCl. The
organic layer was washed with brine, dried over MgSO₄,
20 and concentrated in vacuo to give 13.5 g (89%) of
dimesylate intermediate as a clear yellowish oil: ¹H
NMR (CDCl₃) δ 2.12 (quintet, J = 4.5 Hz, 4H), 3.58 (s,
6H), 4.38 (t, J = 5.4 Hz)

Step 2: Preparation of propyl mesylate intermediate

To a solution of 2.4 g (5.2 mmol) of 5-(4'-
hydroxyphenyl)-7-(dimethylamino)tetrahydrobenz-
othiepine-1,1-dioxide (obtained from Example 1402, Step
10) and 6.0 g (26.1 mmol) of dimesylate intermediate
30 (obtained from Step 1) in 50 mL of acetone was added

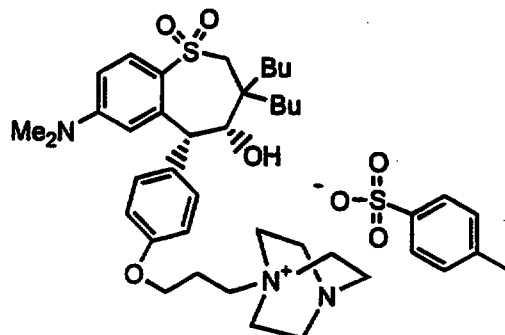
183

3.6 g (26.1 mmol) of K_2CO_3 . The reaction was heated to reflux overnight then cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 36% ethyl acetate/hexanes afforded 2.8 g (90%) of the propyl mesylate intermediate as a white foam: ^1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 (AB_q, $J_{AB} = 15.0$ Hz, $J = 46.9$ Hz, 4.09-4.18 (m, 3H), 4.48 (t, $J = 6.0$ Hz, 2H), 5.49 (s, 1H), 6.11 (s, 1H), 6.65 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.94 (d, $J = 8.9$ Hz, 1H).

Step 3: Preparation of quaternary salt

To a solution of 1.2 g (2.0 mmol) of propyl mesylate intermediate (obtained from Step 2) in 20 ml of acetonitrile was added 0.3g (2.9 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction mixture was stirred at 60 °C for three hours, then cooled to ambient temperature and concentrated in vacuo. Purification by trituration with methylene chloride/ethyl ether gave 1.3 g (91%) of the desired title compound as a white solid: mp. (dec) 230-235 °C; ^1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m, 2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (AB_q, $J_{AB} = 15.6$ Hz, $J = 42.2$ Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, 6H), 3.73-3.83 (m, 2H), 4.06-4.17 9m, 3H), 5.47 (s, 1H), 5.97 (s, 1H), 6.51 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 1H). MS (ES+) m/e 612.4. HRMS (ES+) Calc'd for $C_{35}H_{54}N_3O_4S^+$: 612.3835. Found: 612.3840.

184

Example 1407

5 (4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-
10 azoniabicyclo[2.2.2]octane, 4-methylbenzenesulfonate
(salt)

Step 1: Preparation of propyl tosylate intermediate

A solution of 5-(4'-hydroxyphenyl)-7-(
15 (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0
g, 10.9 mmol, obtained from Example 1402, Step 10) in
acetone (100 mL) at 25 °C under N₂ was treated with
powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3-
propanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.),
and the resulting mixture was stirred at 65 °C for 21
20 hours. The cream-colored slurry was cooled to 25 °C
and was filtered through a sintered glass funnel. The
filtrate was concentrated and the residue was dissolved
in EtOAc (150 mL). The organic layer was washed with
saturated aqueous NaHCO₃ (2 x 150 mL) and saturated
25 aqueous NaCl (2 x 150 mL), and was dried (MgSO₄) and
concentrated in vacuo to provide a pale orange oil.
Purification by flash chromatography (4.4 x 35 cm
silica, 20-30% EtOAc/hexane) afforded the propyl
tosylate intermediate (6.0 g, 80%) as a white foam: ¹H
30 NMR (CDCl₃) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63

185

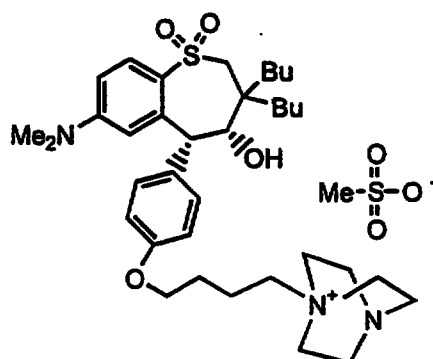
(m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (s, 3H), 2.81 (s, 6H), 3.06 (ABq, $J = 15.1$ Hz, $J = 49.0$ Hz, 2H), 4.01 (t, $J = 5.3$ Hz, 2H), 4.10 (m, 1H), 4.26 (t, $J = 5.9$ Hz, 2H), 5.29 (s, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.51 (dd, $J = 8.9, 1.8$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.88 (d, $J = 8.9$ Hz, 1H).

Step 2: Preparation of quaternary salt

A solution of the propyl tosylate intermediate (1.05 g, 1.56 mmol, obtained from Step 1) in acetonitrile (15 mL) at 25 °C under N_2 was treated with diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, 1.5 eq.) and stirred at 50 °C for 6 hours, then at 25 °C for 14 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to provide an amber oil. The residue was dissolved in a minimal amount of CH_2Cl_2 (5 mL) and diluted with Et_2O (100 mL) while vigorously stirring for 4 hours, during which time a white solid precipitated. The white solid was collected (Et_2O wash) to give the desired title compound (1.11 g, 90%) as a white amorphous solid: mp 136.5-142 °C (decomposed); ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), 2.18 (m, 1H), 2.22 (m, 2H), 2.27 (s, 3H), 2.78 (s, 6H), 3.07 (ABq, $J = 15.1$ Hz, $J = 39.5$ Hz, 2H), 3.49 (br s, 6H), 3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), 4.09 (d, $J = 7.3$ Hz, 1H), 5.46 (s, 1H), 5.96 (d, $J = 2.4$ Hz, 1H), 6.49 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.87 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $C_{35}H_{54}N_3O_4S$: 612.3835. Found: 612.3832.

35

186

Example 1408

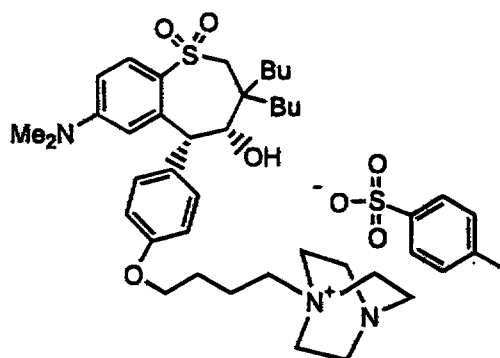
5 (4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-
azoniabicyclo[2.2.2]octanemethanesulfonate (salt)

10 Step 1: Preparation of butyl mesylate intermediate

A mixture of 1.00 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 mmol) of potassium carbonate in 20 mL of acetone was stirred at reflux overnight. The mixture was concentrated in vacuo and the crude was dissolved in 30 mL of ethyl acetate. The insoluble solid was filtered off and the filtrate was concentrated in vacuo. The resulting white foam was chromatographed through silica gel column, and eluted with 30% ethyl acetate/hexane to give 1.02 g (77%) of butyl mesylate intermediate as a white solid: ^1H NMR (CDCl_3) δ 0.90 (m, 6H), 1.20-1.67 (m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), 3.04 (s, 3H), 3.08 (ABq, 2H), 4.05 (t, J = 5.55 Hz, 2H), 4.11 (d, J = 6.90 Hz, 1H), 4.35 (t, J = 6.0 Hz, 2H), 5.49 (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H).

Step 2: Preparation of ester intermediate

A solution of 520 mg (0.85 mmol) of butyl mesylate
 intermediate (obtained from Step 1) and 191 mg (1.71
 mmol) of DABCO in 10 mL of acetonitrile was stirred at
 80 °C for 4 hours. The reaction mixture was
 concentrated in vacuo to yield a white foam. The foam
 was crushed and washed with ether. The solid was
 filtered off and dried in vacuo to give 540 mg (88%) of
 the desired title compound which was recrystallized
 from methylene chloride and acetone as a white solid:
 mp 248-251 °C; ¹H NMR (CDCl₃) δ 0.91 (m, 6H), 1.14-1.47
 (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H),
 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, J
 = 7.1 Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s,
 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 8.9 Hz,
 2.6 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.1
 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H).

Example 1409

(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-
 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
 benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-
 azoniabicyclo[2.2.2]octane-4-methylbenzenesulfonate
 (salt)

Step 1: Preparation of propyl tosylate intermediate

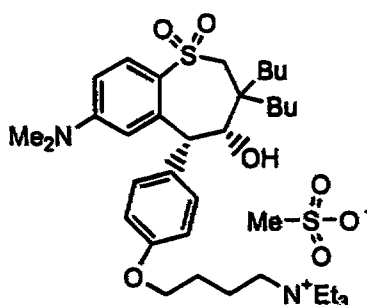
A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N₂ was treated with powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4-butanediol di-p-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting solution was stirred at 65 °C for 21 hours. The cream-colored slurry was cooled to 25 °C and filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL). The extract was dried (MgSO₄) and concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.10-1.44 (br m, 10H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43 (s, 3H), 2.80 (s, 6H), 3.03 (ABq, J = 15.1 Hz, J = 46.3 Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), 5.96 (s, 1H), 6.46 (dd, J = 8.9, 1.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.83 (m, 1H).

Step 2: Preparation of quaternary salt

A solution of propyl tosylate intermediate (5.8 g, 8.5 mmol, obtained from Step 1) in acetonitrile (100 mL) at 25 °C under N₂ was treated with diazabicyclo[2.2.2]octane (DABCO, 1.1 g, 10.1 mmol, 1.2 eq.) and stirred at 45 °C for 6 hours. The pale yellow solution was cooled to 25 °C and concentrated in vacuo to provide an off-white solid. The residue was dissolved in a minimal amount of CH₂Cl₂ (5 mL) and diluted with Et₂O (100 mL) while vigorously stirring

189

for 3 hours, during which time a white solid precipitated. The white solid was collected and recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp
 223-231 °C (decomposed); ¹H NMR (CDCl₃) δ 0.86 (m, 6H),
 1.09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m,
 1H), 2.25 (s, 3H), 2.75 (s, 6H), 3.03 (ABq, *J* = 15.1
 Hz, *J* = 30.0 Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H),
 3.89 (m, 2H), 4.07 (d, *J* = 7.5 Hz, 1H), 5.39 (s, 2H),
 5.97 (d, *J* = 1.6 Hz, 1H), 6.44 (dd, *J* = 8.9, 2.0 Hz,
 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.1 Hz,
 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.1 Hz,
 2H), 7.80 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for
 C₃₆H₅₆N₃O₄S: 626.3992. Found: 626.3994. Anal. Calc'd for
 C₄₃H₆₃N₃O₇S₂: C, 64.71; H, 7.96; N, 5.27. Found: C, 64.36;
 H, 8.10; N, 5.32.

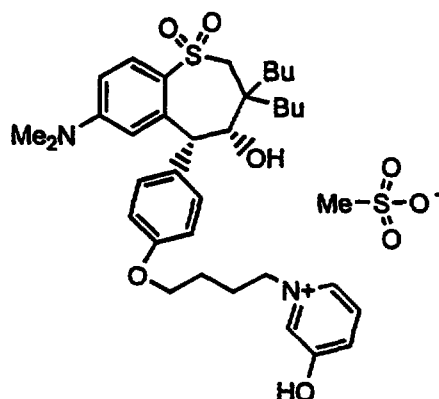
Example 1410

(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]-N,N,N-triethyl-1-butanaminium

A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile was heated at 50 °C for 2 days. The solvent was evaporated and the residue was triturated with ether

190

and ethyl acetate to afford 500 mg (43%) of product as a semi-solid. ^1H NMR (CDCl_3) δ 0.8 (m, 6 H), 1-1.6 (m, 24 H), 2.1 (m, 1 H), 2.6 (s, 3 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m, 8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS m/e 615.

Example 1411

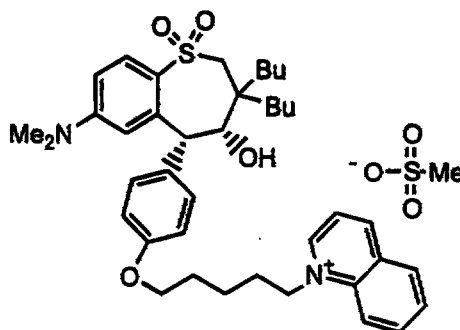
(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium, methanesulfonate (salt)

A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL of dimethylformamide was heated at 70 °C for 20 hours. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 990 mg (86%) of product as a semi-solid: ^1H NMR (CDCl_3) δ 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2 H), 2-2.4 (m, 3 H), 2.9 (s, 6 H), 3.1 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J

191

= 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.7 (m, 1 H), 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (s, 1 H). MS m/e 609.

5

Example 1412

10 (4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]pentyl]quinolinium,
methanesulfonate (salt)

Step 1: Preparation of pentyl mesylate intermediate

15

To a stirred solution of 231 mg (5.79 mmol, 60% disp.) of NaH in 22 mL of DMF was added 2.05g (4.45 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the mixture was added 18.02 g (55.63 mmol) of 1,5-diiodopentane and the solution was stirred overnight at ambient temperature. DMF was removed by high vacuum and the residue was extracted with ethyl acetate and washed with brine.

20

25

The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pentyl mesylate intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s,

192

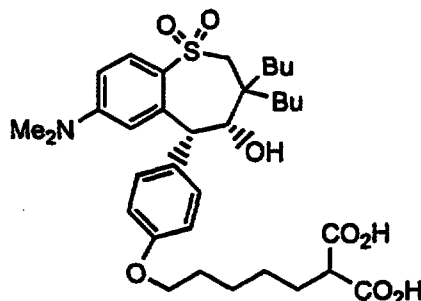
1H), 5.42 (s, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of quaternary salt

To 1.0g (1.53 mmol) of the pentyl mesylate intermediate (obtained from Step 1) was added 3.94 g (30.5 mmol) of quinoline and 30 mL of acetonitrile. The solution was heated at 45 °C under N₂ for 10 days.

The concentrated residue was purified by reverse phase C18 column chromatography. The obtained material was exchanged to its mesylate anion by ion exchange chromatography to give the desired title compound as a solid: mp 136 °C; ¹H NMR (CDCl₃) δ 0.95 (q, 6H), 1.05-2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.28 (t, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), 7.9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 10.2 (d, 1H). HRMS. Calc'd for C₄₀H₅₃N₂O₄S: 657.3726. Found: 657.3736. Anal. Calc'd for C₄₀H₅₃N₂O₄S·CH₃O₃S: C, 65.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, 7.42; N, 3.56; S, 8.41.

Example 1413



(4S-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]propanedioic acid

Step 1: Preparation of pentyl bromide intermediate

To a stirred solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was added 6.0 g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and the mixture was stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of dibenzyl ester intermediate

To the mixture of 59 mg (1.476 mmol, 60% disp) of NaH in 27 mL of THF and 9 mL of DMF at 0 °C was added 0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min. To the solution was added 0.5987 g (0.984 mmol) of the pentyl bromide intermediate, and the mixture was stirred at 80 °C overnight. Solvent was removed in vacuo, and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the dibenzyl ester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, 2H), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s,

194

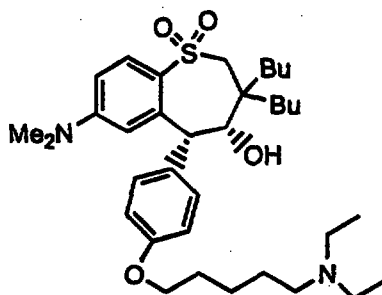
1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

Step 3: Preparation of diacid

5 A suspension of 0.539 g (0.664 mmol) of the dibenzyl ester intermediate (obtained from Step 2) and 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate
10 was concentrated to give the desired title compound as a solid: mp 118 °C; ¹H NMR (CDCl₃) δ 0.9 (d, 6H), 1.05-2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 3.95 (s, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H).
15 HRMS. Calc'd for C₃₄H₄₉NO₈S: 632.3257. Found: 632.3264. Anal. Calc'd for C₃₄H₄₉NO₈S: C, 64.63; H, 7.82; N, 2.22; S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93.

Example 1414

20



(4R-cis)-3,3-Dibutyl-5-[4-[[5-(diethylamino)pentyl]oxy]phenyl]-7-(dimethylamino)-
25 2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl iodide intermediate

To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (3
30 g, 6.53 mmol, obtained from Example 1402, Step 10) in

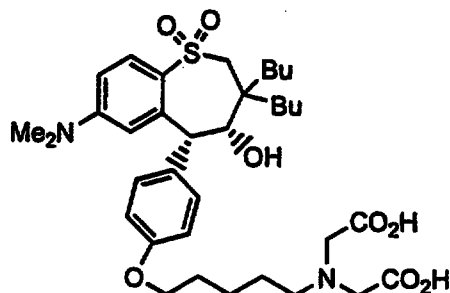
195

100 mL of dimethylformamide was added 198 mg (7.83 mmol) of 95% sodium hydride. The mixture was stirred 15 minutes at room temperature and diiodopentane was added. After one hour at room temperature the mixture was diluted in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 mmol) of the pentyl iodide intermediate: ¹H NMR (CDCl₃) δ 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, 4 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.9 (d, J = 7 Hz, 1 H).

Step 2: Preparation of amine

A solution of 550 mg (0.76 mmol) of the pentyl iodide intermediate (obtained from Step 1) and 279 mg (3.81 mmol) of diethylamine in 3 mL of acetonitrile was stirred at 100 °C overnight. The mixture was concentrated in vacuo to yield a yellowish brown foam. The foam was dissolved in 10 mL of ethyl acetate and washed with 50 mL of saturated sodium carbonate solution twice. The ethyl acetate layer was dried over magnesium sulfate and concentrated to yield 390 mg (85%) of the desired title compound as a yellow foamy solid: ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.20-1.47 (m, 12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m, 1H), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), 5.48 (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 9.0 Hz, 1H).

196

Example 1415

5

(4R-cis)-N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

10

Step 1: Preparation of diester intermediate

15

A mixture of 8.6 g (14.1 mmol) of pentyl bromide intermediate (obtained from Example 1413, Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 mmol) of anhydrous Na_2CO_3 was stirred at 160 °C for 3 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The volatiles was removed in vacuo to give 9.6g (95%) of the diester intermediate. ^1H NMR spectrum was consistent with the structure; MS (M+H) m/e 717.

20

Step 2: Preparation of diacid

25

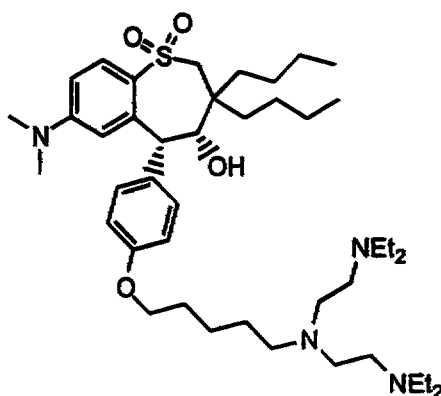
30

The mixture of the diester intermediate (obtained from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75 mL) and water (50 mL) was stirred at 40 °C for 18 hours. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane, filtered to give 8.9g (93%) of the desired title compound as a solid: mp 148-162 °C; ^1H NMR (CD_3OD) δ 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 (t, 1H), 2.8 (s, 6H), 3.15 (ABq, 2H), 3.75 (m, 1H), 4.1 (m, 6H), 5.3 (s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0 (d,

197

2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) *m/e* 661. Anal. Calc'd for $[C_{35}H_{52}N_2O_6S + 1.5H_2O]$: C, 61.11; H, 8.06; N, 4.07; S, 4.66. Found: C, 61.00; H, 7.72; N, 3.89; S, 4.47.

5 Example 1416



(4R-cis)-5-[4-[[5-[bis(2-
(Diethylamino)ethyl]amino]pentyl]oxy]phenyl]-3,3-
10 dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-
benzothiepin-4-ol 1,1-dioxide

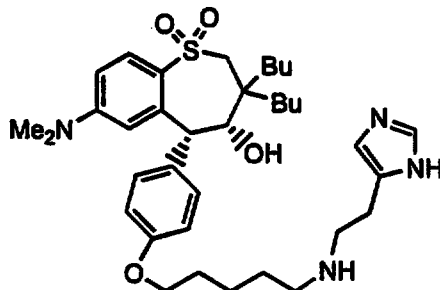
A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) in N,N,N',N'-tetraethyl diethylenetriamine was heated to
15 80 °C for 4 hours. The mixture was dissolved in ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by reverse phase chromatography. The fractions containing
20 the product were concentrated in vacuo, dissolved in ethyl acetate and washed with saturated $NaHCO_3$. The residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick oil. ^1H NMR ($CDCl_3$) δ 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (s, 6 H),
25 2.9 (d, *J* = 15 Hz, 1 H), 3.1 (d, *J* = 15 Hz, 1 H), 3.9 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.4 (s, 1 H), 6.0 (s, 1 H), 6.4 (m, 1 H), 6.9 (d, *J* = 9 Hz, 2 H), 7.4

198

(d, $J = 9$ Hz, 2 H), 7.8 (d, $J = 7$ Hz, 1 H). MS (M+H) m/e 743.

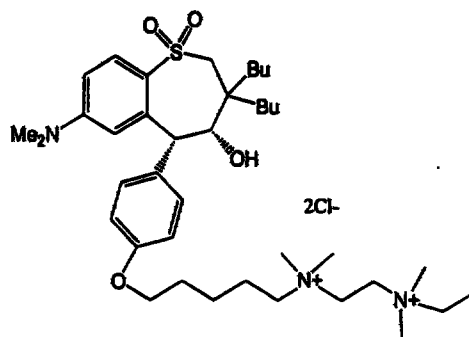
Example 1417

5



(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-[[2-(1H-imidazol-4-yl)ethyl]amino]pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50 °C for 17 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO₃. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with ether to afford 588 mg (60%) of the desired title compound as a semi-solid: ¹H NMR (CDCl₃) δ 0.9 (m, 6 H), 1-1.7 (m, 14 H), 1.9 (m, 3 H), 2.0 (m, 2 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (m, 3 H), 3.2 (m, 2 H), 4.0 (m, 2 H), 4.1 (m, 3 H), 5.5 (s, 1 H), 6.0 (s, 1 H), 6.5 (m, 1 H), 6.8 (s, 1 H), 6.9 (d, $J = 9$ Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, $J = 8$ Hz, 1 H). MS (M+H) m/e 639.

Example 1418

- 5 **(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-**
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]pentyl]-N'-ethyl-N,N,N',N'-
tetramethyl-1,2-ethanediaminium dichloride
- 10 Step 1: Preparation of pentyl bromide intermediate
A mixture of 5-(4'-hydroxyphenyl)-7-
(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
(1.680g, 3.66 mmol, obtained from Example 1402, Step
10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of
15 DMF was stirred in a dry 100 mL round-bottom flask
under N₂. To this solution was added 1,5-
dibromopentane (6.0 mL/44.0 mmol), and the resulting
mixture was stirred for 18 hours. The reaction was
diluted with brine (100 mL) and H₂O (20 mL), and the
20 mixture was extracted with EtOAc (3x50 mL). Organic
layers were combined, dried (MgSO₄), filtered and
concentrated in vacuo. Purification by filtration
through silica gel eluting with 20% EtOAc/hexane and
evaporation in vacuo gave pentyl bromide intermediate
25 as a white foamy solid (1.783g, 80%): ¹H NMR (CDCl₃) δ
0.84-0.95 (m, 6H), 1.02-1.56 (m, 10H), 1.58-1.70 (m,
3H), 1.78-2.03 (m, 4H), 2.15-2.24 (m, 1H), 2.77 (s,
1H), 2.80 (s, 6H), 3.05 (ABq, 2H), 3.42 (t, 2H), 3.98
(t, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50
30 (dd, 1H), 6.91 (d, 2H), 7.40 (d, 2H), 7.88 (d, 1H).

Step 2: Preparation of mono-quaternary salt

The mixture of pentyl bromide intermediate (0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'-tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL of acetonitrile was stirred at 40 °C for 12 hours, and the reaction mixture was concentrated in vacuo to give an off-white foamy solid (1.052g). The crude product was dissolved in acetonitrile (1.5 mL) and triturated with ethyl ether. The solvent was decanted to yield a sticky solid. This trituration method was repeated twice, and the resulting sticky solid was concentrated in vacuo to give the mono-quaternary salt as an off-white foamy solid (0.951g, 94%): ¹H NMR (CDCl₃) δ 0.81 (t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03-2.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H), 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60-3.75 (m, 4H), 3.90 (t, 2H), 4.01 (s, 1H), 5.37 (s, 1H), 5.92 (s, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d, 2H), 7.77 (d, 1H).

Step 3: Preparation of di-quaternary salt

The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N₂, sealed, equipped with magnetic stirrer, and heated to 50 °C. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to 0 °C overnight, the resulting solid was filtered, washed with ethyl ether and concentrated in vacuo to yield the di-quaternary salt as an off-white solid (1.046g, 92%): ¹H NMR (CD₃OD) δ 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16

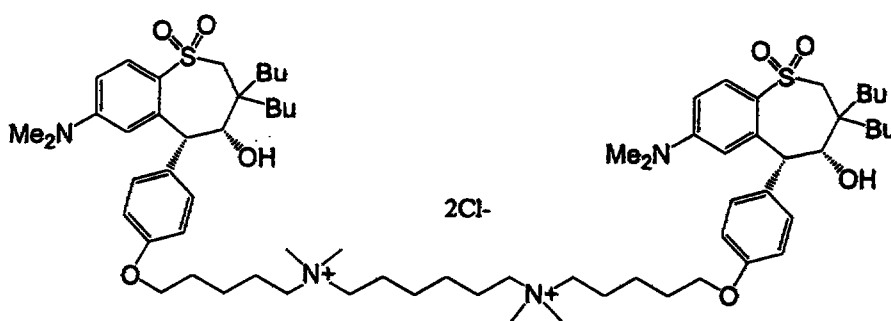
201

(t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H),
 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-
 3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H),
 6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d,
 1H).

Step 4: Preparation of quaternary di-chloride salt

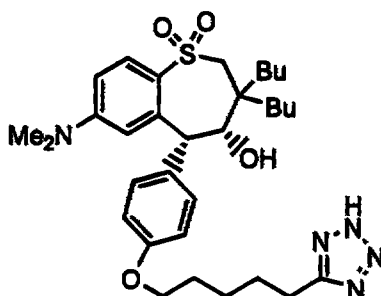
The iodobromosalt (obtained from Step 3) was
 converted to its corresponding dichloride salt using
 Biorad AG 2X8 resin and eluting with 70%
 H₂O/acetonitrile to give the desired title compound as
 a white foamy solid (0.746g, 84%): mp 193.0-197.0 °C;
¹H NMR (CD₃OD) δ 0.59 (t, J = 6.0 Hz, 6H), 0.70-1.12 (m,
 9H), 1.16 (t, J = 6.6 Hz, 3H), 1.24-1.90 (m, 9H), 2.50
 (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H),
 3.24-3.50 (m, 4H), 3.68 (s, 2H), 3.81 (s, 2H), 4.16 (s,
 4H), 5.02 (s, 1H), 5.72 (s, 1H), 6.19 (d, J = 8.4 Hz,
 1H), 6.61 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz,
 2H), 7.46 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for
 C₃₉H₆₇N₃O₄SCl: 708.4541. Found: 708.4598.

Example 1419



[4R-[4a,5a(4R*,5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7-
 (dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-
 dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N,N,N',N'-
 tetramethyl-1,6-hexanediaminium dichloride

The pentyl bromide intermediate (1.002g, 1.64 mmol, obtained from Example 1418, Step 1) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 mmol) in 5 mL of acetonitrile were placed in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N₂, sealed, equipped with magnetic stirrer and heated to 50 °C. After 15 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give an off-white foamy solid (1.141g). The solid was dissolved in acetonitrile and precipitated with ethyl ether. After cooling to 0 °C, the solvent was decanted to yield a sticky off-white solid. This trituration method was repeated, and the resulting sticky solid was concentrated in vacuo to give the desired dibromide salt as an off-white foamy solid (0.843g, quantitative): ¹H NMR (CDCl₃) δ 0.85 (m, 12H), 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, J = 12.3 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 7.8 Hz, 4H), 7.38 (d, J = 7.8 Hz, 4H), 7.83 (d, J = 8.7 Hz, 2H). The dibromide salt was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H₂O/CH₃CN to give the desired title compound as a white foamy solid (0.676g, 86%): mp 178.0-182.0 °C; ¹H NMR (CDCl₃) δ 0.80-0.90 (m, 12H), 1.01-1.70 (m, 30H), 1.75-2.06 (m, 12H), 2.16 (t, J = 12.9 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.33 (s, 12H), 3.49 (br s, 6H), 3.70 (br s, 4H), 3.96 (t, J = 5.4 Hz, 4H), 4.08 (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H), 6.49 (d, J = 9.0 Hz, 1H), 6.50 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 4H), 7.38 (d, J = 8.1 Hz, 4H), 7.84 (d, J = 8.7 Hz, 2H). HRMS. Calc'd for C₃₆H₅₆N₂O₄S: 614.4118. Found: 614.4148.

Example 1420

5 (4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-(1H-tetrazol-5-yl)pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl bromide intermediate

10 To a stirred suspension of 1.01 g (25.4 mmol, 60% oil dispersion) of sodium hydride in 150 mL of DMF was added 9.0g (19.5 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in portions.

15 After 30 minutes the reaction was cooled in a water bath (15 °C) and 4.48 g (195 mmol) of 1,5-dibromopropane was added. The reaction was stirred at ambient temperature for 1.5 hours and quenched with 50 mL of saturated NH₄Cl. The reaction was diluted with

20 ethyl acetate, washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 25% ethyl acetate/hexanes afforded 10.17 g (85%) of the pentyl bromide intermediate as a colorless

25 foam: mp 65-70 °C; ¹H NMR (CDCl₃) δ 0.84-0.98 (m, 6H), 1.04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, J = 6.8 Hz, 2H), 1.94 (p, J = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), 2.82 (s, 6H), 3.06 (AB_q, J_{AB} = 15.2, 45.3 Hz, 2H), 3.44 (t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.68 (dd,

30

204

$J = 2.5, 8.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 8.7$ Hz, 1H).

Step 2: Preparation of pentyl nitrile intermediate

5 To a stirred solution of 378 mg (0.621 mmol) of the pentyl bromide intermediate (obtained from Step 1) in 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium cyanide. The reaction was stirred at ambient temperature for 16 hours. The reaction was
10 concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to afford 278 mg (93% RPHPLC purity, ca. 75%) of the pentyl nitrile
15 intermediate as a colorless foam: ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.02-1.21 (m, 1H), 1.21-1.52 (m, 19H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, $J = 6.9$ Hz, 2H), 2.83 (s, 6H), 3.08 (AB_q, 15.0, 47.5 Hz, 2H), 4.01 (t, $J = 6.2$ Hz, 2H), 4.1 (s, 1H), 5.49 (s,
20 1H), 6.07 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 2.4, 8.7$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.7$ Hz, 1H). MS (ES, $\text{M}+\text{H}$) m/e 555.

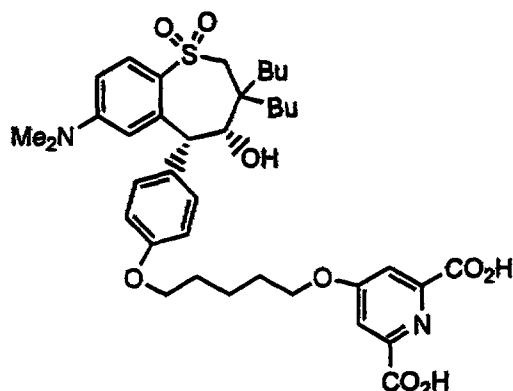
Step 3: Preparation of tetrazole

25 A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80 °C for 60 hours. The reaction was concentrated under a nitrogen stream.
30 Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; ^1H NMR (CDCl_3) δ 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m,
35 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 3.02-3.22 (m, 4H), 3.92-4.06 (m, 2H), 4.16 (s, 1H), 5.47 (s, 1H),

205

6.28 (d, $J = 2.4$ Hz, 1H), 6.74 (dd, $J = 2.7, 8.8$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.98 (d, $J = 8.7$ Hz, 1H). HRMS Calc'd for $C_{32}H_{48}N_5O_4S$: 598.3427. Found: 598.3443.

5

Example 1421

10 (4R-cis)-4-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]oxy]-2,6-pyridinecarboxylic acid

15 Step 1: Preparation of pentyl bromide intermediate

To a solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was add 6.0g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over $MgSO_4$, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ^1H NMR ($CDCl_3$) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4

206

(t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

5 Step 2: Esterification of chelidamic acid

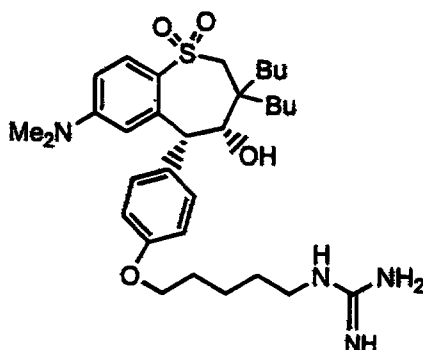
 A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under N₂. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% NaHCO₃, 5% acetic acid, H₂O, and brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: ¹H NMR (CDCl₃) δ 5.4 (s, 4H), 7.4 (m, 12H).

20 Step 3: Preparation of pyridinyl benzyl ester intermediate

 A solution of 79 mg (1.972 mmol, 60% disp) of NaH and 0.716g (1.972 mmol) of dibenzyl chelidamic ester (obtained from Step 2) in 17.5 mL of DMF was stirred at ambient temperature for 1 hour. To the solution was added 1.0 g (1.643 mmol) of the pentyl bromide intermediate and the mixture was stirred under N₂ overnight at 40 °C. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pyridinyl dibenzyl ester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.0 (t, 2H), 4.1 (s, 1H), 5.4 (s, 4H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H), 7.78 (s, 2H), 7.9 (d, 1H).

Step 4: Preparation of pyridinyl diacid

A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 143 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRMS. Calc'd for C₃₈H₅₀N₂O₉S: 711.3315. Found: 711.3322. Anal. Calc'd for C₃₈H₅₀N₂O₉S: C, 64.20; H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

Example 1422

(4R-cis) - [5 - [4 - [3,3-Dibutyl-7 - (dimethylamino) - 2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]guanidine

Step 1: Preparation of pentyl azide intermediate

To a stirred solution of 200 mg (0.328 mmol) of the pentyl bromide intermediate (obtained from Example 1420, Step 1) in 0.75 mL of DMSO was added 32 mg (0.493

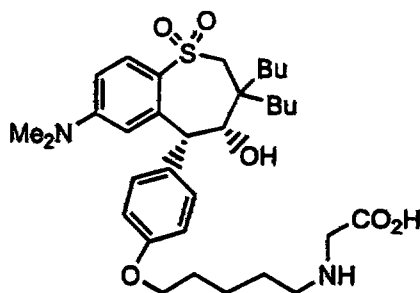
mmol) of sodium azide and a catalytic amount of sodium iodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to afford 155 mg (92% RPHPLC purity, about 76% yield) of the pentyl azide intermediate as a colorless foam. Sample was used without further purification: mp 45-50 °C; ^1H NMR (CDCl_3) δ 0.83-0.93 (m, 6H), 1.03-1.48 (m, 10H), 1.54-1.74 (m, 5H), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), 2.81 (s, 6H), 3.06 (AB_q , $J_{\text{AB}} = 15.0, 48.0$ Hz, 2H), 3.31 (t, $J = 6.3$ Hz, 2H), 3.98 (t, $J = 6.3$ Hz, 2H), 4.09 (s, 1H), 5.47 (s, 1H), 6.10 (d, $J = 1.8$ Hz, 1H), 6.63 (dd, $J = 2.7, 9.0$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H). MS (FAB, $\text{M}+\text{H}$) m/e 571.

20 Step 2: Preparation of pentyl amine intermediate

To a solution of 0.67 g (1.17 mmol) of the azide intermediate (obtained from Step 1) in 75 mL of ethanol was added 0.10 g of 10% palladium on carbon and the mixture shaken under 49 psi of hydrogen at ambient temperature for 3.5 hours. The reaction was filtered through celite and concentrated in vacuo to give 0.62 g (86% RPHPLC purity, ca. 84%) of pentyl amine intermediate as an off-white foam. The sample was used without further purification: mp 70-85 °C; ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-3.20 (m, 4H), 3.99 (t, $J = 6.0$ Hz, 2H), 4.04-4.14 (m, 1H), 5.49 (s, 1H), 6.00 (d, $J = 1.5$ Hz, 1H), 6.51 (d, $J = 9.0$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.90 (d, $J = 8.7$ Hz, 1H). MS (ES, $\text{M}+\text{H}$) m/e 545.

Step 3: Preparation of guanidine

To a stirred solution of 258 mg (0.474 mmol) of pentyl amino intermediate (obtained from Step 2) and 81 mg (0.551 mmol) of 1H-pyrazole-1-carboxamide hydrochloride in 1.5 mL of DMF was added 71 mg (0.551 mmol) of diisopropylethylamine. The reaction was stirred at ambient temperature for 16 hours. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 120 mg (43%) of the desired title compound as colorless foamy solid: mp 67.0-72.5 °C; ¹H NMR (CDCl₃) δ 0.89-0.93 (m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07-2.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m, 4H), 3.98 (br s, 2H), 4.12 (s, 1H), 5.46 (s, 1H), 6.01 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 2.1, 8.0 Hz, 1H), 6.92 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.89 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for C₃₂H₅₀N₄O₄S: 586.3552. Found (M+H): 587.3620.

Example 1423

(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

Step 1: Preparation of pentyl azide intermediate

To a solution of pentyl bromide intermediate (400 mg, 0.657 mmol, obtained from Example 1420, Step 1) in

210

dimethyl sulfoxide (20 mL) was added sodium azide (47 mg, 0.723 mmol, 1.1 eq), and the resulting clear solution was stirred at 23 °C for 16h. The reaction solution was diluted with 100 mL ethyl acetate, then washed with water (2x 100 mL) and brine (1x 100 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give 390 mg (quantitative) of pentyl azide intermediate as a yellow oil: ¹H NMR (CDCl₃) δ 0.82-0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.82 (s, 6H), 3.08 (q, 2H), 3.44 (t, J = 7.7 Hz, 2H), 3.99 (t, J = 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d, J = 7.58 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 7.14 (ABq, 4H), 7.91 (d, J = 7.8 Hz, 1H).

Step 2: Preparation of amino ester intermediate

A suspension of pentyl azide intermediate (390 mg, 0.684 mmol, obtained from Step 1) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 4.5 hours. The ethanolic suspension was filtered through celite and concentrated in vacuo to give a yellow oil.

The oil was immediately diluted with acetonitrile (15 mL), followed by the addition of triethylamine (0.156 g, 1.54 mmol, 2.25 eq) and bromo acetic acid benzyl ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was stirred at 23 °C for 48 hours. The reaction was concentrated in vacuo, and the residue was dissolved in ethyl acetate (20 mL) and washed with water (2x 20 mL) and brine (1x 20 mL). The organic layer was dried (MgSO₄) and dried in vacuo to give 420 mg (89%) of the amino ester intermediate as a yellow oil: ¹H NMR

(CDCl₃) δ 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.75 (d, J = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s,

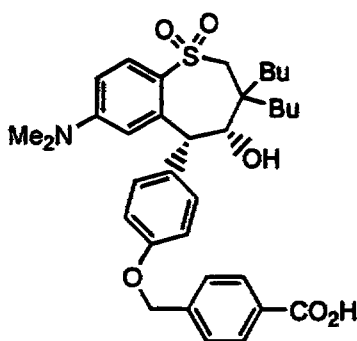
211

1H), 5.147 (s, 1H), 5.46 (s, 1H), 5.98 (d, $J = 7.58$, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, $J = 8.0$ Hz, 1H). MS (ES) m/e 693.

5 Step 3: Preparation of acid

A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.330g of a yellow semi-solid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: ^1H NMR (CDCl_3) δ 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6.40-6.49 (m, 1H), 7.14 (ABq, 4H), 7.85 (t, $J = 7.93$ Hz, 1H). MS (ES) m/e 603.

Example 1424



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]benzoic acid

Step 1: Preparation of benzoate intermediate

To a solution of 0.53 g (1.15 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-

5 thiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 10 mL dimethylformamide was added 35 mg (1.39 mmol) of 95% sodium hydride and stirred for 10 minutes.

To the reaction mixture was added 525 mg (2.29 mmol) methyl 4-(bromomethyl)benzoate and stirred for 16

10 hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.51 g (73%) of the benzoate intermediate: ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.14-

15 1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), 2.80 (s, 6H), 2.99 (d, $J = 15.1$ Hz, 1H), 3.15 (t, $J = 15.1$ Hz, 1H), 3.92 (s, 3H), 4.09-4.15 (m, 1H), 5.17 (s, 2H), 5.49 (s, 1H), 5.94 (d, $J = 2.2$ Hz, 1H), 6.50 (dd, $J = 8.9, 2.6$ Hz, 1H), 7.00 (d, $J = 8.7$ Hz, 2H), 7.43

20 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.93 (d, $J = 8.9$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 2H).

Step 2: Preparation of acid

A solution of 0.51 g (0.84 mmol) of the benzoate

25 intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of $\text{KOSi}(\text{CH}_3)_3$ (Aldrich) in 16 mL THF was stirred for 3.5 hours. The THF was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford

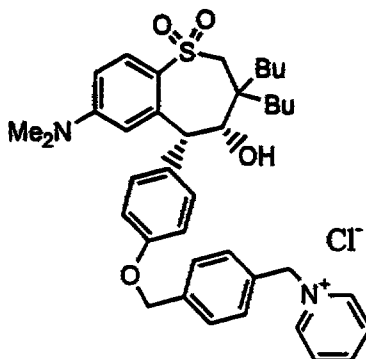
30 0.30 g (60%) of the desired title compound as a white solid: mp 156 - 159 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.84 (s, 6H), 3.02 (d, $J = 15.1$ Hz, 1H), 3.17 (d, $J = 15.1$ Hz, 1H), 4.14 (s, 1H), 5.20 (s, 2H), 5.50

35 (s, 1H), 6.16 (s, 1H), 6.71 (d, $J = 9.1$ Hz, 2H), 7.03 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.57 (d,

213

$J = 8.3$ Hz, 2H), 7.95 (d, $J = 8.9$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 2H). HRMS. Calc'd for $C_{34}H_{44}NO_6S$: 594.2889.
Found: 594.2913.

5 Example 1425



10 (4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-
pyridinium chloride

15 Step 1: Preparation of chlorobenzyl intermediate

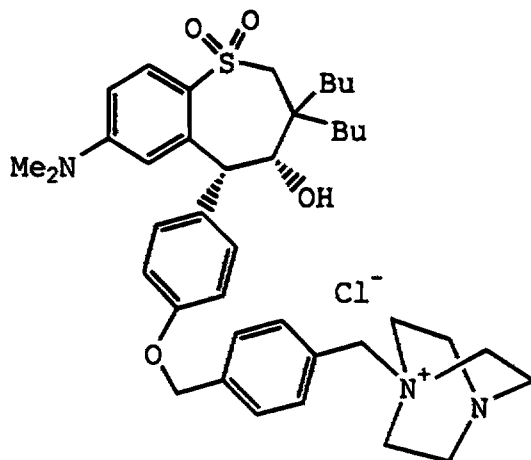
15 A solution of 5-(4'-hydroxyphenyl)-7-(
dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0
g, 10.9 mmol, obtained from Example 1402, Step 10) in
acetone (100 mL) at 25 °C under N_2 was treated with
powdered K_2CO_3 (2.3 g, 16.3 mmol, 1.5 eq.) and α,α' -
20 dichloro-p-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the
resulting solution was stirred at 65 °C for 48 hours.
The reaction mixture was cooled to 25 °C and
concentrated to 1/5 of original volume. The residue
was dissolved in EtOAc (150 mL) and washed with water
25 (2 x 150 mL). The aqueous layer was extracted with
EtOAc (2 x 150 mL) and the combined organic extracts
were washed with saturated aqueous NaCl (2 x 150 mL).
The combined extracts were dried ($MgSO_4$) and
concentrated in vacuo to provide a yellow oil.

214

Purification by flash chromatography (5.4 x 45 cm silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl intermediate (4.7 g, 72%) as a white foam: ^1H NMR (CDCl_3) δ 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H), 1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABq, J = 15.1 Hz, J = 50.0 Hz, 2H), 4.11 (d, J = 8.1 Hz, 1H), 4.60 (s, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.96 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

A solution of the chlorobenzyl intermediate (1.0 g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 mL) at 25 °C under N_2 was treated with pyridine (5 mL) and stirred at 35 °C for 36 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to give the desired title compound (1.08 g, 96%) as a yellow solid: mp 154-156 °C; ^1H NMR (CDCl_3) δ 0.83 (m, 6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), 2.71 (s, 6H), 3.02 (ABq, J = 15.1 Hz, J = 28.4 Hz, 2H), 4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, J = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, J = 7.7 Hz, 4H), 7.73 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.93 (t, J = 6.8 Hz, 1H), 8.34 (t, J = 7.7 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, J = 5.8 Hz, 2H); HRMS. Calc'd for $\text{C}_{29}\text{H}_{49}\text{N}_2\text{O}_4\text{S}$: 641.3413. Found: 641.3425.

Example 1426

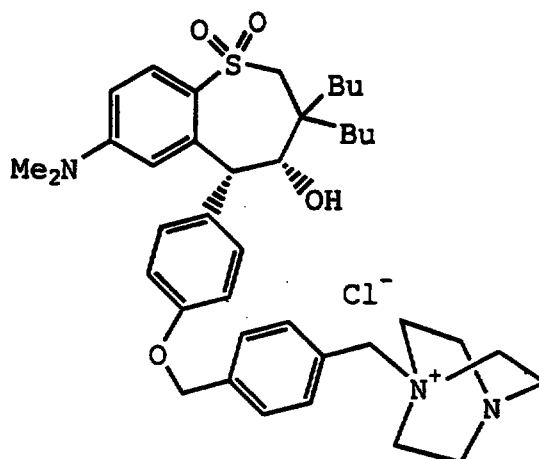
(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-
1-azoniabicyclo[2.2.2]octane chloride

Under N₂, a solution of 8.7 g (14.5 mmol) of the chlorobenzyl intermediate (obtained from a procedure similar to the one outlined in Example 1425, Step 1) in 60 mL of acetonitrile was added dropwise over a 30 min period to a solution of 2.9 g (26.2 mmol) of diazabicyclo[2.2.2]octane (DABCO) in 40 mL of acetonitrile at 35°C; during the addition, a colorless precipitate was formed. The slurry was stirred at 35°C for an additional 2 h. The product was collected and washed with 1 L of acetonitrile to give 9.6 g (93%) the title compound as a colorless crystalline solid: mp 223-230°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m,

216

1H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 2H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.87 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $C_{40}H_{56}N_3O_4S$: 674.3992. Found: 674.4005.

5

Example 1426a

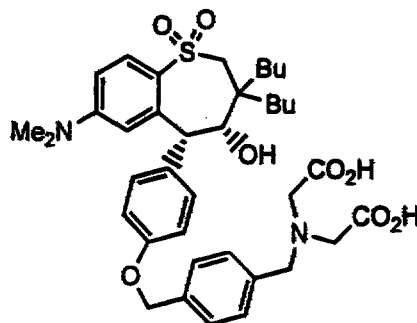
10 (4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

15 A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N_2 was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and stirred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid
20 was collected, washed with CH_3CN and recrystallized from CH_3OH/Et_2O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, $J =$
25 15.1 Hz, $J = 43.3$ Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, $J = 7.7$ Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, $J = 8.9$ Hz, 1H),

217

6.99 (d, $J = 8.0$ Hz, 2H), 7.26 (m, 1H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 2H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.87 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $C_{46}H_{56}N_3O_4S$: 674.3992. Found: 674.4005.

5

Example 1427

10 4R-cis)-N-(Carboxymethyl)-N-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]glycine

15 Step 1: Preparation of chlorobenzyl intermediate

To a stirred solution of 144 mg (3.59 mmol, 60% disp) of NaH in 29 mL of DMF was added 1.5 g (3.26 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 45 min. To the solution was added 7.13 g (40.75 mmol) of dichloro p-xylene, and the mixture was stirred overnight. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the chlorobenzyl intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.1

20

25

218

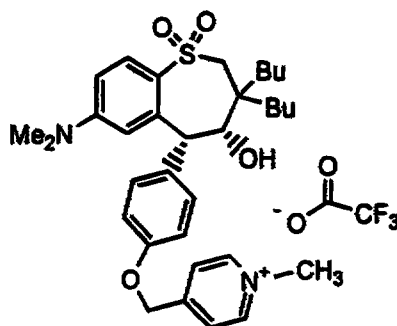
(d, 1H), 4.6 (s, 2H), 5.1 (s, 2H), 5.5 (s, 1H), 6.0 (s, 1H), 6.6 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.8 (d, 1H).

Step 2: Preparation of amino diester

5 A mixture of 1.03 g (1.72 mmol) of chlorobenzyl intermediate (obtained from Step 1), 1.63 g (8.6 mmol) of diethyl amino diacetate, and 0.72 g (8.6 mmol) of NaHCO₃ in 30 mL of DMF was stirred at 100 °C for 6 hours. DMF was removed in vacuo and the residue was
10 extracted with ether and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give amino diester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H),
15 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

Step 3: Preparation of amino diacid

20 A solution of 0.863 g (1.15 mmol) of dibenzyl ester (obtained from Step 2) and 0.232 g (5.52 mmol) of LiOH in 30 mL of THF and 30 mL of water was stirred at 40 °C under N₂ for 4 hours. The reaction mixture was diluted with ether and washed with 1% HCl. The
25 aqueous layer was extracted twice with ether, and the combined extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo to give the desired title compound as a solid: mp 175 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. Calc'd for C₃₈H₅₀N₂O₈S: 695.3366. Found: 695.3359. Anal. Calc'd for C₃₈H₅₀N₂O₈S: C, 65.68; H, 7.25; N, 4.03; S,
30 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62.

Example 1428

- 5 (4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium salt with trifluoroacetic acid (1:1)
- 10 Step 1: Preparation of picolyl intermediate
- To a stirred solution of 12.0 g (26.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% oil dispersion, 35 mmol) of sodium hydride and the reaction stirred at ambient temperature for one hour.
- 15 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride was treated with cold saturated NaHCO₃ solution and extracted with diethyl ether. The ethereal extracts were washed with brine, dried over MgSO₄, and filtered.
- 20 The reaction was cooled in an ice bath and the solution of 4-picolyl chloride in diethyl ether was added. The reaction was stirred at ambient temperature for 17 hours. The reaction was quenched with 25 mL of saturated NH₄Cl, diluted with 600 mL ethyl acetate washed with 4X250 mL water, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-prep 500) using 60% ethyl acetate/hexanes afforded 11.05 g (77%) of the picolinyll intermediate as a colorless solid: mp 95-98
- 25
- 30

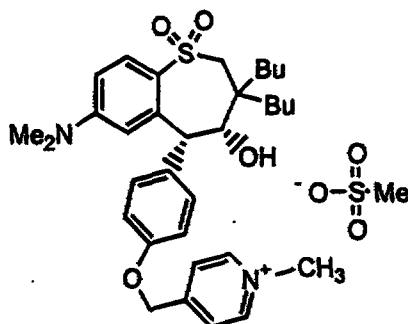
220

°C; ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (s, 6H), 3.07 (AB_q , $J_{\text{AB}} = 15.3, 49.6$ Hz, 2H), 4.10 (d, $J = 7.5$ Hz, 1H), 5.15 (s, 2H), 5.50 (s, 1H), 5.94 (d, $J = 2.7$ Hz, 1H), 6.51 (dd, $J = 2.4, 8.7$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 2H), 7.39 (d, 6.0 Hz, 2H), 7.44 (s, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 9.0$ Hz, 2H), 8.63 (dd, $J = 1.6, 4.8$ Hz, 2H).

10 Step 2: Preparation of quaternary salt

To a stirred solution of 0.41 g (0.74 mmol) of picolinyl intermediate (obtained from Step 1) in 10 mL of acetonitrile and 3 mL of dichloromethane was added 137 mg (0.97 mmol) of iodomethane. The reaction was stirred at ambient temperature for 16 hours, then concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60-55% water/acetonitrile afforded 0.304 g (60%) of the desired title compound as a colorless solid: mp 96-99

20 °C; ^1H NMR (CDCl_3) δ 0.85-0.95 (m, 6H), 1.03-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, 6H), 3.09 (AB_q , $J_{\text{AB}} = 15.0, 27.9$ Hz, 2H), 4.11 (s, 1H), 4.46 (s, 3H), 5.37 (s, 2H), 5.50 (s, 1H), 6.07 (d, $J = 2.4$ Hz, 1H), 6.61 (dd, $J = 2.5, 8.7$ Hz, 1H), 7.02 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 7.2$ Hz, 2H), 7.90 (d, $J = 8.7$ Hz, 1H), 8.14 (d, $J = 6.3$ Hz, 2H), 8.80 (d, $J = 6.6$ Hz, 2H). HRMS Calc'd for $\text{C}_{33}\text{H}_{45}\text{N}_2\text{O}_4\text{S}$: 565.3100. Found: 565.3125.

Example 1429

5 (4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium, methanesulfonate (salt)

10 To a stirred solution of 6.5 g (11.8 mmol) of picolyl intermediate (obtained from Example 1428, Step 1) in 140 mL of acetonitrile heated at 70 °C was added 1.56 g (14.6 mmol) methanesulfonic acid methyl ester. Heating was continued at 70 °C for 15 hours. The

15 reaction was cooled and diluted with 50 mL of ethyl acetate. The solid was collected by vacuum filtration to give 6.14 g (79%). The filtrate was concentrated in vacuo and the residue crystallized from hot acetonitrile to give 1.09 g (14%). A total of 7.23 g

20 (93%) of the desired title compound was obtained as an off-white solid: mp 232-233.5 °C; ¹H NMR (CDCl₃) δ 0.66-0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, 9H), 1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (s, 1H), 2.56 (s, 3H), 2.63 (s, 6H), 2.91 (AB_q, J = 16.5, 24.0 Hz, 2H), 3.88 (s, 1H), 4.40 (s, 3H), 5.21 (s, 3H),

25 5.78 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 2.5, 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.7 Hz, 1H), 8.0 (d, J = 6.6 Hz, 2H), 9.02 (d, J = 6.6 Hz, 2H). HRMS Calc'd for C₃₃H₄₅N₂O₄S: 565.3100. Found: 656.3087. Anal. Calc'd for

30

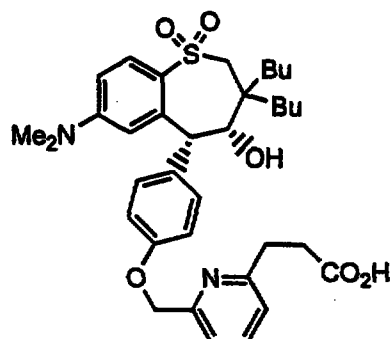
222

$C_{34}H_{48}N_2O_7S_2$: C, 61.79; H, 7.32; N, 4.24; S, 9.70.

Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

Example 1430

5



10 (4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

Step 1: Preparation of picolinyll chloride intermediate

To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1g, 2.1 mmol, obtained from Example 1402, Step 10) in acetone (50 mL) was added anhydrous K_2CO_3 (0.45g, 3.2 mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and 2,6-bischloromethylpyridine (1.2g, 10.8 mmol). The flask was equipped with nitrogen gas adapter and magnetic stirrer. The reaction was heated to reflux for overnight. After 18 hours, the reaction was diluted with ether and washed with water and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatographic purification through silica gel, eluting with 25% EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride intermediate as an oil (0.70g, 55%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H),

223

5.95 (s, 1H), 6.50 (d, 1H), 7.0 (d, 2H), 7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

Step 2: Preparation of pyridinyl malonate intermediate

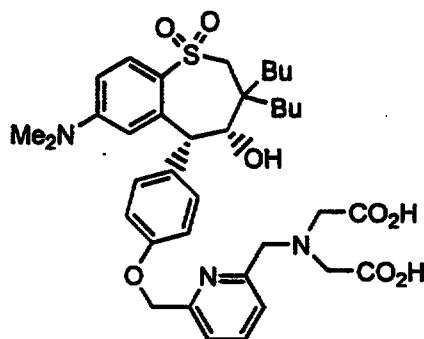
5 Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0 mL) and sodium hydride (0.13g, 3.3 mmol) were placed in a dry three-neck flask. The flask was equipped with nitrogen gas adapter and magnetic stirrer. The picolyl chloride intermediate (1g, 1.67 mmol) was added and
10 heated at 90°C for overnight. The reaction was cooled and extracted with 5% HCl with methylene chloride and washed with water (25 mL), and brine (50 mL). The organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by C-18 reversed
15 phase column eluting with 50% acetonitrile/water and gave pyridinyl malonate intermediate as a white foamy solid (1g, 71%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05
20 (d, 1H), 4.16 (t, 1H), 5.02 (s, 2H), 5.08 (s, 4H), 5.44 (s, 1H), 5.97 (s, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m, 12H), 7.5 (t, 1H), 7.9 (d, 1H).

Step 3: Preparation of pyridinyl acid

25 The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flask. The reaction was stirred at ambient temperature overnight.
30 After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo gave the desired title compound as a white solid (0.44g, 90%): mp 105-
35 107 °C; ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s,

224

6H), 3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (s, 1H), 5.30 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for $C_{35}H_{46}N_2O_6S$: 623.3155. Found: 623.3188.

Example 1431

(4R-cis)-N-(Carboxymethyl)-N-[[6-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinyl]methyl]glycine

Step 1: Preparation of pyridinyl diester intermediate

A mixture of diethyl aminodiacetate (8g, 68 mmol) and sodium carbonate (0.63g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160 °C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H), 6.02 (s, 1H), 6.60

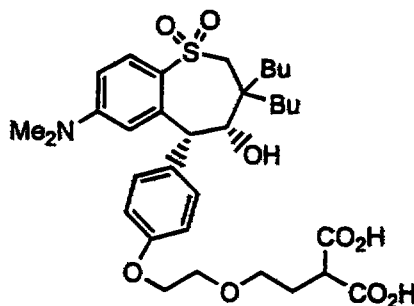
225

(d, 1H), 7.10 (d, 2H), 7.50 (m, 3H), 7.61 (d, 1H), 7.80 (t, 1H), 7.95 (d, 1H). HRMS. Calc'd for $C_{41}H_{57}N_3O_8S$: 752.3945. Found: 752.3948.

5 Step 2: Preparation of pyridinyl diacid

A mixture of pyridine-aminodiacetate intermediate (0.7g, 0.93 mmol, obtained from Step 1), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (25.0 mL, 1:1) was stirred at 40 °C overnight (18 hours). The reaction mixture was diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to give the desired title compound as a white solid (0.44g, 90%): mp 153-155 °C; ^1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for $C_{37}H_{49}N_3O_8S$: 696.3319. Found: 696.3331.

Example 1432



(4S-cis) - [2 - [2 - [4 - [3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethyl]propanedioic acid

Step 1: Preparation of bromoethyl ether intermediate

To a stirred solution of 0.192 g (4.785 mmol, 60% disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 30 min. To the solution was added 13.2 g (54.38 mmol) of bis(2-bromoethyl)ether, and stirring was continued at ambient temperature under N₂ overnight. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give bromoethyl ether intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of diester intermediate

To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH in 45 mL of THF and 15 mL of DMF at 0 °C was added 1.33 g (4.68 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min, followed by the addition of 0.95 g (1.56 mmol) of bromoethyl ether intermediate (obtained from Step 1). The mixture was stirred under N₂ at 80 °C overnight. Solvent was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the diester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m,

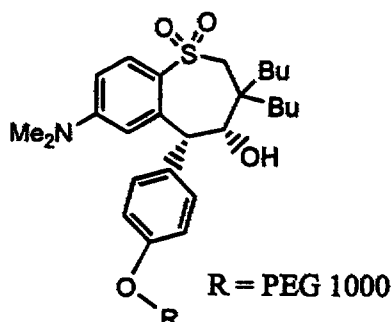
227

3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 2H), 7.9 (d, 1H).

5 Step 3: Preparation of diacid

A suspension of 0.761 g (0.935 mmol) of the diester intermediate (obtained from Step 2) and 35 mg of 10% Pd/C in 25 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 119.5 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.47 (q, 2H), 3.58 (s, 1H), 3.78 (t, 2H), 4.08 (d, 1H), 4.15 (t, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.8 (d, 1H). HRMS. Calc'd for C₃₃H₄₇NO₉S: 632.2893. Found: 632.2882. Anal. Calc'd for C₃₃H₄₇NO₉S: C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; H, 7.56; N, 2.13; S, 4.92.

Example 1433



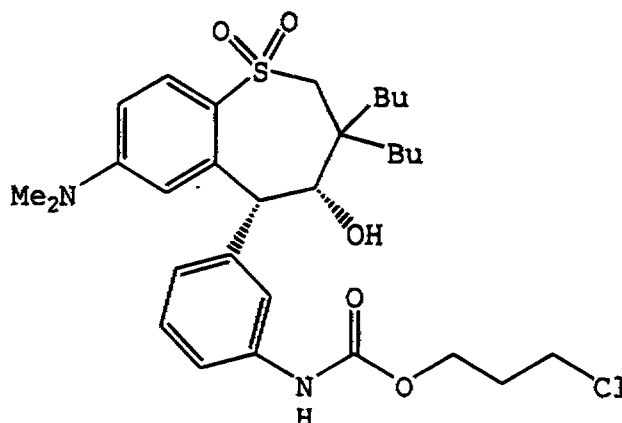
(4R-cis)-a-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]-w-methoxypoly(oxy-1,2-ethanediyl)]

Step 1: Preparation of monomethyl PEG mesylate intermediate

To a solution of 20 g of monomethyl ether PEG in 100 mL of methylene chloride was added 2.2 g (22 mmol) of triethyl amine, and to the resulting solution at 0°C was added dropwise 2.5 g (22 mmol) of methanesulfonyl chloride. The resulting solution was stirred overnight at ambient temperature, and the triethyl amine hydrochloride was filtered off to give the monomethyl PEG mesylate intermediate which was used in the next Step without further purification and characterization.

Step 2: Preparation of polyethylene-linked benzothiepine

A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7 g (1.52 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 5.5 mL of DMF was stirred at ambient temperature under N₂ for 30 min. To the solution was added 0.55 g (0.51 mmol) of the mesylate PEG intermediate (obtained from Step 1) in 5.5 mL of DMF, and the resulting solution was stirred overnight under N₂ at 50 °C. DMF was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the desired title compound as an oil: ¹H NMR (CDCl₃) δ 0.9 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 4H), 3.5-3.85 (m, 95H), 4.1 (s, 1H), 4.15 (t, 2H), 5.5 (s, 1H), 6.05 (s, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Example 1434**Preparation of:**

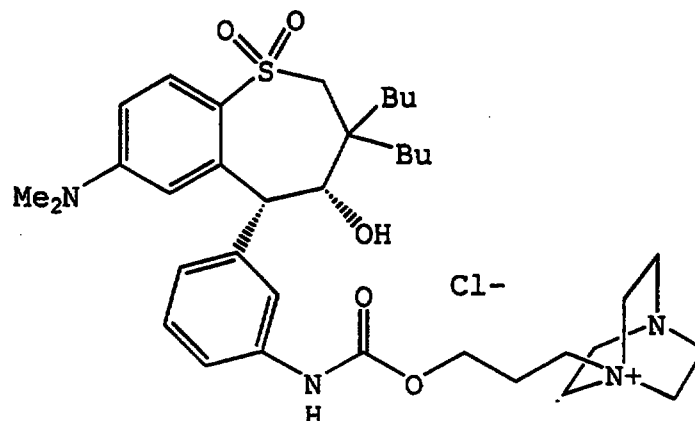
5

The 3-aminobenzothiepine prepared in Step 5 of Example 1398 (0.380g, 0.828 mmol), sodium hydroxide (0.35 mL, 0.875 mmol, 10% in H₂O) and toluene (0.50 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and cooled to 0 °C. A solution of 3-chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in CH₂Cl₂/ THF) was added. After 3.5 hrs, toluene (3.0 mL) was added, and the mixture was washed with H₂O (2x4 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with 20% EtOAc/hexane and concentrated in vacuo gave a white solid (0.269g, 56%). ¹H NMR (CDCl₃) δ 0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J = 6.3 Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (s, 6H), 3.07 (ABq, 2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, 1H), 4.33 (t, J = 6.0 Hz, 2H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M + H). Calc'd for C₃₀H₄₄N₂O₅SCl: 579.2659. Found: 579.2691.

Example 1435

Preparation of:

5



1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700 mmol) and acetonitrile (1.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and heated to 37 °C. A solution of the product of Example 1434 (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was added. After 24 hrs, the reaction mixture was cooled to R.T. and concentrated in vacuo. The crude product was dissolved in acetonitrile (2.0 mL) and precipitated with ethyl ether (10.0 mL). The precipitate was filtered to yield a white solid. This trituration method was repeated, followed by concentrated in vacuo to give a white solid (0.185g, 62%). mp 218.0-225.0 °C; ¹H NMR (CD₃OD) δ 0.90 (m, 6H), 1.05-1.55 (m, 10H), 1.16 (t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), 2.76 (s, 6H), 3.10 (m, 2H), 3.17 (t, J = 7.2 Hz, 6H), 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, J = 5.4 Hz, 2H), 5.31 (s, 1H), 6.10 (s, 1H), 6.55 (d, J = 7.2 Hz,

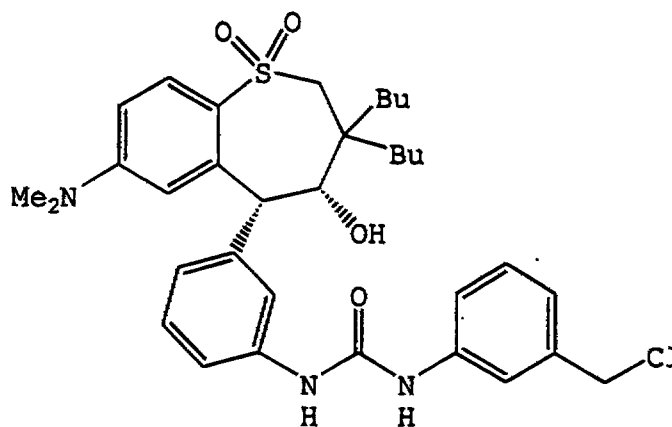
10
15
20
25

231

1H), 7.25 (d, J = 6.9 Hz, 1H), 7.33-7.42 (m, 2H), 7.56 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H). HRMS. Calc'd for C₃₆H₅₅N₄O₅SCl: 655.3893. Found: 655.3880.

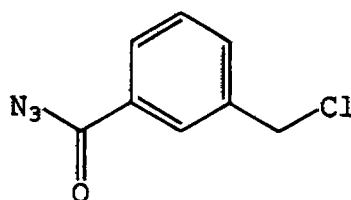
5 Example 1436

Preparation of:



10

Step 1. Preparation of:



15 3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol)
and acetone (8.0 mL) were combined in a 25 mL round-
bottom flask. The reaction flask was cooled to 0°C,
and an aqueous solution of sodium azide (1.56g in 5.50
mL/24.0 mmol) was added. After 1.5 hrs, the reaction
20 mixture was poured into ice water (80.0 mL), extracted
with ethyl ether (2x25 mL), dried (MgSO₄), and
concentrated in vacuo to give a colorless oil (2.660g,
86%). ¹H NMR (CDCl₃) δ 4.62 (s, 2H), 7.47 (t, J = 7.8
Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 7.8 Hz,
25 1H), 8.05 (s, 1H).

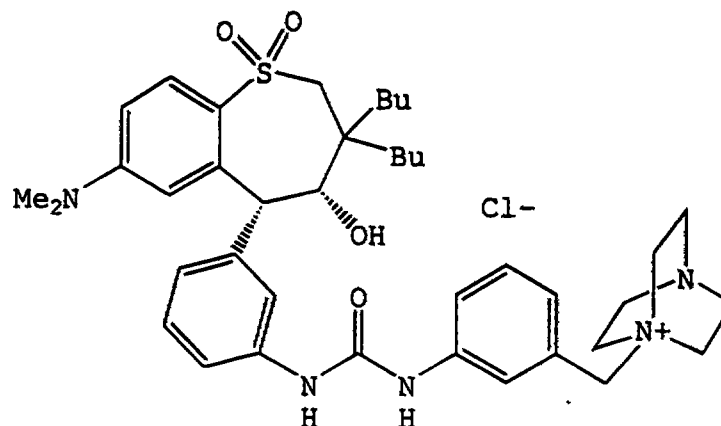
Step 2.

5 3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol)
and toluene (2.0 mL) were combined in a 10 mL round-
bottom flask. The reaction flask was purged with N₂,
equipped with magnetic stirrer, and heated to 110 °C.
After 2 hrs, the reaction mixture was cooled to R.T,
10 and the 3-aminobenzothiepine prepared in Step 5 of
Example 1398 (0.365g, 0.796 mmol) was added. After
2.25 hrs, the mixture was heated to 50 °C. After 0.75
hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol)
was added, and the reaction mixture was heated to
15 reflux. After 0.5 hrs, the reaction mixture was cooled
to R.T. and concentrated in vacuo. Purification by
flash chromatography on silica gel eluting with 20-30%
EtOAc/hexane and concentrated in vacuo gave a white
foamy solid (0.309g, 62%). ¹H NMR (CDCl₃) δ 0.71 (t,
20 J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60
(m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s,
6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s,
2H), 5.42 (s, 1H), 6.07 (s, 1H), 6.99 (d, J = 7.5 Hz),
7.18-7.26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H),
25 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H).
HRMS (M + Li). Calculated for C₃₄H₄₄N₃O₄SClLi:
632.2901. Found: 632.2889.

Example 1437

Preparation of:

5

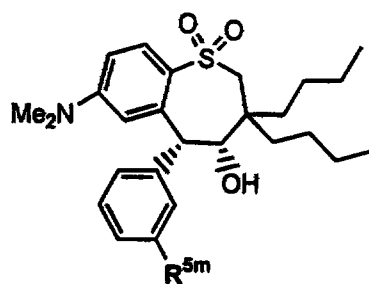


1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol) and acetonitrile (1.00 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂ and equipped with magnetic stirrer. A solution of the product of Example 1436 (0.262g, 0.418 mmol) in acetonitrile (2.70 mL) was added. After 2.5 hrs, a white precipitate had had formed. Ethyl ether (6.0 mL) was added, and the precipitate was filtered, washed with ethyl ether, and dried in vacuo to yield a white solid (0.250g, 80%). mp 246.0-248.0 °C; ¹H NMR (CD₃OD) δ 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11 (m, 1H), 2.74 (s, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12 (s, 1H), 4.39 (s, 2H), 5.31 (s, 1H), 6.11 (s, 1H), 6.52 (dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m, 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS. Calculated for C₄₀H₅₆N₅O₄SCl: 702.4053. Found: 702.4064. Anal. Calculated for C₄₀H₅₆N₅O₄SCl: C, 65.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: C, 64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89.

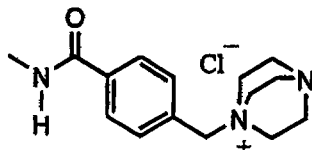
Examples 1438 - 1454

- 5 The compounds of Examples 1438 through 1454 can be prepared in accordance with one or more of the synthetic schemes previously disclosed in this application or using methods known to those skilled in the art.

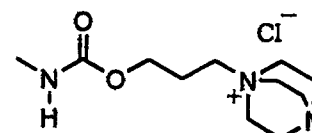
235

R^{5m}

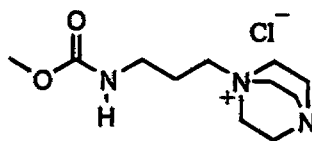
1438.



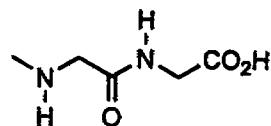
1439.



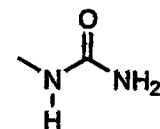
1440.



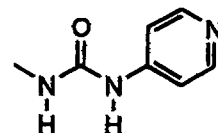
1441.



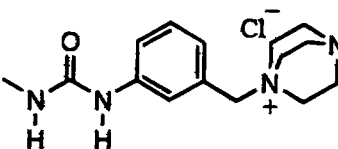
1442.



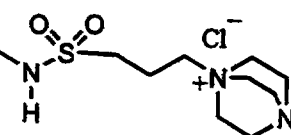
1443.



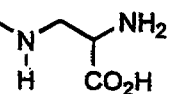
1444.



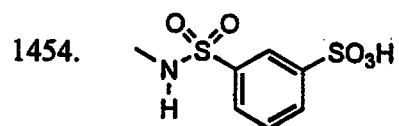
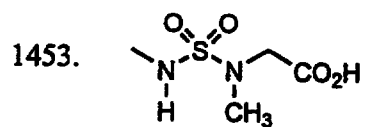
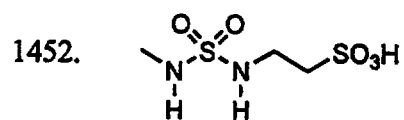
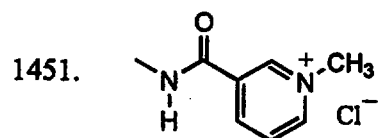
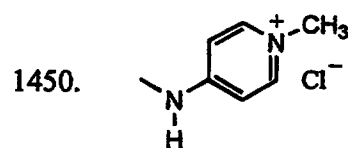
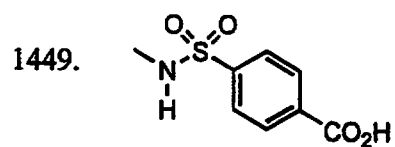
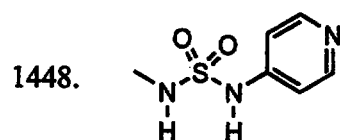
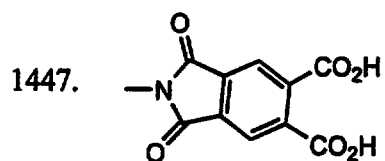
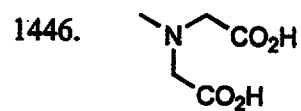
1445.



1446.



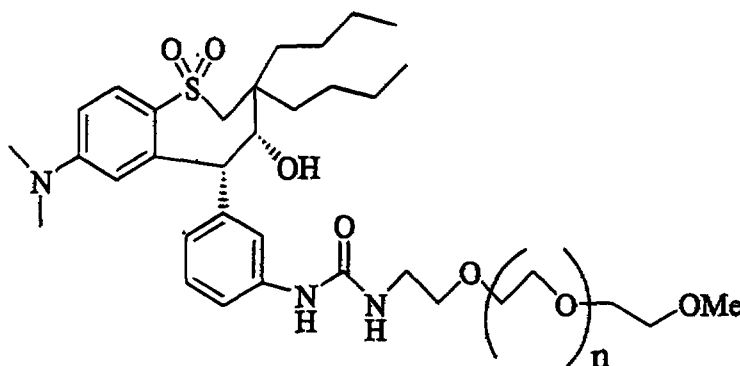
236

R^{5m}

Example 1455

Preparation of:

5



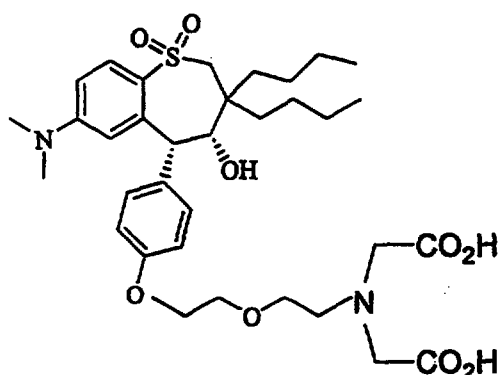
The 3-aminobenzothiepine of step 5 of Example 1398 (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), and CDCl₃ (0.7 mL) were combined in an 8 mm NMR tube. The tube was purged with N₂. After 72 hrs, the reaction mixture was heated to 50 °C. After 24 hrs, an additional aliquot of the 3-aminobenzothiepine of step 5 of Example 1398 (0.0077g/0.017 mmol) was added. After 24 hrs, the reaction mixture was transferred to a 2 mL vial and evaporated to dryness with a N₂ purge. The resulting white solid was dissolved in hot ethyl ether (2.0 mL) and ethyl acetate (0.057 mL/4 drops), cooled to precipitate and filtered. This precipitation procedure was repeated until no starting material was detected in the precipitate (TLC: SiO₂/80% EtOAc/hexanes). Concentrated in vacuo to give a white solid (0.0838g/51%). ¹H NMR (CDCl₃) δ 0.82-0.90 (m, 6H), 1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, 1H), 2.18 (bt, 1H), 2.34 (s, 2H), 2.78 (s, 6H), 3.04 (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz,

238

2H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy data also verified desired product.

Example 1456

Preparation of:



A mixture of 0.845 g (10.7 mmol) of 5-R-[4-(2-bromoethoxyethoxy)phenyl-3,3-dibutyl-7-dimethylamino-4-R-hydroxybenzothiepine-1,1-dioxide (Example 32, Step 1), 11.45 g of diethyl iminodiacetate, and 1.14 g of sodium carbonate was held at 160 °C for 3.5 hours, diluted with brine and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with brine, dried (MgSO₄) and concentrated in vacuum. The residue was kugelrohr distilled at 0.5 torr at 120 °C to remove excess diethyl iminodiacetate to give 1.0 g of a residue. A mixture of this residue, 0.8 g of lithium hydroxide, 25 ml of tetrahydrofuran, and 25 ml of water was held at 45 °C for 3 days and concentrated in vacuum to remove tetrahydrofuran. The residual aqueous solution was diluted with 25 ml of water and acidified to pH 2 and extracted with CH₂Cl₂ (2x50 ml). The CH₂Cl₂ layer was dried (MgSO₄) and concentrated in vacuum. The

239

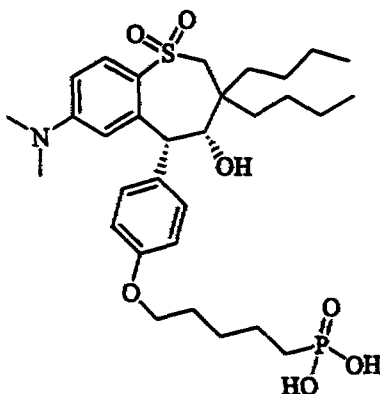
residual solid was dissolved in hot CH_2Cl_2 and triturated with ether. The precipitate was collected to give 0.86 g of solid, MS (negative FAB), m/e 685 ($\text{M}^+ + \text{Na}$).

5

Example 1457

Preparation of:

10



15

A solution of 500 mg of desired 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (Example 1402, Step 10) (1.09 mmol) in 5 mL of dimethylformamide was added via a syringe to a stirred solution of 36 mg of 95% NaH (1.41 mmol) in 5 mL of dimethylformamide at -10°C in an acetone-dry ice bath. The resulting solution was stirred at -10°C for 30 minutes. A solution of 1.25 g of 1,5-dibromopentane (5.45 mmol) in 5 mL of dimethylformamide was then added. The mixture was stirred at -10°C for another 30 minutes and allowed to warm up to room temperature and stirred for 1 hour. The reaction mixture was quenched with water at 0°C and extracted with ethyl acetate. The ethyl acetate layer was dried over MgSO_4 and concentrated in vacuo. The crude product was

25

240

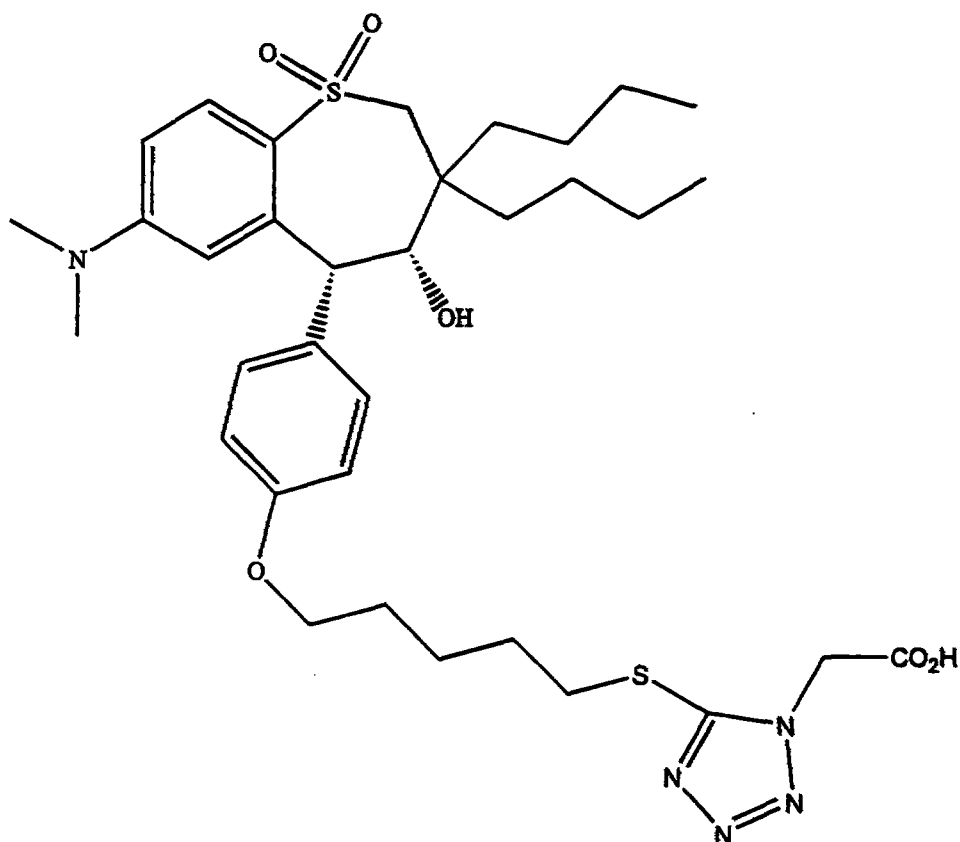
chromatographed on silica gel column with 15% ethyl acetate/hexane to give 470 mg of the bromide intermediate (71%) as a white solid: ^1H NMR (CDCl_3) δ 0.91 (m, 6H), 1.20-1.67 (m, 13H), 1.80 -2.00 (m, 4H), 2.22 (m, 1H), 2.82 (s, 6H), 3.08 (Abq, 2H), 3.46 (t, J = 6.9 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.1 (s, 1H), 5.49 (s, 1H), 6.00 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H).

A stirred solution of 400 mg of the bromide intermediate (0.66 mmol) in 2 mL of tris(trimethylsilyl) phosphite was refluxed at 100 °C overnight. The reaction mixture was cooled to room temperature and 30 mL of 50% methanol/water solution was added. The mixture was stirred at room temperature for 5 hours. The mixture was concentrated in vacuo and the resulting aqueous solution was extracted with CH_2Cl_2 . The CH_2Cl_2 solution was dried over MgSO_4 and concentrated in vacuo to yield a yellowish oil. The oil was dissolved in CH_2Cl_2 and triturated with ethyl acetate to give 202 mg of the desired product (50%) as a white solid. ^1H NMR (CDCl_3) δ 0.90 (m, 6H), 1.14-2.10 (m, 21H), 2.81 (s, 6H), 3.07 (ABq, 3.98 (m, 3H), 4.11 (s, 1H), 5.48 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.53 (dd, J = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H).

Example 1458

Preparation of:

5



10

A mixture of 0.325 g (1.78 mmol) of 5-mercaptotetrazoleacetic acid sodium salt, 1.0 g of potassium carbonate, and 30 ml of dimethylformamide was stirred for 2 hours then was charged with 1.06 g (1.74 mmol) of 5-R-[4-(5-bromopentoxo)phenyl-3,3-dibutyl-7-dimethylamino-4-R-hydroxybenzothiepine-1,1-dioxide (Example 1413, Step 1). The reaction mixture was stirred for 20 hours at room temperature and

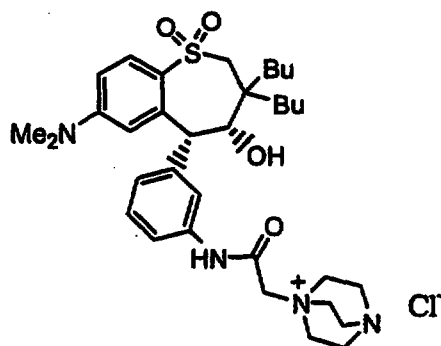
15

242

concentrated in vacuum. The residue was stirred in ether and water (100 ml each). A waxy material resulted that was insoluble to both the ether and aqueous layers. The waxy material was combined with the aqueous layer and was acidified with concentrated HCl and extracted with CH₂Cl₂. The CH₂Cl₂ layer was dried (MgSO₄) and concentrated in vacuum to yield 1.35 g of a syrup, MS (negative FAB), m/e 686 (M⁺ -1); NMR (CDCl₃), 8.0 (d, 1H, 7 Hz), 7.50 (d, 2H, 7 Hz), 7.00 (d, 2H, 7 Hz), 6.7 (d, 1H, 7 Hz), 6.2 (s, 1H), 5.6 (s, 1H), 5.15 (s, 2H), 4.2 (s, 1H), 4.1 (s, 2H), 3.7 (s, 2H), 3.1-3.2 (ABq, 2H), 2.9 (s, 6H), 2.3 (t, 2H, 8 Hz), 0.9-2.0 (m, 24H).

Example 1459

Preparation of:



(4R-cis)-1-[N-[3-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]]phenylacetamido]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

A solution of the aniline derivative prepared in Example 1398, Step 5 (1.0 g, 2.2 mmol) in dichloromethane (10 mL) at 0 °C under N₂ was treated with N,N-di-isopropyl-ethylamine (0.53 mL, 3.1 mmol,

243

1.4 eq.), followed by the dropwise addition of chloroacetyl chloride (0.21 mL, 2.6 mmol, 1.2 eq.) over a 10 minute period. The reaction mixture was stirred and allowed to warm to 25 °C over a 2 hour period. The mixture was quenched by the addition of 1N HCl (25 mL) and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (30 mL), and were dried (MgSO₄) and concentrated to give a pale yellow oil which crystallized upon standing. The white crystals were collected and washed with hexane (50 mL) to give a chloroacetyl intermediate (0.74 g, 63%) as a pale yellow solid: ¹H NMR (CDCl₃) δ 0.95 (m, 6H), 1.15-1.71 (br m, 11H), 2.24 (m, 1H), 2.85 (s, 6H), 3.12 (ABq, J = 15.0 Hz, J = 48.8 Hz, 2H), 4.15 (d, J = 6.2 Hz, 1H), 4.23 (s, 2H), 5.57 (s, 1H), 6.05 (m, 1H), 6.58 (dd, J = 8.9, 2.4 Hz, 1H), 7.37-7.49 (m, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.9 Hz, 1H), 8.30 (s, 1H).

20

A solution of the chloroacetyl intermediate (26 mg, 0.05 mmol) in acetonitrile (1 mL) at 50 °C under N₂ was treated with diazabicyclo[2.2.2]octane (DABCO, 10 mg, 0.09 mmol, 1.8 eq.) and stirred at 50 °C for 2 hours. The reaction mixture was allowed to cool to 25 °C and was concentrated to form a residue. The residue was dissolved in warm acetonitrile and tert-butyl methyl ether was added. The mixture was allowed to stand overnight during which time crystals formed. The resulting white solid was collected and washed with tert-butyl methyl ether (25 mL) to give the title compound (17 mg, 55%) as a white crystalline solid: ¹H NMR (CDCl₃) δ 0.88 (m, 6H), 1.08-1.42 (br m, 8H), 1.45-1.80 (br m, 4H), 2.14 (m, 1H), 2.75 (s, 6H), 3.08 (ABq, J = 15.1 Hz, J = 34.3 Hz, 2H), 3.21 (m, 6H), 3.79 (m, 6H), 4.12 (s, 1H), 4.62 (s, 2H), 5.41 (s, 1H), 5.99 (m,

35

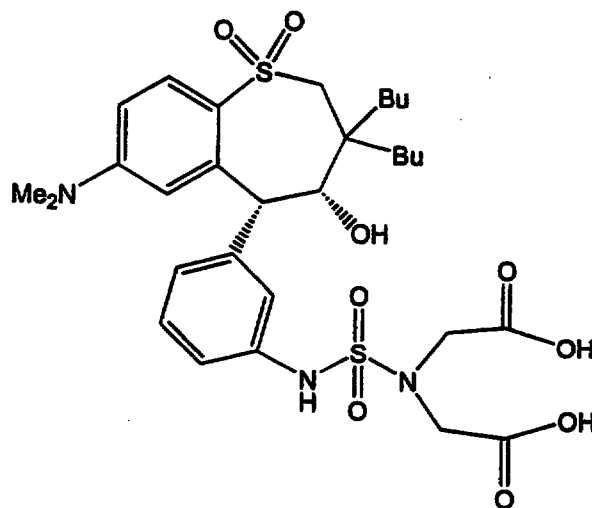
244

1H), 6.48 (d, $J = 8.9$ Hz, 1H), 7.33 (m, 1H), 7.70 (br s, 1H), 7.87 (d, $J = 8.6$ Hz, 1H), 7.93 (s, 1H), 11.3 (s, 1H); HRMS. Calc'd for $C_{34}H_{51}N_4O_4S$: 611.3631. Found: 611.3638.

5

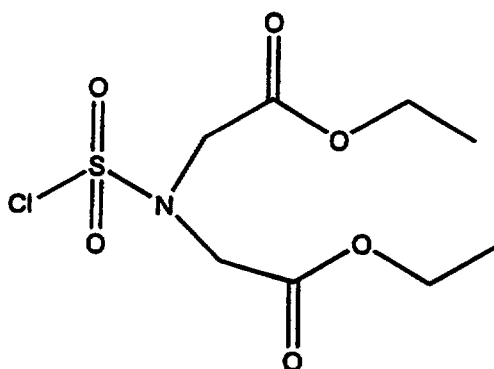
Example 1460

Preparation of:



10

Step 1: Preparation of diethyl iminodiacetato-sulfonamoyl chloride



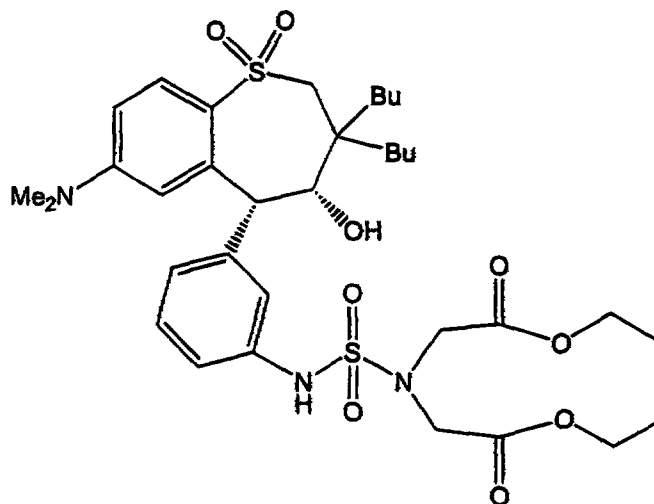
15

Sulfuryl chloride (27.552g/204.1 mmol) and chloroform (50.0 mL) were combined in a 250 mL round-bottom flask. The reaction flask was purged with N₂,

245

equipped with magnetic stirrer, and cooled to 0 °C. A solution of diethyl iminodiacetate (18.902g/99.9 mmol) and triethylamine (10.112g/99.9 mmol) was added dropwise while maintaining the temperature of the solution below 20 °C. After the addition was completed, the reaction mixture was allowed to warm to room temperature. After 2 hours, the reaction mixture was poured into ice water (100 mL) and mixed well. The organic layer was separated, washed with 10% aq. HCl (50 mL) and chilled water (2 x 50 mL), dried (CaCl₂), filtered and concentrated in vacuo to give an amber liquid (5.706g/20%). ¹H NMR (CDCl₃) δ 1.30 (t, 6H), 4.23 (q, 4H), 4.38 (s, 4H). HRMS (EI/M + H). Calc'd for C₈H₁₅NO₆SCl: 288.0309. Found: 288.0300.

Step 2: Preparation of:



The 3-aminobenzothiepine of step 5 of Example 1398 (0.503g/1.097 mmol), toluene (5.00 mL), diisopropylethylamine (0.148g/1.148 mmol), and the diethyl iminodiacetato-sulfonamoyl chloride prepared in step 1 of this Example (0.650g/2.260 mmol) were combined in a 25 mL round-bottom flask. The reaction flask was purged with N₂ and equipped with magnetic stirrer. After 18 hours, additional diisopropylethylamine (0.074g/0.574 mmol) and diethyl iminodiacetato-

246

sulfonamoyl chloride (0.181g/0.628 mmol) were added. After 24 hours, dichloromethane (75.0 mL) was added. The mixture was washed with aqueous NaHCO_3 (25.0 mL), aqueous NaCl (25.0 mL), dried (MgSO_4), and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with 30% ethyl acetate/hexane and concentrated in vacuo gave a white solid (0.349g/45%).

^1H NMR (CDCl_3) δ 0.91 (m, 6H), 1.10-1.70 (m, 10H), 1.27 (t, $J = 7.2$ Hz, 6H), 1.90 (m, 1H), 2.21 (m, 1H), 2.81 (s, 6H), 3.09 (dd, $J = 36.6, 15.3$ Hz, 2H), 4.11-4.24 (m, 9H), 5.50 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.24-7.38 (m, 5H), 7.44 (bs, 1H), 7.90 (d, $J = 9.0$ Hz, 1H). HRMS (ESI/M + H). Calc'd for $\text{C}_{34}\text{H}_{52}\text{N}_3\text{O}_9\text{S}_2$: 710.3145. Found: 710.3158.

Step 3: Preparation of Title Compound:

The benzothiepine prepared in step 2 of this Example (0.224g/0.316 mmol) and tetrahydrofuran (1.00 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2 and equipped with magnetic stirrer. A solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.030g/0.715 mmol) in water (0.50 mL) was added. After 4 hours, additional $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.015g/0.357 mmol) was added. After 30 minutes, water (6.0 mL) was added. The aqueous mixture was washed with diethyl ether (4 x 4.0 mL), and acidified with aqueous 3.0 N HCl (0.40 mL). After 18 hours, a white precipitate had formed, which was filtered, washed with water (2.0 mL) and concentrated in vacuo. Precipitation from acetonitrile/diethyl ether/hexanes and recrystallization from *t*-butyl methyl ether/diethyl ether gave a white crystalline solid (0.109g/53%). ^1H NMR (CD_3OD) δ 0.89 (m, 6H), 1.05-1.50 (m, 10H), 1.68 (m, 1H), 2.16 (m, 1H), 2.89 (s, 6H), 3.13 (m, 2H), 4.07 (s, 4H), 4.18 (s, 1H), 5.45 (s, 1H), 6.52 (s, 1H), 6.93

247

(d, $J = 8.7$ Hz, 1H), 7.19 (d, $J = 6.6$ Hz, 1H), 7.35 (m, 3H), 7.70 (bs, 1H), 7.99 (d, $J = 8.7$ Hz, 1H) HRMS (ESI/M + H). Calc'd for $C_{30}H_{44}N_3O_9S_2$: 654.2519. Found: 654.2512.

5

As one skilled in the art will appreciate, where a non-enantioselective synthesis is employed in any of the above examples and an enantiomeric-enriched final product is desired, the enantiomeric-enriched final product can be obtained by use of chiral chromatographic purification at an appropriate stage of the synthesis. For example, where the synthesis proceeds through the intermediate 5-(4'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide which is then demethylated to form the intermediate 5-(4'-hydroxyphenyl)-7-(dimethylamino)-tetrahydrobenzothiepine-1,1-dioxide, the 5-(4'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide preferably is subjected to a chiral chromatographic purification step prior to demethylation. The separated enantiomer is then demethylated to yield the enantiomeric-enriched intermediate 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide for use in the next step of the synthesis. By way of further illustration, chiral chromatographic purification could be performed immediately prior to Step 7 of Example 1398a using a column such as a Chiralpak AD column with an ethanol/heptane mobile phase (5%-10% ethanol v/v) at a wavelength of 220 nm. The separated enantiomer is then used as an intermediate in Step 7 of the synthesis thereby resulting in an enantiomeric-enriched final product.

Similarly, where the synthesis proceeds through the intermediate 5-(3'-methoxyphenyl)-7-

(dimethylamino)- tetrahydrobenzothiepine-1,1-dioxide
which is then demethylated to form the intermediate 5-
(3'-hydroxyphenyl)-7-

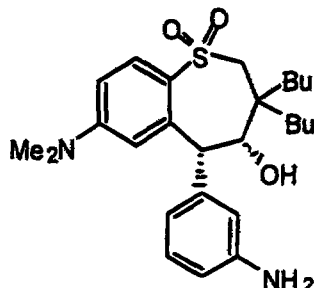
5 (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the
5- (3'-methoxyphenyl)-7- (dimethylamino)-
tetrahydrobenzothiepine-1,1-dioxide preferably is
subjected to a chiral chromatographic purification step
prior to demethylation. The separated enantiomer is
then demethylated to yield the enantiomeric-enriched
10 intermediate 5-(3'-hydroxyphenyl)-7-(dimethylamino)-
tetrahydrobenzothiepine-1,1-dioxide for use in the next
step of the synthesis. By way of further illustration,
chiral chromatographic purification could be performed
immediately prior to Step 9 of Example 1400 with the
15 separated enantiomer then used as the intermediate in
Step 9 of the synthesis thereby resulting in an
enantiomeric-enriched final product.

Further, chiral chromatographic purification can
be used where the synthesis proceeds through the
20 intermediate 5-(3' or 4'-aminophenyl)-7-
(dimethylamino)tetrahydro-benzothiepine-1,1-dioxide,
such as in the Example Corresponding To Scheme XII. For
example, chiral chromatographic purification could be
performed immediately following Step 5 of the Example
25 Corresponding To Scheme XII to yield the enantiomeric-
enriched intermediate 5-(3' or 4'-aminophenyl)-7-
(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide for
use in the next step of the synthesis.

Alternatively, an enantioselective synthesis, such
30 as the one described in Example 1461 below, could be
used to provide the desired enantiomeric-enriched 5-(3'
or 4'-aminophenyl)-7-
(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
intermediate.

Example 1461

Preparation of:



5

Step 1: Preparation of triflic intermediate

A solution of 10.17 g (22.13 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (prepared in Step 7 of Example 1398a) in pyridine (42 mL) at 0° C under nitrogen gas was treated with triflic anhydride (4.1 mL, 24.4 mmol, 1.1 equivalents) dropwise. Upon completion of the addition, the bath was removed and the reaction stirred at room temperature for 21 hours. The pyridine was removed in vacuo, the resulting oil was taken up in water (100 mL) and extracted three times with ethyl acetate (45 mL each). The combined organics were washed with 2N HCl (100 mL), 10% CuSO₄ (100 mL) and brine (100 mL), and then dried over MgSO₄, filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (25% ethyl acetate in hexane) to afford the desired title compound as a pale yellow foam (11.42 g, 87.2%): ¹H NMR (CD₃OD) δ 0.85-1.0 (m, 6H), 1.0-1.15 (m, 10H), 1.76 (t, J = 12.6 Hz, 1 H), 2.12 (t, J = 13 Hz, 1H), 2.79 (s, 6H), 3.1-3.2 (q_{AB}, 2H), 4.05 (s, 1H), 5.42 (s, 1H), 5.88 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 8.9, 2.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.49 (d, J

250

= 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.66 (s, 1H), 7.77 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of Imine

5 To a solution of 11.41 g (19.28 mmol) of the triflate (prepared in Step 1 above), palladium (II) acetate (433 mg, 1.93 mmol, 10 mol%), racemic 2,2'-bis-(biphenylphosphenyl)-1,1'-binaphthyl (1.41 g, 2.26 mmol, 12 mol%) and cesium carbonate (8.86 g, 27.2 mmol, 10 2.0 equivalents) in 114 mL of tetrahydrofuran was added 6.6 mL (39.4 mmol, 2.0 equivalents) of benzophenone imine. The mixture was stirred at reflux for four hours, filtered through celite and the solvent removed in vacuo providing 19.11 g of a deep red foam: ¹H NMR 15 (CDOD₃) δ 0.8-1.45 (m, 16H), 1.6-1.75 (m, 1H), 1.9-2.05 (m, 1 H), 2.78 (s, 6H), 2.98-3.15 (q_{AB}, 2H), 3.88 (s, 1H), 5.17 (s, 1H), 5.92 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 9.1, 2.7 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 6.80 (br s, 1H), 7.0-7.12 (m, 2H), 7.15-7.25 (m, 3H), 7.35- 20 7.52 (m, 7H), 7.52-7.68 (m, 2H), 7.71 (d, J = 7.9 Hz, 1H).

Step 3: Preparation of Aniline

25 To a solution of 19.1 g (theoretically 19.3 mmol) of the crude imine (prepared in Step 2 above) in methanol (200 mL) was added sodium acetate (6.33 g, 77.2 mmol, 4 equivalents) and hydroxylamine hydrochloride (4.02 g, 57.9 mmol, 3 equivalents). After stirring one hour, 1N sodium hydroxide (100 mL) 30 was added and the mixture extracted with methylene chloride (2 X 100 mL, 1 X 50 mL). The combined organics were washed with brine (100 mL), dried over MgSO₄, filtered and the solvent evaporated. The residue was purified by chromatography on silica gel 35 (50% ethyl acetate in hexane) to afford the desired title compound as a yellow foam (8.64 g, 97.9%): ¹H NMR

251

(CD₃OD) δ 0.86-0.97 (m, 6H), 1.07-1.52 (m, 10H), 1.76 (t, J = 12.6 Hz, 1 H), 2.10 (t, J = 11.5 Hz, 1H), 2.79 (s, 6H), 3.05-3.18 (q_{AB}, 2H), 4.10 (s, 1H), 5.22 (s, 1H), 6.19 (s, 1H), 6.54 (dd, J = 8.9, 1.9 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.82 (s, 1H), 6.86 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H).

BIOLOGICAL ASSAYS

The utility of the compounds of the present invention is shown by the following assays. These assays are performed in vitro and in animal models essentially using a procedure recognized to show the utility of the present invention.

In Vitro Assay of compounds that inhibit IBAT-mediated uptake of [¹⁴C]-Taurocholate (TC) in H14 Cells

Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded at 60,000 cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

On the day of assay, the cell monolayer is gently washed once with 100 μ l assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin- (FAF)BSA).

To each well 50 μ l of a two-fold concentrate of test compound in assay buffer is added along with 50 μ l of 6 μ M [¹⁴C]-taurocholate in assay buffer (final concentration of 3 μ M [¹⁴C]-taurocholate). The cell culture plates are incubated 2 hours at 37° C prior to gently washing each well twice with 100 μ l 4° C Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed

once with 100 μ l 4° C PBS without (FAF)BSA. To each 200 μ l of liquid scintillation counting fluid is added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay of compounds that inhibit uptake of [¹⁴C]-Alanine

The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

In Vivo Assay of compounds that inhibit Rat Ileal uptake of [¹⁴C]-Taurocholate into Bile

(See "Metabolism of 3 α ,7 β -dihydroxy-7 α -methyl-5 β -cholanoic acid and 3 α ,7 β -dihydroxy-7 α -methyl-5 β -cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum).

20 ml of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is monitored continuously. At the start

253

of the experiment, 2.0 ml of control sample ($[^{14}\text{C}]$ -taurocholate @ 0.05 μM /ml with 5 mM cold taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is
5 infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions are collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS (using a 30 ml syringe), and then
10 the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is initiated as described above but this with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile sampled every 3 min
15 for the first 27 min. If necessary, a third perfusion is performed as above that typically contains the control sample.

20 Measurement of Hepatic Cholesterol Concentration
(HEPATIC CHOL)

Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in
25 isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) *Clin. Chem.* 20, 470.

30 Measurement of Hepatic HMG CoA-Reductase Activity (HMG
COA)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material
35 was resuspended in buffer and an aliquot was assayed for HMG CoA reductase activity by incubating for 60

minutes at 37° C in the presence of ¹⁴C-HMG-CoA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) *J. Lipid Res.* 31, 2159).

Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

Measurement of Hepatic Cholesterol 7- α -Hydroxylase Activity (7 α -OHase)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for cholesterol 7- α -hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was

255

separated by injecting an aliquot of the extract onto a C₁₈ reversed phase HPLC column and quantitating the eluted material using UV detection at 240nm.

(Reference: Horton, J. D., et al. (1994) *J. Clin. Invest.* 93, 2084).

5

Rat Gavage Assay

Male Wister rats (275-300g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:0 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight.

10

Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

15

20

Measurement of Fecal Bile Acid Concentration (FBA)

Total fecal output from individually housed hamsters was collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed.

Approximately 0.1 gram was weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was measured enzymatically using the 3 α -hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., et al. (1981) *Clin. Chem.* 27, 1352).

25

30

[³H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

35

Rabbit Ileal brush border membranes were prepared

from frozen ileal mucosa by the calcium precipitation method describe by Malathi et al. (Reference: (1979) *Biochimica Biophysica Acta*, 554, 259). The method for measuring taurocholate was essentially as described by Kramer et al. (Reference: (1992) *Biochimica Biophysica Acta*, 1111, 93) except the assay volume was 200 μ l instead of 100 μ l. Briefly, at room temperature a 190 μ l solution containing 2 μ M [^{3} H]-taurocholate(0.75 μ Ci), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was incubated for 5 sec with 10 μ l of brush border membrane vesicles (60-120 μ g protein). The incubation was initiated by the addition of the BBMV while vortexing and the reaction was stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 μ m pore) and an additional 5 ml wash with stop buffer.

Acyl-CoA;cholesterol Acyl Transferase (ACAT)

Hamster liver and rat intestinal microsomes were prepared from tissue as described previously (Reference: (1980) *J. Biol. Chem.* 255, 9098) and used as a source of ACAT enzyme. The assay consisted of a 2.0 ml incubation containing 24 μ M Oleoyl-CoA (0.05 μ Ci) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 μ g of microsomal protein. The assay was initiated by the addition of oleoyl-CoA. The reaction went for 5 min at 37° C and was terminated by the addition of 8.0 ml of chloroform/ methanol (2:1). To the extraction was added 125 μ g of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction were separated by centrifugation after thorough vortexing. The chloroform phase was taken to dryness and then spotted on a silica gel 60 TLC plate and developed in

257

hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

5

TABLE 11

Rat Gavage Assay Data for Some Additional Compounds
of the Present Invention

Compound of Example No.	Study No.	Dose (mg/kg/day)	Delta (micromoles fecal bile acid per day)
1402	28	5	58.2
		.2	1.3
		.04	0.3
1402	30	2	50.3
		.4	40.9
		.08	48.5
		.016	22.9
1403	30	2	41.6
		.4	35.2
		.08	11.9
		.016	3
1404	28	5	93.7
		.2	59.1
		.04	33.5
1406	32	2	47.8
		.4	31.6
		.08	12.8
		.016	-8.5
1407	32	2	51.9
		.4	30.1
		.08	27.5
		.016	6.4
1407	33	2	35
		.4	12.7
		.08	-.04
		.016	-4.5
1408	29	2	41.2
		.4	36.8
		.08	16.8
		.016	-3.3
1408	37	2	26.2
		.4	45.2
		.08	26.3
		.016	6.6

258

1409	33	2 .4 .08 .016	19.2 28.7 14.1 -1.7
1409	41	2 .4 .08 .016	44.2 35.9 14.5 11
1410	33	32.4 34.3 27.9 9.3	
1410	35	2 .4 .08 .016	26.2 36.5 18.5 20.4
1411	34	2 .4 .08 .016	63.4 54.1 33 22.3
1413	26	5 .2 .04	52.3 42.4 19
1414	27	5 .2 .04	45.2 39.5 14.3
1414	31	2 .4 .08 .016	41.5 33.7 29 3.8
1415	28	5 .2 .04	59.9 48.1 23.9
1415	37	2 .4 .08 .016	48.9 25.7 27.1 12.7
1416	29	2 .4 .08 .016	46.1 21.9 25 -7.8
1417	31	2 .4 .08 .016	51.4 42 39.6 29.3
1418	29	2 .4 .08 .016	20.3 29.5 -4.6 -10
1419	31	2 .4	28.5 13.9

		.08	10.3
		.016	5.8
1420	31	2	53.1
		.4	45
		.08	38.1
		.016	29.6
1421	32	2	57.8
		.4	27.7
		.08	25.3
		.016	4.7
1423	34	2	56.5
		.4	69.3
		.08	35.3
		.016	14.4
1425	21	5	91.8
		.2	100.
		.04	66.4
1425	30	2	44.6
		.4	62
		.08	69.5
		.016	31.6
1425	40	2	48.3
		.4	45
		.08	31.2
		.016	30
1426	33	2	52.4
		.4	19.5
		.08	23.1
		.016	24.6
1426	35	2	37.7
		.4	41.7
		.08	40.5
		.016	24.6
1426	39	2	54.3
		.4	48.7
		.08	51.8
		.016	26.8
1426	43	2	40.8
		.4	21.7
		.08	5.9
		.016	4.1
1427	40	2	36.7
		.4	35.8
		.08	27.3
		.016	13.8
1428	34	2	40.4
		.4	64.9
		.08	24.4
		.016	12.2
1428	42	2	46
		.4	40.7

260

		.08	26
		.016	1.1
1429	41	2	34.5
		.4	24.9
		.08	18.7
		.016	9.2
1429	42	2	47.1
		.4	31.1
		.08	35.5
		.016	4.8
1430	30	2	51.2
		.4	50.4
		.08	20.7
		.016	-5.6
1431	32	28.3	
		45.8	
		21.9	
		1.1	
1432	28	5	36.2
		.2	9.7
		.04	2.4
1433	24	20	66.5
		2	47.4
		.2	26.5

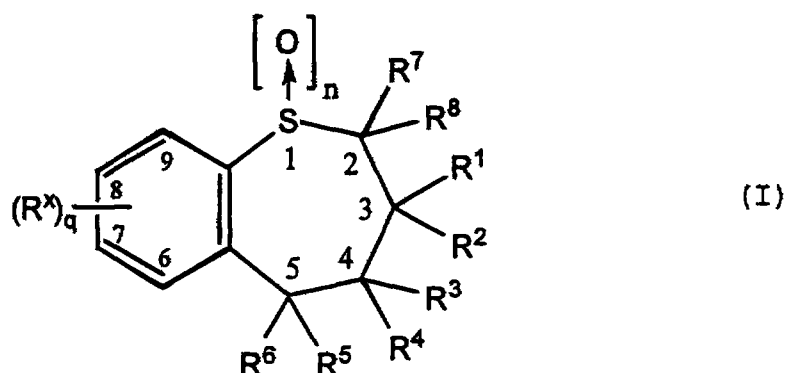
5 The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

10 The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

15

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more OR^{13a} ,

wherein R^{13a} is selected from the group consisting of alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,



R^{13a} is optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M ; and

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$,



* C L M S *

$P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,
wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo , $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with



one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} ,



$\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S(O)}\text{R}^{13}$, $\text{S(O)}_2\text{R}^{13}$, SO_3R^{13} , $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$,
 $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM ,
 $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C(O)}\text{R}^{13}$, $\text{C(O)}\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C(O)}\text{R}^{13}$, $\text{C(O)}\text{OM}$,
 COR^{13} , OR^{18} , $\text{S(O)}_n\text{NR}^{18}$, $\text{NR}^{13}\text{R}^{18}$, $\text{NR}^{18}\text{OR}^{14}$, $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,
 $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, amino acid, peptide, polypeptide, and
 carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,
 polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl,
 polyether, quaternary heterocycle, and quaternary
 heteroaryl can be further substituted with OR^9 , NR^9R^{10} ,
 $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S(O)}\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN ,
 halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO(OR}^{16})\text{OR}^{17}$,
 $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{C(O)}\text{OM}$, and

wherein R^{18} is selected from the group consisting of
 acyl, arylalkoxycarbonyl, arylalkyl, heterocycle,
 heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl,
 heterocycle, heteroaryl, alkyl, quaternary heterocycle,
 and quaternary heteroaryl optionally are substituted with
 one or more substituents selected from the group
 consisting of OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S(O)}\text{R}^9$,
 SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $\text{CONR}^9\text{R}^{10}$, SO_3R^9 ,
 SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO(OR}^{16})\text{OR}^{17}$, and $\text{C(O)}\text{OM}$,

wherein in R^x , one or more carbons are optionally
 replaced by O, NR^{13} , $\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^{13}\text{A}^-$,
 PR^{13} , $\text{P(O)}\text{R}^{13}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, phenylene, amino acid,
 peptide, polypeptide, carbohydrate, polyether, or
 polyalkyl,

wherein in said polyalkyl, phenylene, amino acid,



peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

2. A compound of claim 1 wherein:

R^5 is phenyl substituted with OR^{13a} ;

R^{13a} is independently selected from the group consisting of alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, and carboxyalkylaminocarbonylalkyl; and

R^{13a} is optionally substituted with one or more groups selected from the group consisting of carboxy, quaternary heterocycle, quaternary heteroaryl, and NR^9R^{10} .

3. A compound of claim 1 wherein n is 1 or 2.

4. A compound of claim 1 wherein R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl.

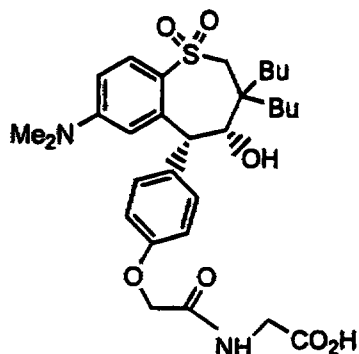


5. A compound of claim 1 wherein R^7 and R^8 are hydrogen.
6. A compound of claim 1 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 .
7. A compound of claim 1 wherein R^3 is hydrogen and R^4 is hydroxy.
8. A compound of claim 1 wherein one or more R^* are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.
9. A compound of claim 1 wherein one or more R^* are independently selected from methoxy and dimethylamino.
10. A compound of claim 1 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl.
11. A compound of claim 1 wherein R^1 and R^2 are independently selected from the group consisting alkyl.
12. A compound of claim 1 wherein R^1 and R^2 are the same alkyl.
13. A compound of claim 1 wherein R^1 and R^2 are each n-butyl.
14. A compound of claim 1 wherein
n is 1 or 2;
 R^1 and R^2 are n-butyl;
 R^3 and R^6 are hydrogen;
 R^4 is hydroxy;

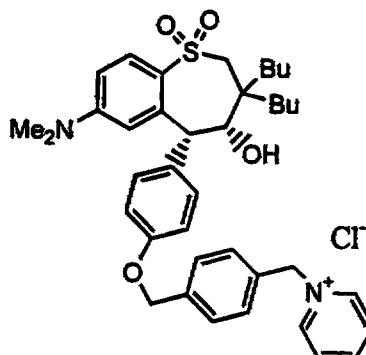


R⁷ and R⁸ are hydrogen; and
one or more R^x are independently selected from methoxy
and dimethylamino.

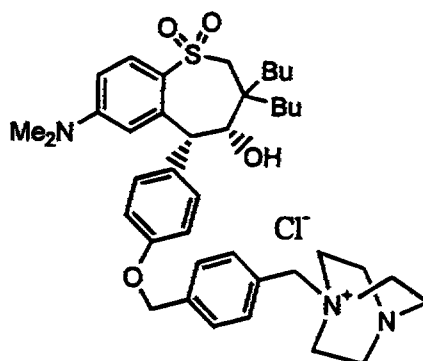
15. A compound of claim 1 having the structural formula:



16. A compound of claim 1 having the structural formula:

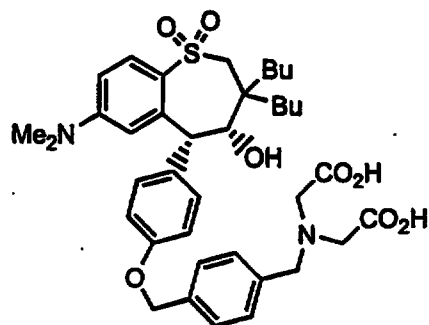


17. A compound of claim 1 having the structural formula:

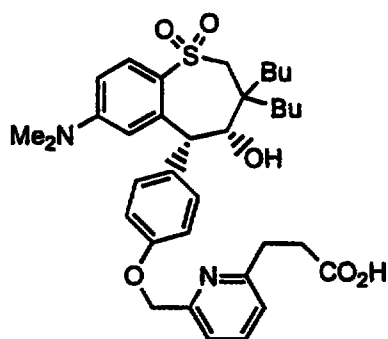


270

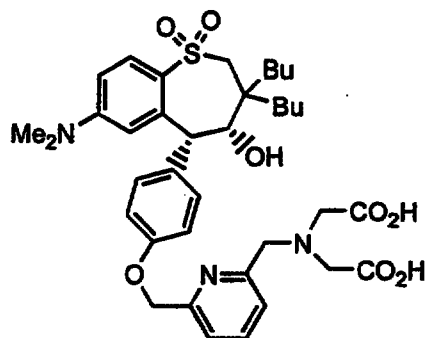
18. A compound of claim 1 having the structural formula:



19. A compound of claim 1 having the structural formula:

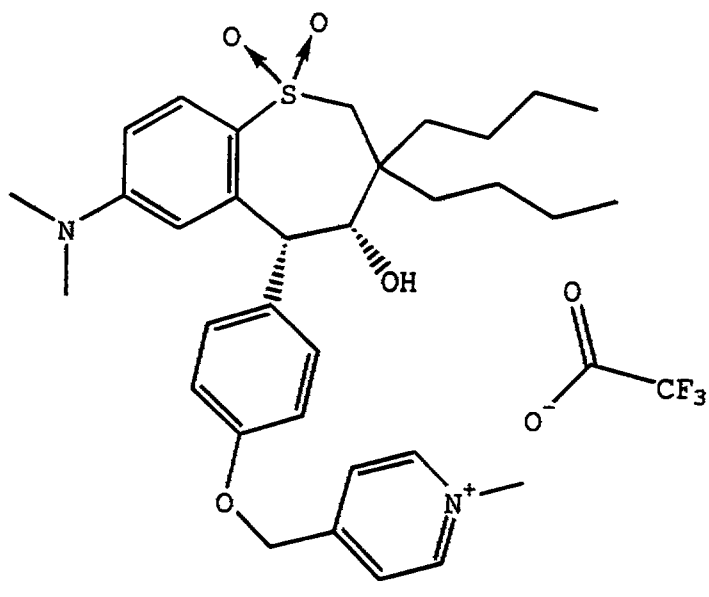
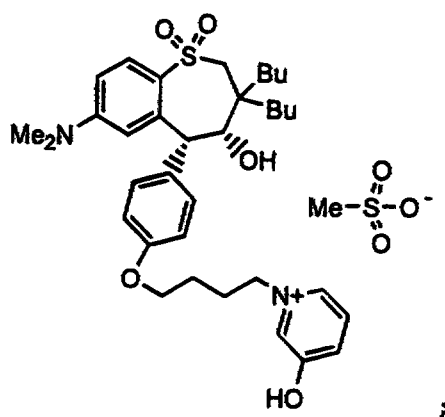
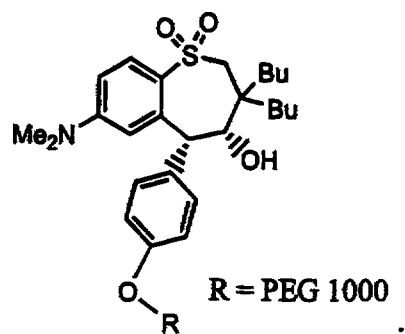


20. A compound of claim 1 having the structural formula:

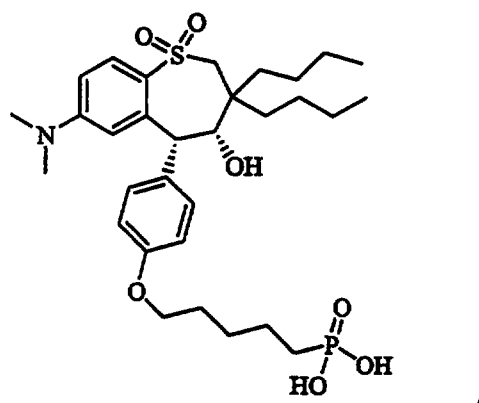
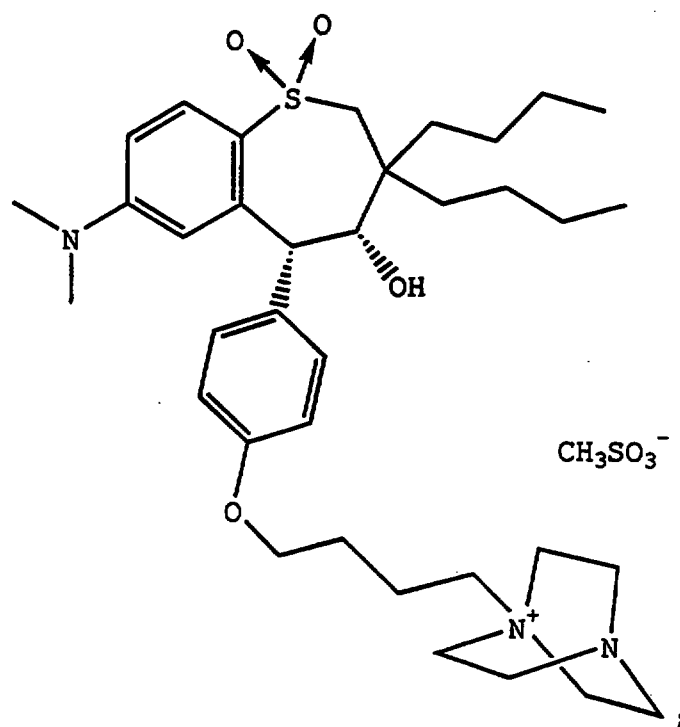


271

21. A compound selected from the group consisting of:

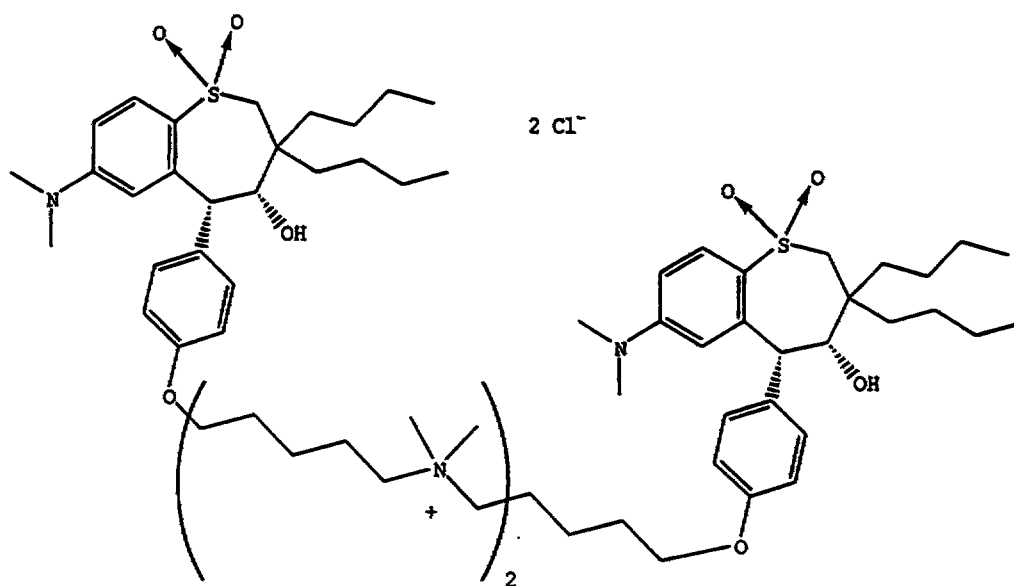


272

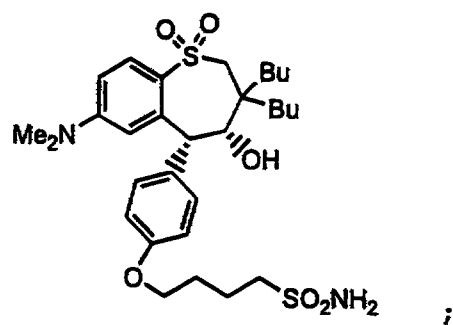
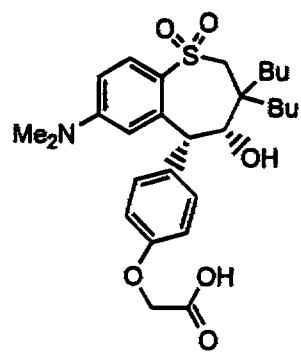


* C L M S *

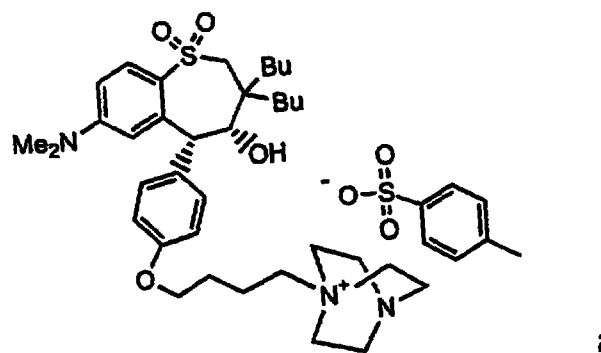
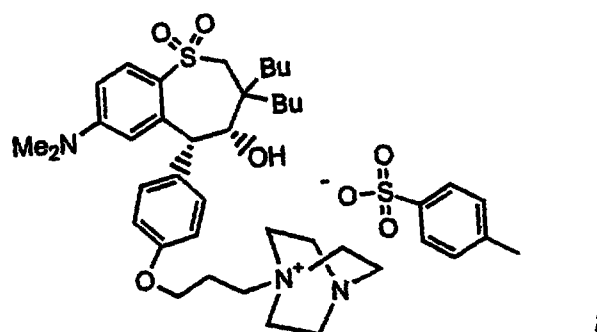
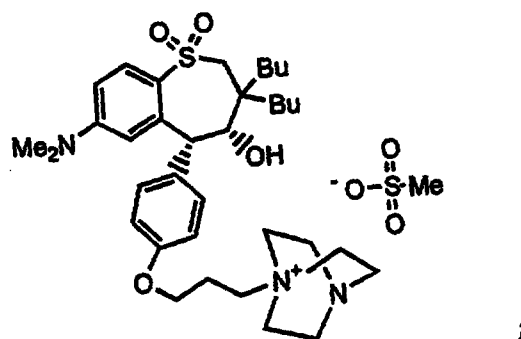
273



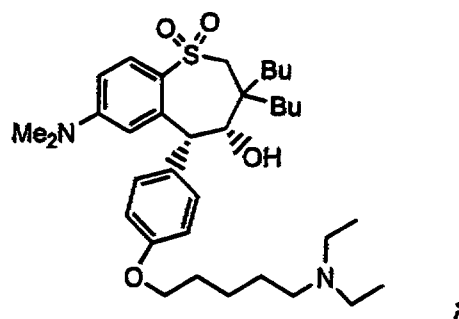
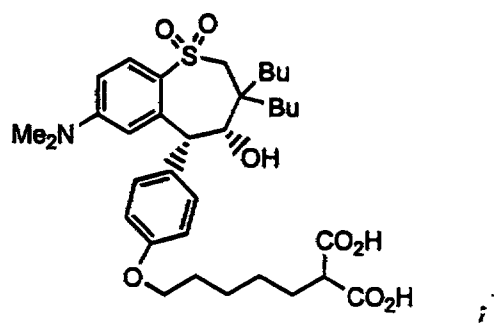
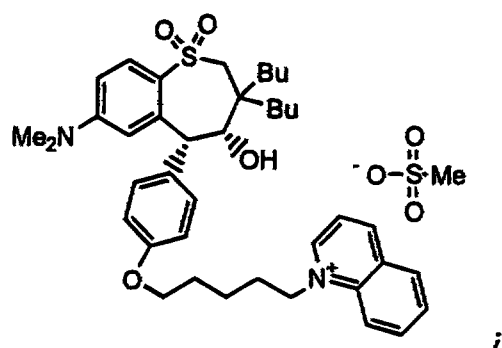
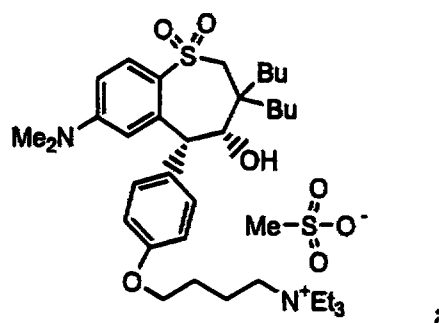
1



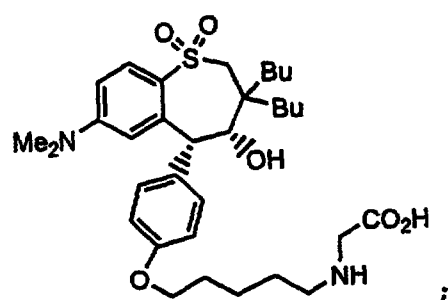
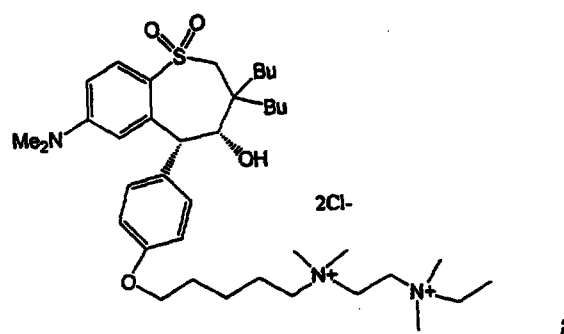
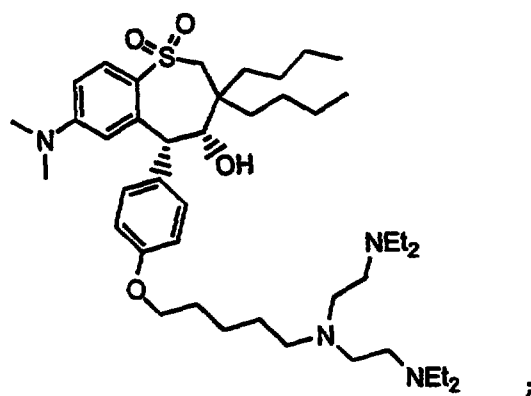
274



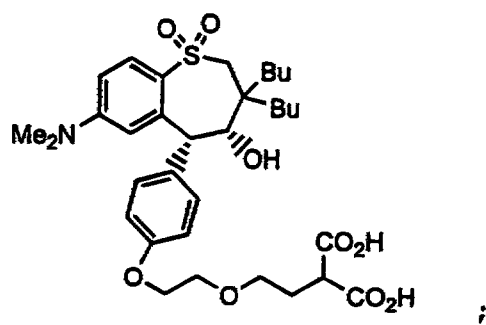
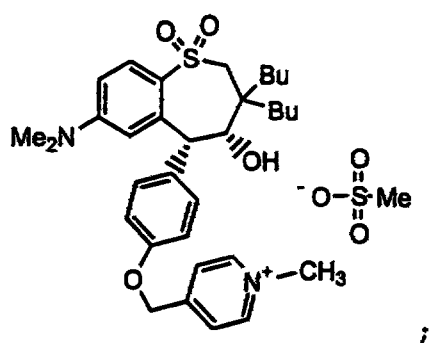
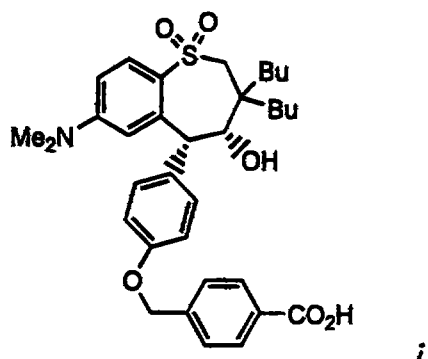
275



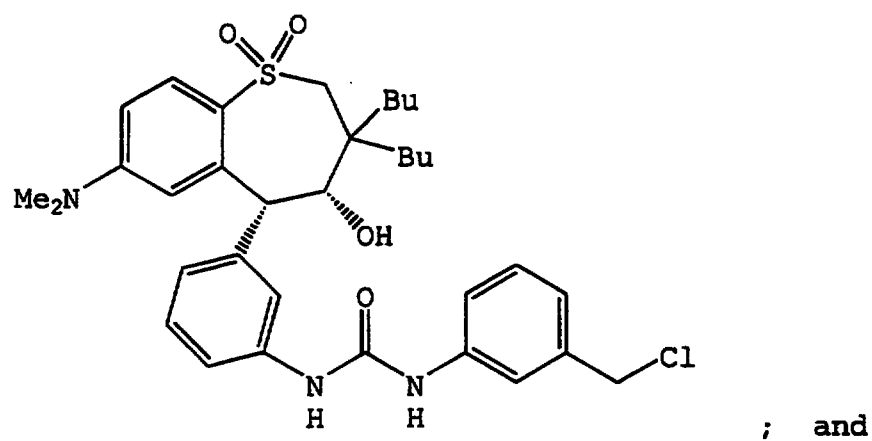
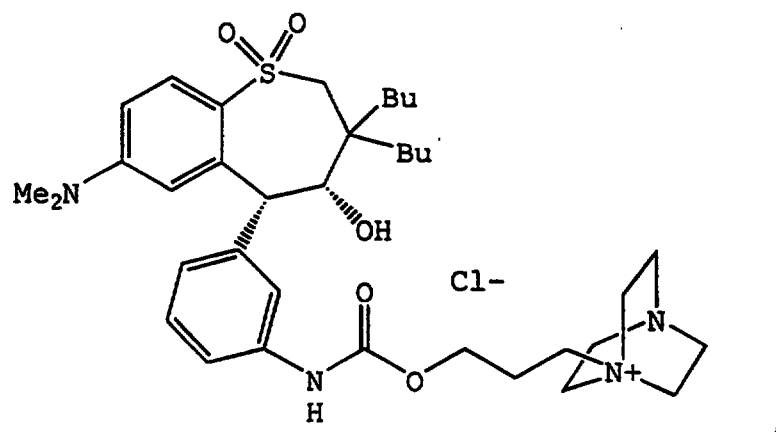
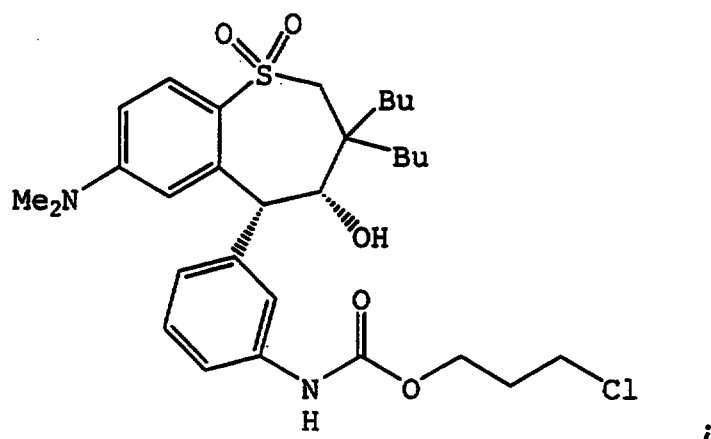
276



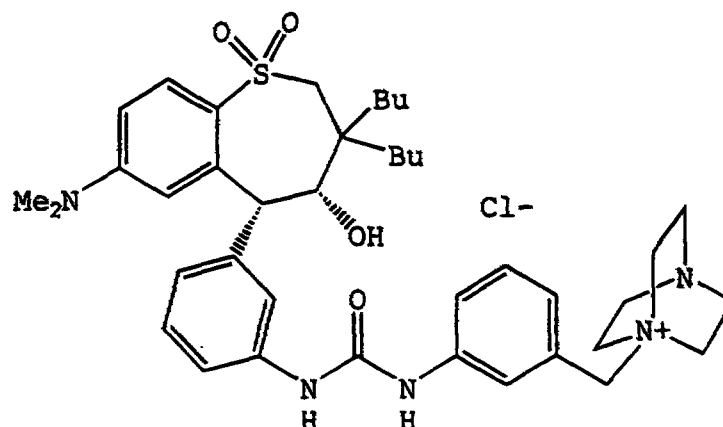
277



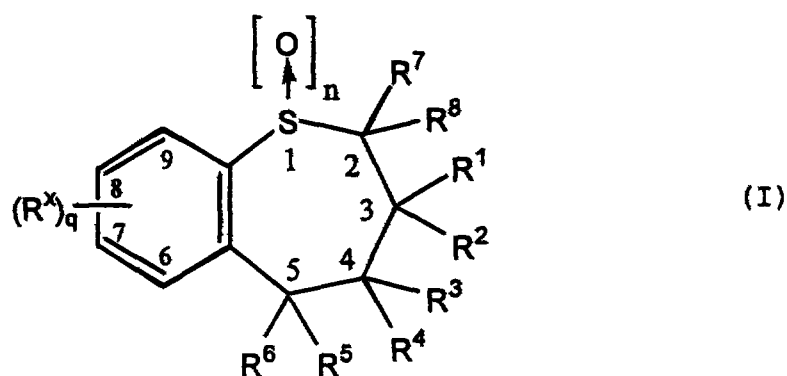
278



279



22. A compound of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 ,



$S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, alkoxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon



atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more OR^{13b} ,

wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13b} is substituted with one or more groups selected from the group consisting of carboxyalkyl, heterocycle, heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, or guanidiny, and

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,



wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl,



* C L H S *

heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyll, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM ,



$\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , OR^{18} , $\text{S}(\text{O})\text{NR}^{18}$, $\text{NR}^{13}\text{R}^{18}$, $\text{NR}^{18}\text{OR}^{14}$, $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{C}(\text{O})\text{OM}$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_3R^9 , SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, and $\text{C}(\text{O})\text{OM}$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^{13}\text{A}^-$, PR^{13} , $\text{P}(\text{O})\text{R}^{13}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S,



* C L M S *

SO, SO₂, S⁺R⁹A⁻, PR⁹, P⁺R⁹R¹⁰A⁻, or P(O)R⁹;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, P(O)R¹³R¹⁴, P⁺R¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

23. A compound of claim 22 wherein:

R⁵ is phenyl substituted with OR^{13b};

R^{13b} is independently selected from the group consisting of alkyl, quaternary heteroarylalkyl, and quaternary heterocyclalkyl; and

R^{13b} is substituted with one or more groups selected from the group consisting of heterocycle, heteroaryl, and guanidinyll.

24. A compound of claim 22 wherein n is 1 or 2.

25. A compound of claim 22 wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen and alkyl.

26. A compound of claim 22 wherein R⁷ and R⁸ are hydrogen.

27. A compound of claim 22 wherein R³ and R⁴ are independently selected from the group consisting of



hydrogen and OR⁹.

28. A compound of claim 22 wherein R³ is hydrogen and R⁴ is hydroxy.

29. A compound of claim 22 wherein one or more R^x are independently selected from the group consisting of OR¹³ and NR¹³R¹⁴.

30. A compound of claim 22 wherein one or more R^x are independently selected from methoxy and dimethylamino.

31. A compound of claim 22 wherein R¹ and R² are independently selected from the group consisting of hydrogen and alkyl.

32. A compound of claim 22 wherein R¹ and R² are independently selected from the group consisting alkyl.

33. A compound of claim 22 wherein R¹ and R² are the same alkyl.

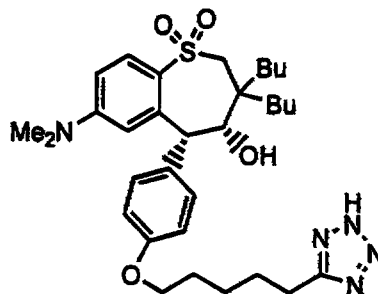
34. A compound of claim 22 wherein R¹ and R² are each n-butyl.

35. A compound of claim 22 wherein
n is 1 or 2;
R¹ and R² are n-butyl;
R³ and R⁶ are hydrogen;
R⁴ is hydroxy;
R⁷ and R⁸ are hydrogen; and
one or more R^x are independently selected from methoxy and dimethylamino.

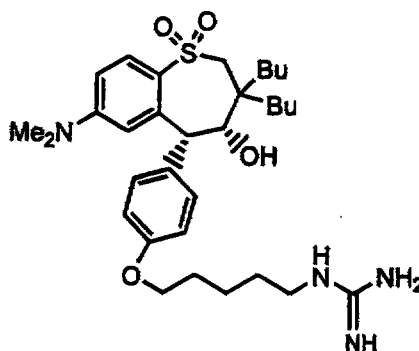


287

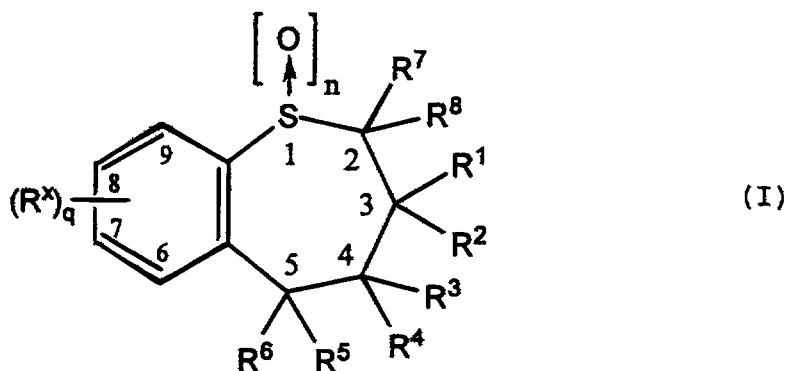
36. A compound of claim 22 having the structural formula:



37. A compound of claim 22 having the structural formula:



38. A compound of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;



R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, alkoxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,



wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more OR^{13b} ,

wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkoxyalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13b} is substituted with one or more groups selected from the group consisting of OR^{9a} , $NR^{9a}R^{10}$, $N^+R^{9a}R^{11}R^{12}A^-$, SR^{9a} , $S(O)R^{9a}$, SO_2R^{9a} , SO_3R^{9a} , CO_2R^{9a} , $CONR^{9a}R^{10}$, $SO_2NR^{9a}R^{10}$, $P^+R^{9a}R^{10}R^{11}A^-$, and $S^+R^{9a}R^{10}A^-$,

wherein A^- is an pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation, and

wherein R^{9a} is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, and carboxyalkylaminoalkyl;



* C L M S *

can optionally have one or more carbons replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 , $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidinyl, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals



selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN , halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and



wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^X , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, or

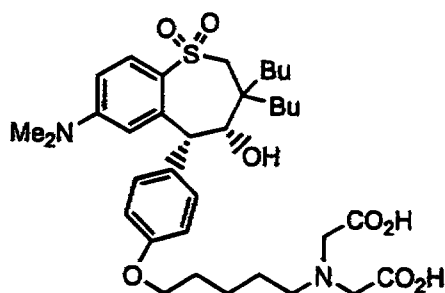
a pharmaceutically acceptable salt, solvate, or prodrug thereof.



39. A compound of claim 38 wherein:
R⁵ is phenyl substituted with OR^{13b};
R^{13b} is selected from the group consisting of alkyl and alkoxyalkyl; and
R^{13b} is substituted with one or more groups selected from the group consisting of OR^{9a} and NR^{9a}R¹⁰; and
R^{9a} is selected from the group consisting of carboxyalkyl, carboxyheteroaryl, and carboxyheterocycle; and
R¹⁰ is carboxyalkyl.
40. A compound of claim 38 wherein n is 1 or 2.
41. A compound of claim 38 wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen and alkyl.
42. A compound of claim 38 wherein R⁷ and R⁸ are hydrogen.
43. A compound of claim 38 wherein R³ and R⁴ are independently selected from the group consisting of hydrogen and OR⁹.
44. A compound of claim 38 wherein R³ is hydrogen and R⁴ is hydroxy.
45. A compound of claim 38 wherein one or more R^x are independently selected from the group consisting of OR¹³ and NR¹³R¹⁴.
46. A compound of claim 38 wherein one or more R^x are independently selected from methoxy and dimethylamino.

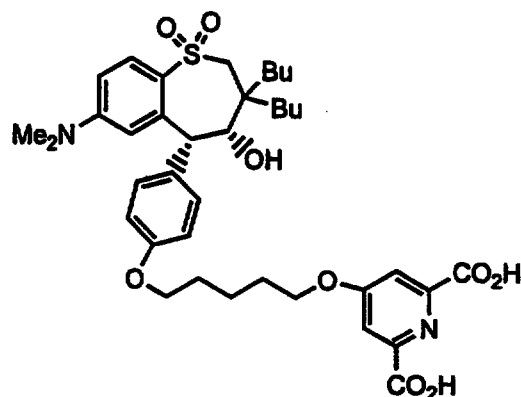


47. A compound of claim 38 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl.
48. A compound of claim 38 wherein R^1 and R^2 are independently selected from the group consisting alkyl.
49. A compound of claim 38 wherein R^1 and R^2 are the same alkyl.
50. A compound of claim 38 wherein R^1 and R^2 are each n-butyl.
51. A compound of claim 38 wherein
n is 1 or 2;
 R^1 and R^2 are n-butyl;
 R^3 and R^6 are hydrogen;
 R^4 is hydroxy;
 R^7 and R^8 are hydrogen; and
one or more R^x are independently selected from methoxy and dimethylamino.
52. A compound of claim 38 having the structural formula:

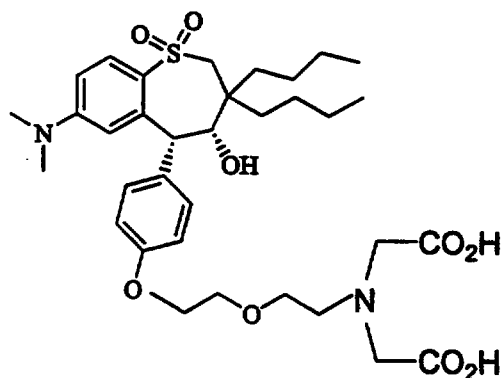


296

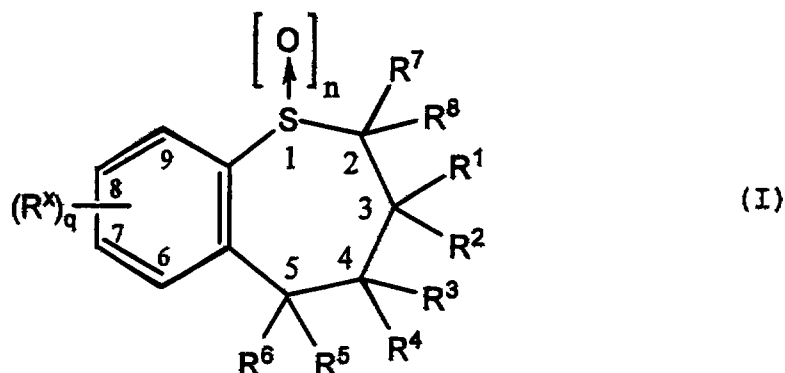
53. A compound of claim 38 having the structural formula:



54. A compound of claim 38 having the structural formula:



55. A compound of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl,



carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more OR^{13b} ,

wherein R^{13b} is selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13b} is substituted with one or more groups selected



* C L M S *

from the group consisting of

carboxyalkylheterocyclylthio, $\text{NR}^9\text{R}^{10a}$, $\text{CONR}^9\text{R}^{10a}$,
 $\text{SO}_2\text{NR}^9\text{R}^{10a}$, $\text{P}^+\text{R}^9\text{R}^{10a}\text{R}^{11}\text{A}^-$, and $\text{S}^+\text{R}^9\text{R}^{10a}\text{A}^-$,

wherein A^- is a pharmaceutically acceptable anion
 and M is a pharmaceutically acceptable cation,

wherein R^{10a} is selected from the group consisting
 of carboxyalkyl, carboalkoxyalkyl, carboxyalkylamino,
 heteroarylalkyl, and heterocyclylalkyl; or

R^6 is selected from the group consisting of H,
 alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle,
 quaternary heterocycle, OR^{30} , SR^9 , S(O)R^9 , SO_2R^9 , and
 SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,
 heterocycle, quaternary heterocycle, and quaternary
 heteroaryl can be substituted with one or more
 substituent groups independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, polyalkyl,
 polyether, aryl, haloalkyl, cycloalkyl, heterocycle,
 arylalkyl, quaternary heterocycle, quaternary heteroaryl,
 halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , S(O)R^{13} , SO_2R^{13} ,
 SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN , OM ,
 SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C(O)NR}^{13}\text{R}^{14}$, C(O)OM , COR^{13} , $\text{NR}^{13}\text{C(O)R}^{14}$,
 $\text{NR}^{13}\text{C(O)NR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{CO}_2\text{R}^{14}$, OC(O)R^{13} , $\text{OC(O)NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{SOR}^{14}$,
 $\text{NR}^{13}\text{SO}_2\text{R}^{14}$, $\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $\text{P(O)R}^{13}\text{R}^{14}$,
 $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P(OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,
 wherein:

A^- is a pharmaceutically acceptable anion and M is a
 pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether,
 aryl, haloalkyl, cycloalkyl, and heterocycle can be



further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo , $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidinyl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$,



SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM ,
 $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and
 $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from
the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which
they are attached form a mono- or polycyclic heterocycle
that is optionally substituted with one or more radicals
selected from the group consisting of oxo, carboxy and
quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to
which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl,
alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,
ammoniumalkyl, alkylammoniumalkyl, arylalkyl,
carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,
carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl,
heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group
consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the
group consisting of H, alkyl, alkenyl, alkynyl,
polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl,
cycloalkyl, heterocycle, heteroaryl, polyether,
quaternary heterocycle, quaternary heteroaryl, OR^{13} ,
 $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, $\text{S}(\text{O})_2\text{R}^{13}$, SO_3R^{13} , $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$,
 $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM ,
 $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{OM}$,
 COR^{13} , OR^{18} , $\text{S}(\text{O})_n\text{NR}^{18}$, $\text{NR}^{13}\text{R}^{18}$, $\text{NR}^{18}\text{OR}^{14}$, $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,
 $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, amino acid, peptide, polypeptide, and



carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^X , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,



* C L M S *

alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

56. A compound of claim 55 wherein:

R^5 is phenyl substituted with OR^{13b} ;

R^{13b} is alkyl; and

R^{13b} is substituted with carboxyalkylheterocyclylthio or NR^9R^{10a} ; and

R^9 is hydrogen; and

R^{10} is heteroarylalkyl.

57. A compound of claim 55 wherein n is 1 or 2.

58. A compound of claim 55 wherein R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl.

59. A compound of claim 55 wherein R^7 and R^8 are hydrogen.

60. A compound of claim 55 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 .

61. A compound of claim 55 wherein R^3 is hydrogen and R^4 is hydroxy.



* C L M S *

62. A compound of claim 55 wherein one or more R^x are independently selected from the group consisting of OR^{13} and $NR^{13}R^{14}$.

63. A compound of claim 55 wherein one or more R^x are independently selected from methoxy and dimethylamino.

64. A compound of claim 55 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl.

65. A compound of claim 55 wherein R^1 and R^2 are independently selected from the group consisting alkyl.

66. A compound of claim 55 wherein R^1 and R^2 are the same alkyl.

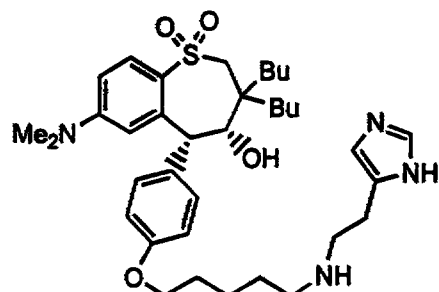
67. A compound of claim 55 wherein R^1 and R^2 are each n-butyl.

68. A compound of claim 55 wherein
n is 1 or 2;
 R^1 and R^2 are n-butyl;
 R^3 and R^6 are hydrogen;
 R^4 is hydroxy;
 R^7 and R^8 are hydrogen; and
one or more R^x are independently selected from methoxy and dimethylamino.

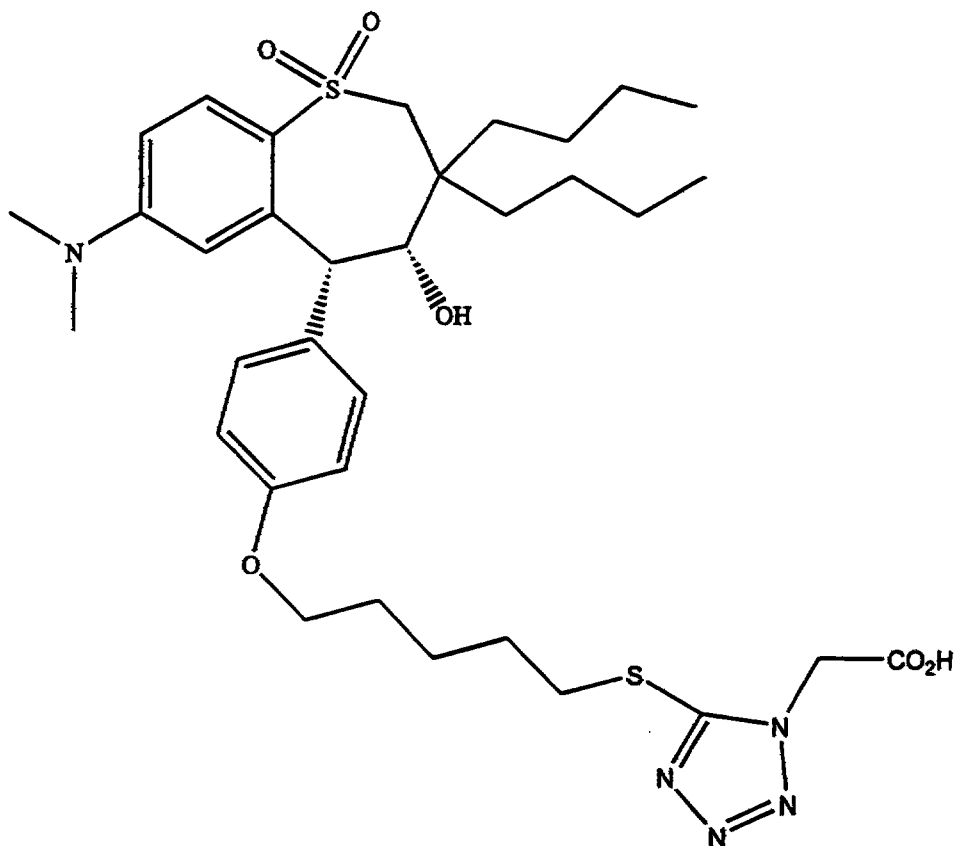


* C L M S *

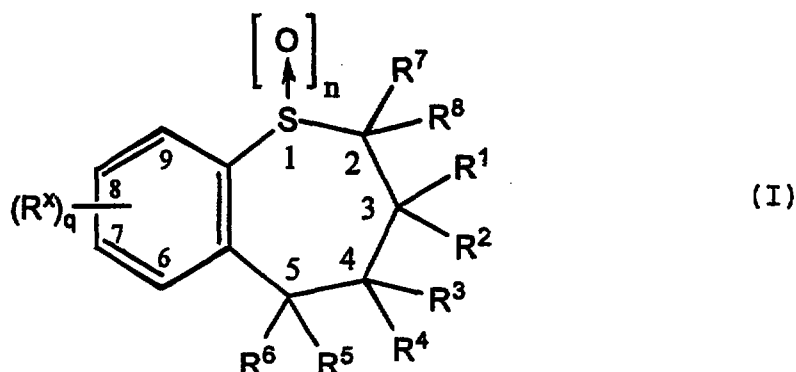
69. A compound of claim 55 having the structural formula:



70. A compound of claim 55 having the structural formula:



71. A compound of formula (I):



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^WA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl,



carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is aryl substituted with one or more substituent groups independently selected from the group consisting of $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, and $NR^{13}SO_2NR^{14}R^{15}$,

wherein:

R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,



alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M ; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,



heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,



alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl,



* C L M S *

carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group



consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^X , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

72. A compound of claim 71 wherein R^5 is aryl substituted with a radical selected from the group consisting of $NR^{13}C(O)NR^{14}R^{15}$ and $NR^{13}CO_2R^{14}$.

73. A compound of claim 71 wherein R^5 is phenyl substituted with a radical selected from the group



consisting of $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$ and $\text{NR}^{13}\text{CO}_2\text{R}^{14}$.

74. A compound of claim 71 wherein n is 1 or 2.

75. A compound of claim 71 wherein R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl.

76. A compound of claim 71 wherein R^7 and R^8 are hydrogen.

77. A compound of claim 71 wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 .

78. A compound of claim 71 wherein R^3 is hydrogen and R^4 is hydroxy.

79. A compound of claim 71 wherein one or more R^x are independently selected from the group consisting of OR^{13} and $\text{NR}^{13}\text{R}^{14}$.

80. A compound of claim 71 wherein one or more R^x are independently selected from methoxy and dimethylamino.

81. A compound of claim 71 wherein R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl.

82. A compound of claim 71 wherein R^1 and R^2 are independently selected from the group consisting alkyl.

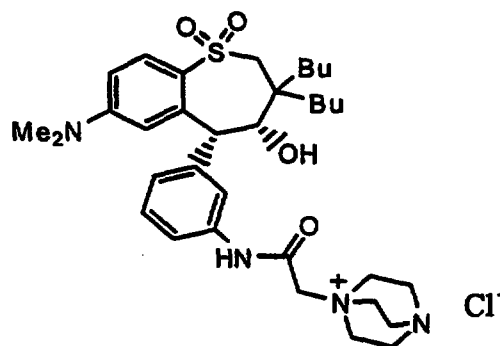


83. A compound of claim 71 wherein R^1 and R^2 are the same alkyl.

84. A compound of claim 71 wherein R^1 and R^2 are each n-butyl.

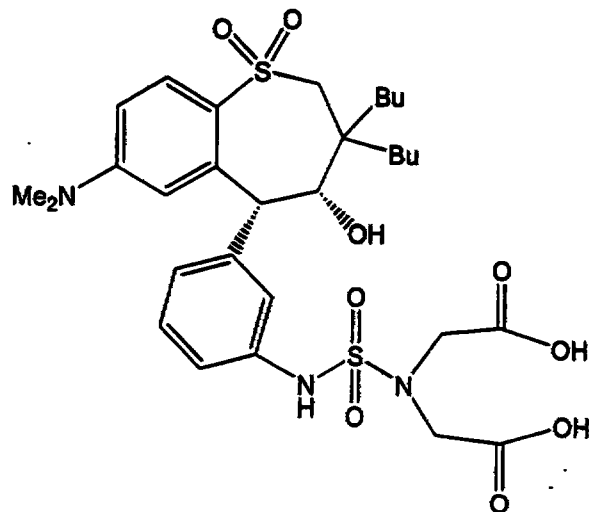
85. A compound of claim 71 wherein
n is 1 or 2;
 R^1 and R^2 are n-butyl;
 R^3 and R^6 are hydrogen;
 R^4 is hydroxy;
 R^7 and R^8 are hydrogen; and
one or more R^x are independently selected from methoxy and dimethylamino.

86. Compound of claim 71 having the structural formula:

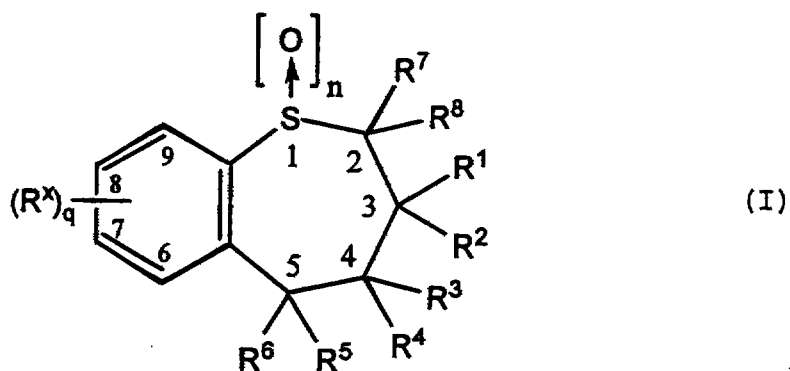


315

87. A compound of claim 71 having the structural formula:



88. A compound of formula I:



wherein:

q is 1 or 2;

n is 2;

R^1 and R^2 are each alkyl;

R^3 is hydroxy;

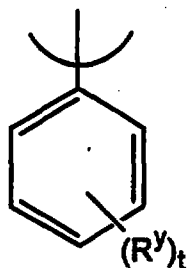
R^4 and R^6 are hydrogen;

R^5 has the formula (II)

1



316



(II)

wherein t is an integer from 0 to 5;

one or more R^y are OR^{13} ;

R^{13} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, aryl, arylalkyl, alkylarylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, quaternary heteroarylalkyl, and alkoxyalkyl;

said R^{13} alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl groups optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide;

R^{13} is optionally substituted with one or more groups selected from the group consisting of sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein A^- is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation,

R^9 and R^{10} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, and alkylammoniumalkyl;

R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl,



arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH; or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and

R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M;

R^7 and R^8 are hydrogen; and

one or more R^* are independently selected from the group consisting of alkoxy, alkylamino and dialkylamino; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

89. A compound of claim 88 wherein R^1 and R^2 are each n-butyl.

90. A compound of claim 89 wherein t is 1, R^y is OR^{13} , and R^{13} is as defined in claim 88.

91. A compound of claim 90 wherein one or more R^* are independently selected from methoxy and dimethylamino.

92. A compound of claim 90 wherein R^* is dimethylamino.

93. A compound of claim 90 wherein:

t is 1;

R^y is para- OR^{13} ; and



94. A compound of claim 90 wherein:

t is 1;

R^y is meta-OR¹³; and

R¹³ is as defined in claim 88.

95. A compound of claim 90 having the 4R,5R configuration.

96. A pharmaceutical composition comprising an anti-hyperlipidemic condition effective amount of a compound of any one of claims 1 to 95, and a pharmaceutically acceptable carrier.

97. A pharmaceutical composition comprising an anti-atherosclerotic effective amount of a compound of any one of claims 1 to 95, and a pharmaceutically acceptable carrier.

98. A pharmaceutical composition comprising an anti-hypercholesterolemia effective amount of a compound of any one of claims 1 to 95, and a pharmaceutically acceptable carrier.

99. A method for the prophylaxis or treatment of a hyperlipidemic condition comprising administering to a patient in need thereof a composition of claim 96 in unit dosage form.

100. A method for the prophylaxis or treatment of an atherosclerotic condition comprising administering to a patient in need thereof a composition of claim 97 unit dosage form.

101. A method for the prophylaxis or treatment of hypercholesterolemia comprising administering to a



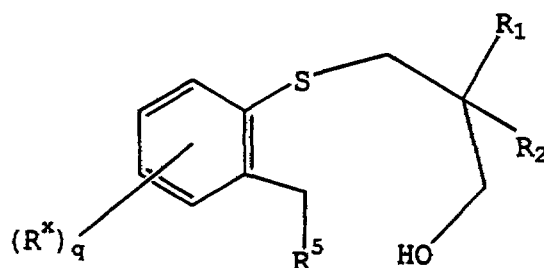
patient in need thereof a composition of claim 98 in unit dosage form.

102. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of a hyperlipidemic condition.

103. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of an atherosclerotic condition.

104. Use of a compound of any one of claims 1 to 95 in the preparation of a medicament for use in the prophylaxis or treatment of hypercholesterolemia condition.

105. A process for the preparation of a compound having the formula:



106. XLI

comprising:

treating a thiophenol with an abstracting agent;
coupling the thiophenyl and a cyclic sulfate to form an intermediate comprising a sulfate group; and
removing the sulfate group of the intermediate to form the compound of formula XLI;
wherein



q is an integer from 1 to 4;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^+A^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 ,

$N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^+ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 is hydroxy;

R^4 is hydrogen;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more



substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary



heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, carboxyalkylheterocyclthio, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,



carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are hydrogen; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

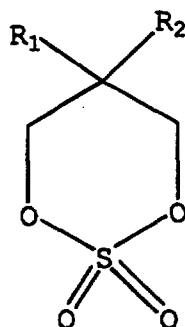
wherein in said polyalkyl, phenylene, amino acid,



peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

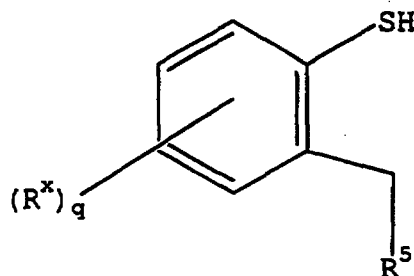
wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{13}\text{R}^{12}\text{A}^-$.

106. The process of claim 105 wherein the cyclic sulfate has the formula:



XL

and the thiophenol has the formula:



XVIII A

wherein R^1 , R^2 , R^5 , R^x and q are as defined in claim



105.

107. The process of claim 105 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

108. The process of claim 107 wherein the hydrolyzing agent is a mineral acid.

109. The process of claim 107 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

110. The process of claim 106 wherein the abstracting agent is a base having a pH of at least about 10.

111. The process of claim 106 wherein the abstracting agent is an alkali metal hydride.

112. The process of claim 106 wherein the abstracting agent is sodium hydride.

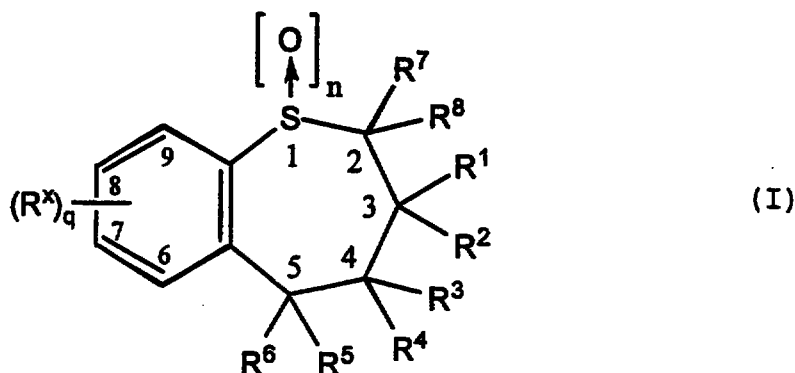
113 The process of claim 106 wherein R^1 and R^2 are independently selected from alkyl.

114. The process of claim 106 wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

115. The process of claim 106 wherein R^1 and R^2 are n-butyl.



116. A process for the preparation of a compound having the formula I:



comprising:

reacting a cyclic sulfate with a thiophenol to form an alcohol;

oxidizing said alcohol to form a sulfone-aldehyde;

and

cyclizing said sulfone-aldehyde to form the compound of formula I;

wherein:

q is an integer from 1 to 4;

n is 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R¹¹A⁻, SR⁹, S⁺R⁹R¹⁰A⁻, P⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹,



$N^+R^9R^{10}A^-$, S, SO, SO₂, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene, wherein R⁹, R¹⁰, and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R¹ and R² taken together with the carbon to which they are attached form C₃-C₁₀ cycloalkyl;

R³ is hydroxy;

R⁴ is hydrogen;

R⁵ and R⁶ are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR³⁰, SR⁹, S(O)R⁹, SO₂R⁹, and SO₃R⁹,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, NR¹³C(O)R¹⁴, NR¹³C(O)NR¹⁴R¹⁵, NR¹³CO₂R¹⁴, OC(O)R¹³, OC(O)NR¹³R¹⁴, NR¹³SOR¹⁴, NR¹³SO₂R¹⁴, NR¹³SONR¹⁴R¹⁵, NR¹³SO₂NR¹⁴R¹⁵, P(O)R¹³R¹⁴, $P^+R^{13}R^{14}R^{15}A^-$, P(OR¹³)OR¹⁴, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, wherein:

A⁻ is a pharmaceutically acceptable anion and M is a



* C L M S *

pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary



heterocyclalkyl, quaternary heteroarylalkyl,
 guanidiny, carboxyalkylheterocyclalkylthio, OR^9 , NR^9R^{10} ,
 $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN,
 halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$,
 $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from
 the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which
 they are attached form a mono- or polycyclic heterocycle
 that is optionally substituted with one or more radicals
 selected from the group consisting of oxo, carboxy and
 quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to
 which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl,
 alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,
 ammoniumalkyl, alkylammoniumalkyl, arylalkyl,
 carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,
 carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl,
 heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are hydrogen; and

one or more R^x are independently selected from the
 group consisting of H, alkyl, alkenyl, alkynyl,
 polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl,
 cycloalkyl, heterocycle, heteroaryl, polyether,
 quaternary heterocycle, quaternary heteroaryl, OR^{13} ,
 $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$,
 $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$,
 $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$,
 $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid,
 peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl,



polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

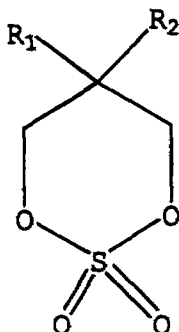
wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$.

117. The process of claim 116 wherein the cyclic sulfate has the formula:

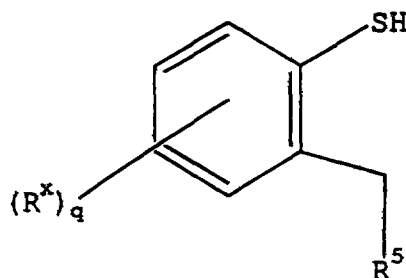


331



XL

and the thiophenol has the formula:



XVIII A

wherein R^1 , R^2 , R^5 , R^* and q are as defined in claim 116.

118. The process of claim 117 wherein R^1 and R^2 are independently selected from alkyl.

119. The process of claim 117 wherein wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

120. The process of claim 117 wherein R^1 and R^2 are n-butyl.

121. The process of claim 117 wherein the alcohol is oxidized with an oxidizing agent to form an aldehyde.



122. The process of claim 121 wherein the aldehyde is oxidized with an oxidizing agent to form a sulfone-aldehyde.

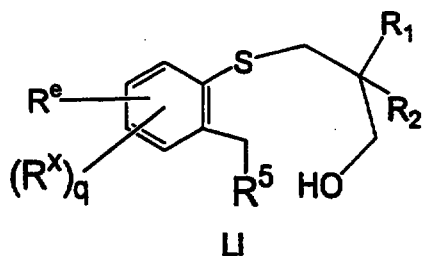
123. The process of claim 117 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9.

124. The process of claim 117 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is an alkali alkoxide base.

125. The process of claim 117 wherein the sulfone-aldehyde is cyclized with potassium tert-butoxide.

126. The process of claim 117 wherein the alcohol is oxidized with pyridinium chlorochromate to form an aldehyde; the aldehyde is oxidized with metachloroperbenzoic acid to form a sulfone-aldehyde; and the sulfone-aldehyde is cyclized with potassium tert-butoxide.

127. A process for the preparation of a compound having the formula LI:



comprising:

treating a halobenzene with an abstracting agent;
coupling the halobenzene and a cyclic sulfate to form an intermediate comprising a sulfate group; and



removing the sulfate group of the intermediate to form the compound of formula LI; wherein

q is an integer from 1 to 4;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 ,

$N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 is hydroxy;

R^4 is hydrogen;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl,



heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O , NR^7 , $N^+R^7R^8A^-$, S , SO , SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl,



alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl, wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, $\text{P}(\text{O})\text{R}^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, carboxyalkylheterocyclthio, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and $\text{C}(\text{O})\text{OM}$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle,



ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are hydrogen; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide,



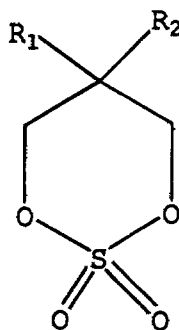
* C L M S *

polypeptide, carbohydrate, polyether, or polyalkyl, wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; and

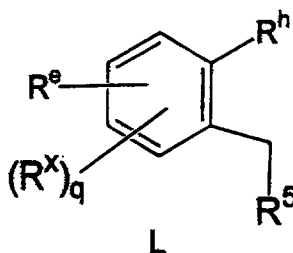
R^e is an electron-withdrawing group located at the para or ortho position.

128. The process of claim 127 wherein the cyclic sulfate has the formula:



XL

and the halobenzene has the formula:



wherein R^h is halogen, and R^1 , R^2 , R^5 , R^x , R^e and q are as defined in claim 127.

129. The process of claim 128 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

130. The process of claim 129 wherein the hydrolyzing agent is a mineral acid.

131. The process of claim 129 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

132. The process of claim 128 wherein the abstracting agent is a dialkali metal sulfide.

133. The process of claim 128 wherein the abstracting agent is dilithium sulfide.

134. The process of claim 128 wherein wherein R^1 and R^2 are independently selected from alkyl.

135. The process of claim 128 wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

136. The process of claim 128 wherein R^1 and R^2 are n-butyl.

137. The process of claim 128 wherein R^h is chloro.

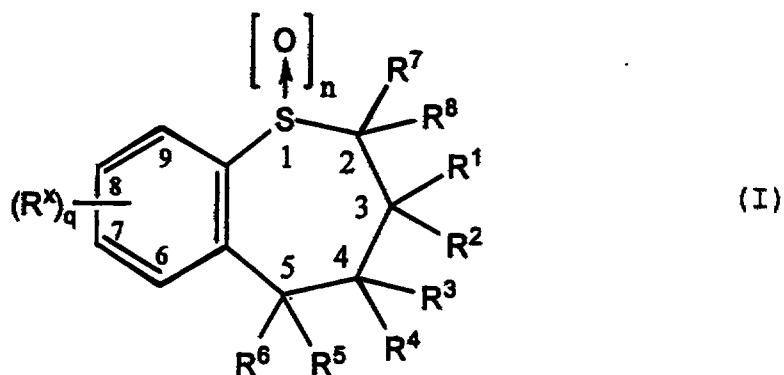
138. The process of claim 128 wherein R^e is p-nitro.

139. A process for the preparation of a compound



* C L H S *

having the formula I:



comprising:

reacting a cyclic sulfate with a halobenzene to form an alcohol;

oxidizing said alcohol to form a sulfone-aldehyde;

and

cyclizing said sulfone-aldehyde to form the compound of formula I;

wherein

q is an integer from 1 to 4;

n is 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR⁹, NR⁹R¹⁰, N⁺R⁹R¹⁰R^wA⁻, SR⁹, S⁺R⁹R¹⁰A⁻, P⁺R⁹R¹⁰R¹¹A⁻, S(O)R⁹, SO₂R⁹, SO₃R⁹, CO₂R⁹, CN, halogen, oxo, and CONR⁹R¹⁰,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR⁹,

N⁺R⁹R¹⁰A⁻, S, SO, SO₂, S⁺R⁹A⁻, P⁺R⁹R¹⁰A⁻, or phenylene, wherein R⁹, R¹⁰, and R^w are independently selected



from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, carboxyalkylaminoalkyl, heteroarylalkyl, heterocyclalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

R^3 is hydroxy;

R^4 is hydrogen;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^{30} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$, wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether,



aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, guanidiny, carboxyalkylheterocyclthio, OR^9 , NR^9R^{10} ,



$N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^{30} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; and

R^7 and R^8 are hydrogen; and

one or more R^* are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} ,



$N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, and alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

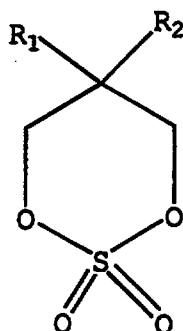
wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$; and

R^8 is an electron-withdrawing group located at the para or ortho position.

140. The process of claim 139 wherein the cyclic sulfate has the formula:

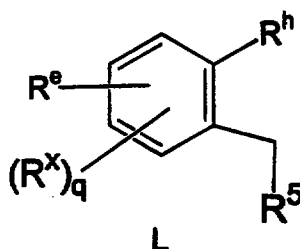


344



XL

and the halobenzene has the formula:



wherein R^1 , R^2 , R^5 , R^x and R^e are as defined in claim 139, and R^h is halogen.

141. The process of claim 140 wherein the sulfate group is removed by treating the intermediate with a hydrolyzing agent.

142. The process of claim 141 wherein the hydrolyzing agent is a mineral acid.

143. The process of claim 140 wherein the hydrolyzing agent is selected from the group consisting of hydrochloric acid and sulfuric acid.

144. The process of claim 140 wherein the abstracting agent is a dialkali metal sulfide.

145. The process of claim 140 wherein the abstracting agent is dilithium sulfide.



* C L M S *

146. The process of claim 140 wherein wherein R^1 and R^2 are independently selected from alkyl.

147. The process of claim 140 wherein R^1 and R^2 are independently selected from the group consisting of ethyl, n-butyl, iso-butyl and pentyl.

148. The process of claim 140 wherein R^1 and R^2 are n-butyl.

149. The process of claim 140 wherein R^h is chloro.

150. The process of claim 140 wherein R^e is p-nitro.

151. The process of claim 140 wherein the alcohol is oxidized with an oxidizing agent to form a sulfone.

152. The process of claim 140 wherein the sulfone is oxidized with an oxidizing agent to form a sulfone-aldehyde.

153. The process of claim 140 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is a base having a pH between about 8 to about 9.

154. The process of claim 140 wherein the sulfone-aldehyde is cyclized with a cyclizing agent that is an alkali alkoxide base.

155. The process of claim 140 wherein the sulfone-aldehyde is cyclized with potassium tert-butoxide.

156. The process of claim 140 wherein the alcohol is oxidized with metachloroperbenzoic acid to form a



346

sulfone; the aldehyde is oxidized with pyridinium chlorochromate to form a sulfone-aldehyde; and the sulfone-aldehyde is cyclized with potassium tert-butoxide.

