



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/33, 31/395, 31/445, 31/495, 31/505, 31/535, C07D 205/08, 211/32, 401/10, 401/12, 403/10, 403/12, 405/10, 405/12, 409/10, 409/12, 411/10, 411/12, 413/10, 413/12</p>	A1	<p>(11) International Publication Number: WO 95/04531</p> <p>(43) International Publication Date: 16 February 1995 (16.02.95)</p>
<p>(21) International Application Number: PCT/US94/08865</p> <p>(22) International Filing Date: 4 August 1994 (04.08.94)</p> <p>(30) Priority Data: 103,846 9 August 1993 (09.08.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 103,846 (CON) Filed on 9 August 1993 (09.08.93)</p> <p>(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): HARTMAN, George, D. [US/US]; 1529 Tennis Circle, Lansdale, PA 19446 (US). PRUGH, John, D. [US/US]; 16 Far View Road, Chalfont, PA 18914 (US). HALCZENKO, Wasył [US/US]; 1308 Sunny Ayr Way, Lansdale, PA 19446 (US). EGBERTSON,</p>		<p>Melissa [US/US]; 1232 Lois Road, Ambler, PA 19002 (US). IHLE, Nathan [US/US]; 2416 Rickert Road, Perkasie, PA 18944 (US).</p> <p>(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KR, KZ, LK, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).</p> <p>Published With international search report.</p>
<p>(54) Title: FIBRINOGEN RECEPTOR ANTAGONISTS</p> <div style="text-align: center; margin: 20px 0;"> <p>(I)</p> </div> <div style="text-align: center; margin: 20px 0;"> <p>(a)</p> </div> <p>(57) Abstract</p> <p>Fibrinogen receptor antagonists having formula (I) for example formula (a).</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTION
FIBRINOGEN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

5 The invention relates generally to modulating cell adhesion and to inhibiting the binding of fibrinogen and other proteins to blood platelets, and inhibiting the aggregation of blood platelets. Fibrinogen is a glycoprotein present in blood plasma that participates in platelet aggregation and in fibrin formation. Platelets
10 are cell-like anucleated fragments, found in the blood of all mammals, that also participate in blood coagulation. Interaction of fibrinogen with the IIb/IIIa receptor site is known to be essential for normal platelet function.

 When a blood vessel is damaged by an injury or other
15 causative factor, platelets adhere to the disrupted subendothelial surface. The adherent platelets subsequently release biologically active constituents and aggregate. Aggregation is initiated by the binding of agonists, such as thrombin, epinephrine, or ADP to specific platelet membrane receptors. Stimulation by agonists results
20 in exposure of latent fibrinogen receptors on the platelet surface, and binding of fibrinogen to the glycoprotein IIb/IIIa receptor complex.

 Attempts have been made to use natural products and synthetic peptides to determine the mechanism of adhesion and platelet aggregation. For example, Rouslahti and Pierschbacher in
25 Science, 238, 491-497 (1987), describe adhesive proteins such as fibronectin, vitronectin, osteopontin, collagens, thrombospondin, fibrinogen, and von Willebrand factor that are present in extracellular matrices and in blood. The proteins contain the tripeptide sequence arginine-glycine-aspartic acid (RGD) as a
30 glycoprotein IIb/IIIa recognition site. These arginine-glycine-aspartic acid containing proteins are recognized by at least one member of a family of structurally related receptors, integrins, which are heterodimeric proteins with two membrane-spanning subunits. The authors state that the conformation of the tripeptide

- 2 -

sequence in the individual proteins may be critical to recognition specificity.

Cheresh in Proc. Nat'l Acad. Sci. U.S.A., 84, 6471-6475, (1987), describes an Arg-Gly-Asp directed adhesion receptor
5 expressed by human endothelial cells that is structurally similar to the IIb/IIIa complex on platelets but is antigenically and functionally distinct. This receptor is directly involved in endothelial cell attachment to fibrinogen, von Willebrand factor, and vitronectin.

Pierschbacher and Rouslahti, in J. of Biol. Chem., 262,
10 (36), 17294-17298 (1987) hypothesized that the Arg-Gly-Asp sequence alone would be a sufficient signal for receptor recognition and binding and that, therefore, the conformation of the tri-peptide sequence would be determinative. Various synthetic peptides were produced and the authors concluded that the stereochemical
15 conformation of Arg-Gly-Asp as influenced by enantiomeric substitutions or additions to this sequence significantly influenced receptor-ligand interaction. The authors further showed that cyclization of a decapeptide by forming a disulfide bridge between non-terminal residues Pen and Cys, rendered the peptide much less
20 effective at inhibiting attachment to fibronectin.

In Proc. Nat'l Acad. Sci. U.S.A., 81, 5985-5988 (1984), the same authors describe tetrapeptide variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Peptides having a tetrapeptide recognition site are described in U.S.
25 Pat. Nos. 4,589,881 and 4,614,517. A number of large polypeptide fragments in the cell-binding domain of fibronectin have cell-attachment activity. For example, see U.S. Pat. Nos. 4,517,686, 4,661,111 and U.S. Pat. No. 4,578,079. Ruggeri et al., Proc. Nat'l Acad. Sci. U.S.A., 83, 5708-5712 (1986) explore a series of
30 synthetic peptides designed in lengths to 16 residues, that contain RGD and a valine attached to the aspartic acid residue of RGD that inhibit fibrinogen binding to platelets. See also Koczewiak et al., Biochem. 23, 1767-1774 (1984); Ginsberg et al., J. Biol. Chem. 260(7), 3931-3936 (1985); and Haverstick et al., Blood 66(4), 946-

- 3 -

952 (1985). Other inhibitors are disclosed in Eur. Pat. App. Nos. 275,748 and 298,820.

A number of low molecular weight polypeptide factors have been isolated from snake venom. These factors apparently have high affinity for the gpIIb/IIIa complex. For example, Huang et al., J. Biol Chem., 262, 16157-16163 (1987); Huang et al., Biochemistry 28, 661-666 (1989) describe the primary structure of the venom trigramin which is a 72 amino acid polypeptide that contains the RGD subunit. Echistatin is another venom which has high affinity for the gpIIb/IIIa complex. This polypeptide contains 49 amino acids and has the RGD subunit and various disulfide bridges. Gan et al., J. Biol. Chem., 263, 19827-19832 (1988). See also, Dennis et al., Proc. Nat'l Acad. Sci. USA, 87, 2471-2475 (1989). However, these snake venom factors also have high affinity for other members of the adhesive protein receptor family including the vitronectin and fibronectin receptors so are not selective for the gpIIb/IIIa complex.

While it is known that the tripeptide sequence Arg-Gly-Asp is present in certain polypeptides that can duplicate or inhibit the cell attachment-promoting effects of fibronectin and vitronectin, the tri-peptide Arg-Gly-Asp has low activity. At present, there is little understanding of how other amino acids coupled to this sequence influence binding specificity. U.S. Pat. No 5,023,233, assigned to Merck & Co., Inc., discloses small cyclic hexapeptides which contain the sequence Arg-Gly-Asp and are useful platelet aggregation inhibitors. U.S. Pat. No. 5,037,808 discloses the use of indolyl platelet-aggregation inhibitors which are believed to act by antagonizing interactions between fibrinogen and/or extracellular matrix proteins and the platelet gpIIb/IIIa receptor. U.S. Pat. No. 5,037,808 discloses guanidino peptide mimetic compounds that retain an Asp residue which inhibit platelet aggregation. The application PCT/US90/02746 describes the use of antibody-polypeptide conjugates wherein said polypeptides contain the Arg-Gly-Asp (RGD) sequence.

- 4 -

The application PCT/US91/00564 discloses the use of large cyclic peptides containing RGD flanked by proline residues which are platelet aggregation inhibitors. The application PCT/US90/03788 discloses small cyclic platelet aggregation inhibitors which are synthetic cyclic pentapeptides containing the tripeptide sequence Arg-Gly-Asp and a thioether linkage in the cycle. The application PCT/US90/05367 published May 2, 1991 also discloses the use of peptides and pseudopeptides such as N-amidino-piperidine-3-carboxylglycyl-L-aspartyl-L-valine that inhibit platelet aggregation and thrombus formation in mammalian blood. The application Eur. Pat. App. No. 91103462.7 discloses linear compounds which can include internal piperazinyl or piperidinyl derivatives. Eur. Pat. App. No. 91300179.8, assigned to Merck & Co., Inc., and published on July 17, 1991 discloses linear polypeptide fibrinogen receptor antagonists. Eur. Pat. App. No. 90101404.3 discloses compounds of the $R^1-A-(W)_a-X-(CH_2)_b-(Y)_c-B-Z-COOR$ wherein R^1 is a guandidino or amidino moiety and A and B are chosen from specific monosubstituted aryl or heterocyclic moieties.

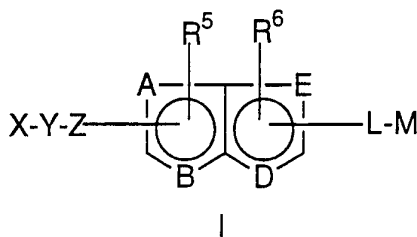
The present invention provides novel fibrinogen receptor antagonists that have significant platelet aggregation inhibitory activity which is useful for prevention of blood clot formation.. A number of very serious diseases and disorders involve hyperthrombotic complications which lead to intravascular thrombi and emboli. Myocardial infarction, stroke, phlebitis and a number of other serious conditions create the need for novel and effective fibrinogen receptor antagonists.

30

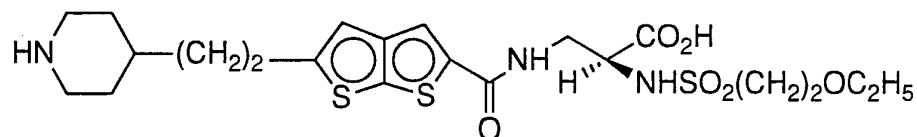
- 5 -

SUMMARY OF THE INVENTION

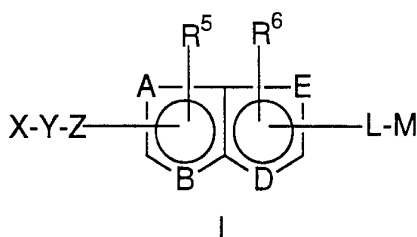
The invention is a fibrinogen receptor antagonist of the formula:



10 for example

DETAILED DESCRIPTION OF THE INVENTION

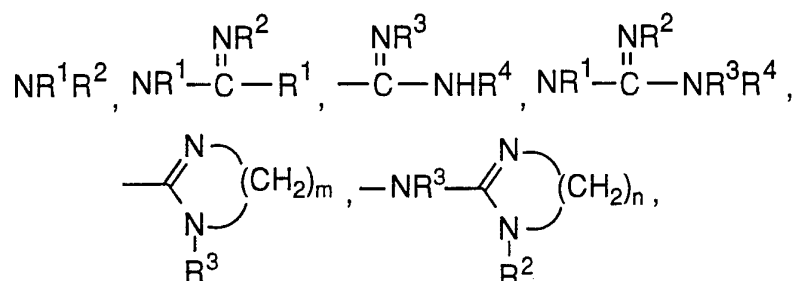
20 This invention pertains to compounds of the general formula I



30 and the pharmaceutically acceptable salts thereof wherein: A, B, D and E are independently selected from C, N, O and S and wherein:

- 6 -

X is



or a 4- to 10- membered mono- or polycyclic aromatic
 or nonaromatic ring system containing 0, 1, 2, 3 or 4
 heteroatoms selected from N, O and S and either
 unsubstituted or substituted with R¹, R², R³ or R⁴,
 wherein R¹, R², R³ and R⁴ are independently selected
 from the group consisting of hydrogen,
 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 oxo,
 thio,
 amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl,
 C₁-6 alkylamino C₀-8 alkyl,
 C₁-6 dialkylamino C₀-8 alkyl,
 C₁-4 alkoxy C₀-6 alkyl,
 carboxy C₀-6 alkyl, C₁-3 alkoxy carbonyl C₀-6 alkyl,
 carboxy C₀-6 alkyloxy, or
 hydroxy C₀-6 alkyl, where m and n are integers
 independently chosen from 2-5;

Y is

C₀-8 alkyl, C₀-8 alkyl (C₄-10 cycloalkyl),
 C₀-8 alkyl-NR³-CO-C₀-8 alkyl,
 C₀-8 alkyl-CONR³-C₀-8 alkyl,
 C₀-8 alkyl-O-C₀-8 alkyl,
 C₀-8 alkyl-S(O_n)-C₀-8 alkyl, or
 C₀-8 alkyl-SO₂-NR³-C₀-8 alkyl-,
 C₀-8 alkyl-NR³-SO₂-C₀-8 alkyl-,

- 7 -

C₀₋₈ alkyl-CO-C₀₋₈ alkyl,(CH₂)₀₋₆ aryl(CH₂)₀₋₆,
$$(CH_2)_{0-6} \text{ aryl} - \overset{\text{O}}{\parallel} \text{C} - (CH_2)_{0-6}, \text{ or}$$

5

$$(CH_2)_{0-6} \text{ aryl} - \overset{\text{O}}{\parallel} \text{C} - \text{NH} - (CH_2)_{0-6};$$

Z and L are independently chosen from

10

$$(CH_2)_m \overset{\text{O}}{\parallel} \text{CNR}^3 (CH_2)_n, (CH_2)_m \text{NR}^3 \overset{\text{O}}{\parallel} \text{C} (CH_2)_n, (CH_2)_m \text{NR}^3 (CH_2)_n$$

15

$$(CH_2)_m \overset{\text{O}}{\parallel} \text{C} (CH_2)_n, (CH_2)_m \overset{\text{S}}{\parallel} \text{C} (CH_2)_n, (CH_2)_m \text{SO}_2 (CH_2)_n,$$
(CH₂)_mS(CH₂)_n, (CH₂)_mSO(CH₂)_n,(CH₂)_mSO₂NR³(CH₂)_n,

20

(CH₂)_mNR³SO₂(CH₂)_n, (CH₂)_mCR³=CR⁴(CH₂)_n,(CH₂)_mC≡C(CH₂)_n, (CH₂)_m, and (CH₂)_mO(CH₂)_n.

where m and n are integers independently chosen from 0-6;

25 R⁵ and R⁶ are independently chosen from:

hydrogen,

C₁₋₆ alkyl,C₀₋₆ alkylcarboxy C₀₋₆ alkyl,C₀₋₆ alkyloxy C₀₋₆ alkyl,

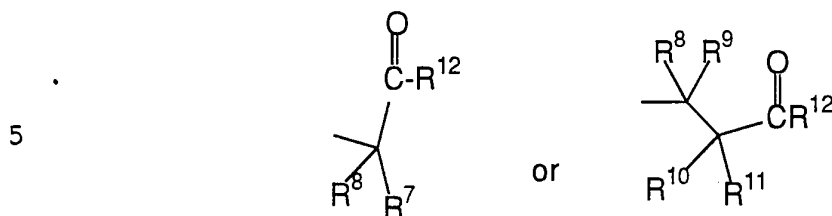
30

hydroxy C₀₋₆ alkyl,aryl C₀₋₆ alkyl, and

halogen;

- 8 -

M is:



wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from:

- 10 hydrogen, fluorine,
 C₁-8 alkyl, hydroxyl, hydroxy C₁-6 alkyl, carboxy C₀-6
 alkyl, C₁-6 alkyloxy, aryl C₀-6 alkyloxy, C₁-6
 alkylcarbonyl, aryl C₀-6
 alkylcarbonyl, C₁-6 alkylcarbonyloxy, aryl C₀-6
 15 alkylcarbonyloxy, C₁-6 alkylaminocarbonyloxy C₀-6
 alkyl,
 C₃-8 cycloalkyl,
 aryl C₀-6 alkyl,
 C₀-6 alkylamino C₀-6 alkyl,
 20 C₀-6 dialkylamino C₀-6 alkyl,
 C₁-8 alkylsulfonylamino C₀-6 alkyl,
 aryl C₀-6 alkylsulfonylamino C₀-6 alkyl,
 C₁-8 alkyloxycarbonylamino C₀-8-alkyl,
 aryl C₀-8 alkyloxycarbonylamino C₀-8 alkyl,
 25 C₁-8 alkylcarbonylamino C₀-6 alkyl,
 aryl C₀-6 alkylcarbonylamino C₀-6 alkyl,
 C₀-8 alkylaminocarbonylamino C₀-6 alkyl,
 aryl C₀-8 alkylaminocarbonylamino C₀-6 alkyl,
 C₀-8 alkylaminosulfonylamino C₀-6 alkyl,
 30 aryl C₀-8 alkylaminosulfonylamino C₀-6 alkyl,
 C₁-6 alkylsulfonyl C₀-6 alkyl,
 aryl C₀-6 alkylsulfonyl C₀-6 alkyl,
 C₁-6 alkylcarbonyl C₀-6 alkyl,
 aryl C₀-6 alkylcarbonyl C₀-6 alkyl,
 C₁-6 alkylthiocarbonylamino C₀-6 alkyl, and

- 9 -

aryl C₀-6 alkylthiocarbonylamino C₀-6 alkyl, and
wherein groups may be unsubstituted or substituted with
one or more substituents selected from R¹ and R²; and

5 R¹² is chosen from
hydroxy,
C₁-8 alkyloxy,
aryl C₀-6 alkyloxy,
C₁-8 alkylcarbonyloxy C₁-4 alkyloxy, and
10 aryl C₀-8 alkylcarbonyloxy C₁-4 alkyloxy, or
an L- or D-amino acid joined by an amide linkage and
wherein the carboxylic acid moiety of said amino acid is
as the free acid or is esterified by C₁-6 alkyl.

15 When substituent R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹,
R¹⁰, R¹¹, R¹², X, Y, Z, L or M includes the definition C₀, (e.g.
aryl C₀ alkyl), the group modified by C₀ is not present in the
substituent.

20 "Aryl" means a mono- or polycyclic system composed
of 5- and 6- membered aromatic rings containing 0, 1, 2, 3, or 4
heteroatoms chosen from N, O or S and either unsubstituted or
substituted with R¹.

"Alkyl" means straight or branched chain alkane, alkene
or alkyne.

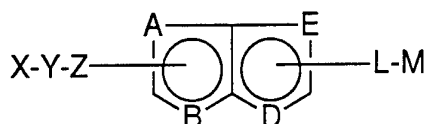
25 "Halogen" includes fluorine, chlorine, iodine and
bromine.

"Oxo" means =O.

"Thio" means =S.

30 A preferred embodiment of the present invention are
compounds of the general formula, and the pharmaceutically
acceptable salts, wherein

- 10 -



5 A, B, D and E are independently chosen from C, N, O and S;

X is $-\text{NR}^1\text{R}^2$, $\text{NR}^1-\overset{\text{NR}^2}{\underset{||}{\text{C}}}-\text{R}^1$, $-\overset{\text{NR}^3}{\underset{||}{\text{C}}}-\text{NHR}^4$,
 $-\text{NR}^1-\overset{\text{NR}^2}{\underset{||}{\text{C}}}\text{NR}^3\text{R}^4$, or a 4- to 10- membered mono- or
 10 polycyclic aromatic or nonaromatic ring system
 containing 0, 1, 2, 3 or 4 heteroatoms selected from N,
 O and S and either unsubstituted or substituted with R^1 ,
 R^2 , R^3 or R^4 , wherein R^1 , R^2 , R^3 and R^4 are
 15 independently selected from the group consisting of
 hydrogen,
 C1-10 alkyl, or
 aryl C0-8 alkyl;

Y is C0-8 alkyl,
 20 C0-8 alkyl- NR^3 -CO-C0-8 alkyl,
 C0-8 alkyl-CONR³-C0-8 alkyl,
 C0-8 alkyl-O-C0-8 alkyl,
 C0-8 alkyl-S(O_n)-C0-8 alkyl, or
 C0-8 alkyl-SO₂-NR³-C0-8 alkyl-;

25 Z and L are independently chosen from:

30 $(\text{CH}_2)_m\overset{\text{O}}{\underset{||}{\text{C}}}\text{NR}^3(\text{CH}_2)_n$, $(\text{CH}_2)_m\text{NR}^3\overset{\text{O}}{\underset{||}{\text{C}}}(\text{CH}_2)_n$,
 $(\text{CH}_2)_m\overset{\text{O}}{\underset{||}{\text{C}}}(\text{CH}_2)_n$, $(\text{CH}_2)_m\text{SO}_2(\text{CH}_2)_n$,
 $(\text{CH}_2)_m\text{SO}_2\text{NR}^3(\text{CH}_2)_n$, $(\text{CH}_2)_m\text{NR}^3\text{SO}_2(\text{CH}_2)_n$, and

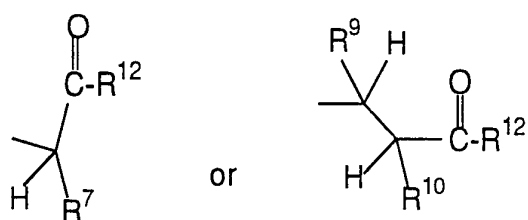
- 11 -

$(CH_2)_m$ where m and n are integers independently chosen from 0-6;

M is:

5

10



wherein R^7 , R^9 , and R^{10} are independently chosen from:

15

20

25

30

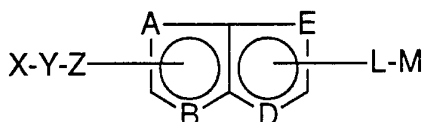
hydrogen, fluorine, hydroxyl,
 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8-alkyl,
 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl, and
 aryl C0-6 alkylcarbonyl C0-6 alkyl;

- 12 -

R¹² is chosen from

hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, and
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy.

A more preferred embodiment of the present invention encompasses compounds of the general formula



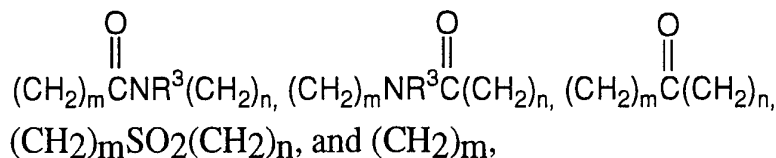
and the pharmaceutically acceptable salts, wherein: A, B, D and E are independently chosen from C, N, O and S, wherein

X is $\text{-NR}^1\text{R}^2$, $\text{-}\overset{\text{NR}^3}{\underset{\text{||}}{\text{C}}}\text{-NHR}^4$ or a 4- to 8- membered nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and O wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

Y is C₀₋₈ alkyl, C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl, C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl, C₀₋₈ alkyl-O-C₀₋₈ alkyl, or C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl;

Z and L are independently chosen from:

- 13 -

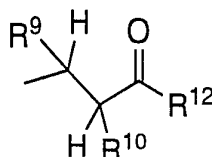


5

where m and n are integers independently chosen from 0-6;

M is:

10

wherein R⁹ and R¹⁰ are independently chosen from:

15

hydrogen, fluorine,

C₁₋₈ alkyl,C₃₋₈ cycloalkyl,aryl C₀₋₆ alkyl,

20

C₀₋₆ alkylamino C₀₋₆ alkyl,C₀₋₆ dialkylamino C₀₋₆ alkyl,C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,

25

aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,aryl C₀₋₈ alkylaminocarbonylamino C₀₋₈ alkyl,

30

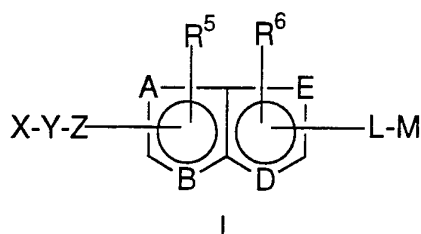
C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,C₁₋₆ alkylcarbonyl C₀₋₆ alkyl, oraryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl; and

- 14 -

R¹² is chosen from

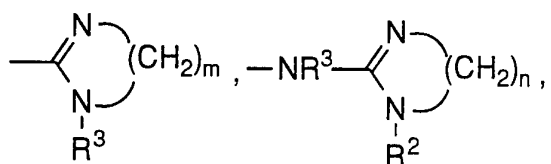
hydroxy,
C₁-8 alkyloxy, and
aryl C₀-6 alkyloxy.

In another preferred embodiment, compounds of the invention have the general formula I



and the pharmaceutically acceptable salts thereof wherein: A, B, D and E are independently selected from C, N, O and S and wherein:

X is

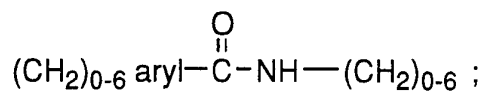
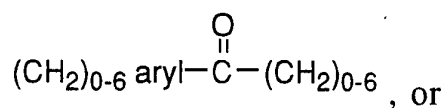


or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R² or R³, wherein R² and R³ are independently selected from the group consisting of hydrogen,
C₁-10 alkyl,
aryl C₀-8 alkyl,
oxo,

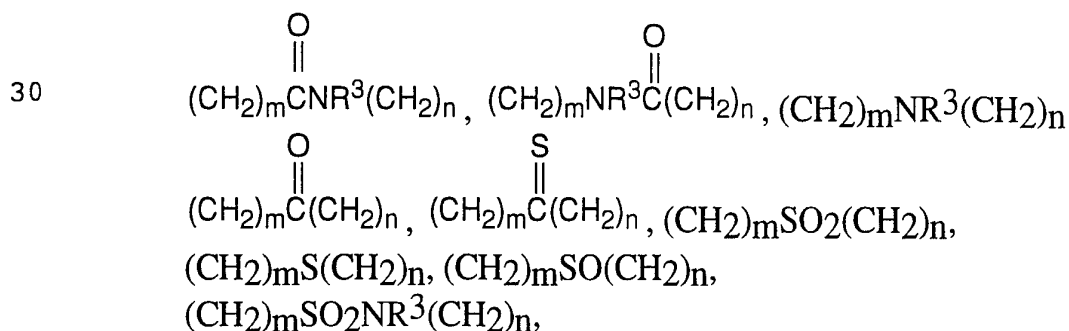
- 15 -

thio,
 amino C0-8 alkyl, C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,
 5 C1-4 alkoxy C0-6 alkyl,
 carboxy C0-6 alkyl, C1-3 alkoxycarbonyl C0-6 alkyl,
 carboxy C0-6 alkyloxy, or
 hydroxy C0-6 alkyl, where m and n are integers
 independently chosen from 2-5;

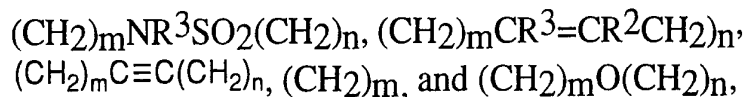
10 Y is C0-8 alkyl, C0-8 alkyl (C4-10 cycloalkyl),
 C0-8 alkyl-NR³-CO-C0-8 alkyl,
 C0-8 alkyl-CONR³-C0-8 alkyl,
 C0-8 alkyl-O-C0-8 alkyl,
 15 C0-8 alkyl-S(O_n)-C0-8 alkyl, or
 C0-8 alkyl-SO₂-NR³-C0-8 alkyl-,
 C0-8 alkyl-NR³-SO₂-C0-8 alkyl-,
 C0-8 alkyl-CO-C0-8 alkyl,
 20 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,



Z and L are independently chosen from



- 16 -

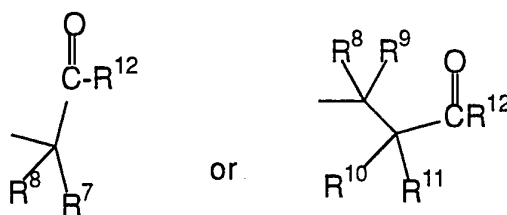


where m and n are integers independently chosen from 0-6;

R⁵ and R⁶ are independently chosen from:

hydrogen,
 C₁₋₆ alkyl,
 C₀₋₆ alkylcarboxy C₀₋₆ alkyl,
 C₀₋₆ alkyloxy C₀₋₆ alkyl,
 hydroxy C₀₋₆ alkyl,
 aryl C₀₋₆ alkyl, and
 halogen;

M is:



wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from:

hydrogen, fluorine,
 C₁₋₈ alkyl, hydroxyl, hydroxy C₁₋₆ alkyl, carboxy C₀₋₆
 alkyl, C₁₋₆ alkyloxy, aryl C₀₋₆ alkyloxy, C₁₋₆
 alkylcarbonyl, aryl C₀₋₆
 alkylcarbonyl, C₁₋₆ alkylcarbonyloxy, aryl C₀₋₆
 alkylcarbonyloxy, C₁₋₆ alkylaminocarbonyloxy,
 C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,

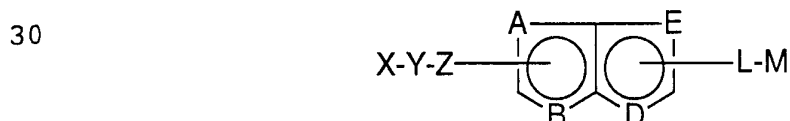
- 17 -

aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 5 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 10 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl,
 aryl C0-6 alkylcarbonyl C0-6 alkyl,
 C1-6 alkylthiocarbonylamino C0-6 alkyl, and
 aryl C0-6 alkylthiocarbonylamino C0-6 alkyl, and
 15 wherein groups may be unsubstituted or substituted with
 one or more substituents selected from R² and R³;

R¹² is chosen from

hydroxy,
 C1-8 alkyloxy,
 20 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy, and
 aryl C0-8 alkylcarbonyloxy C1-4 alkyloxy, or
 an L- or D-amino acid joined by an amide linkage and
 25 wherein the carboxylic acid moiety of said amino acid is
 as the free acid or is esterified by C1-6 alkyl.

More preferably, these compounds, and their
 pharmaceutically acceptable salts, have the formula



wherein A, B, D and E are independently chosen from C, N, O and S;

- 18 -

X is a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with hydrogen, C₁-10 alkyl, or aryl C₀-8 alkyl;

Y is C₀-8 alkyl, C₀-8 alkyl-NR³-CO-C₀-8 alkyl, C₀-8 alkyl-CONR³-C₀-8 alkyl, C₀-8 alkyl-O-C₀-8 alkyl, C₀-8 alkyl-S(O_n)-C₀-8 alkyl, or C₀-8 alkyl-SO₂-NR³-C₀-8 alkyl-;

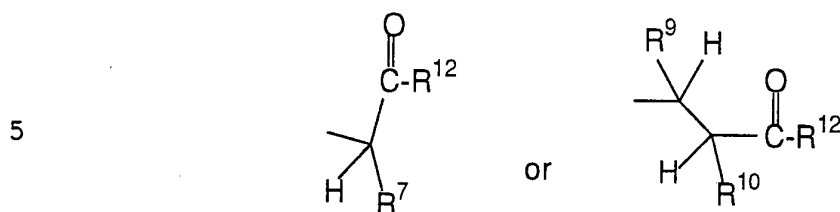
R³ is selected from hydrogen, C₁-10 alkyl, or aryl C₀-8 alkyl;

Z and L are independently chosen from:

(CH₂)_m $\overset{\text{O}}{\parallel}$ CNR³(CH₂)_n, (CH₂)_mNR³ $\overset{\text{O}}{\parallel}$ C(CH₂)_n,
 (CH₂)_m $\overset{\text{O}}{\parallel}$ C(CH₂)_n, (CH₂)_mSO₂(CH₂)_n,
 (CH₂)_mSO₂NR³(CH₂)_n, (CH₂)_mNR³SO₂(CH₂)_n, and
 (CH₂)_m where m and n are integers independently chosen from 0-6;

- 19 -

M is:



wherein R^7 , R^9 , and R^{10} are independently chosen from:

- 10 hydrogen, fluorine, hydroxyl
 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 15 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8-alkyl,
 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 20 C1-8 alkylcarbonylamino C0-6 alkyl,
 aryl 0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 25 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl, and
 aryl C0-6 alkylcarbonyl C0-6 alkyl;

30

R^{12} is chosen from

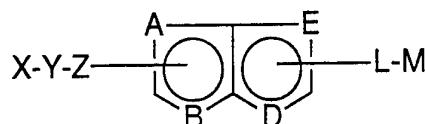
- hydroxy,
 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy, and

- 20 -

aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy.

Even more preferably, these compounds, and their pharmaceutically acceptable salts, have the formula

5



10 wherein: A, B, D and E are independently chosen from C, N, O and S, wherein

X is a 4- to 8- membered nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and O;

15

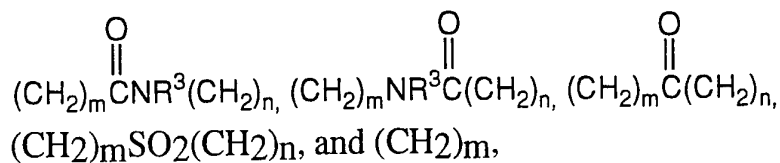
Y is C₀₋₈ alkyl,
C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
C₀₋₈ alkyl-O-C₀₋₈ alkyl, or
C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl;

20

R³ is hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

Z and L are independently chosen from:

25



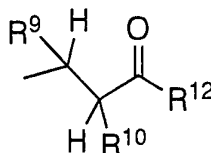
where m and n are integers independently chosen from 0-6;

30

- 21 -

M is:

5

wherein R^9 and R^{10} are independently chosen from:

10

hydrogen, fluorine,

C₁₋₈ alkyl,C₃₋₈ cycloalkyl,aryl C₀₋₆ alkyl,C₀₋₆ alkylamino C₀₋₆ alkyl,

15

C₀₋₆ dialkylamino C₀₋₆ alkyl,C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,

20

C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,aryl C₀₋₈ alkylaminocarbonylamino C₀₋₈ alkyl,C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,

25

aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,C₁₋₆ alkylcarbonyl C₀₋₆ alkyl, oraryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl, and

30

 R^{12} is chosen from

hydroxy,

C₁₋₈ alkyloxy, andaryl C₀₋₆ alkyloxy.

- 22 -

The following examples illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can
5 be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

10

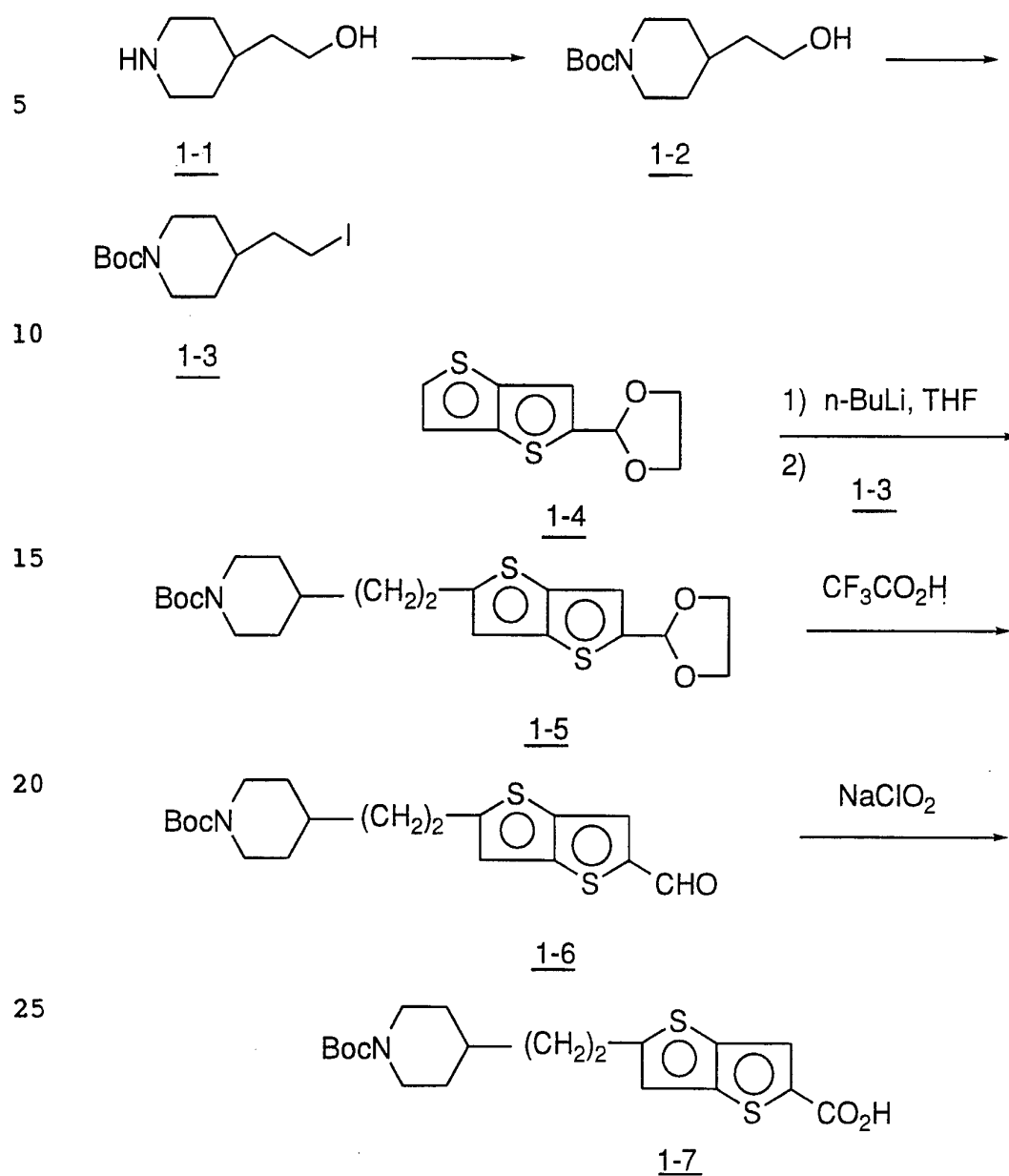
15

20

25

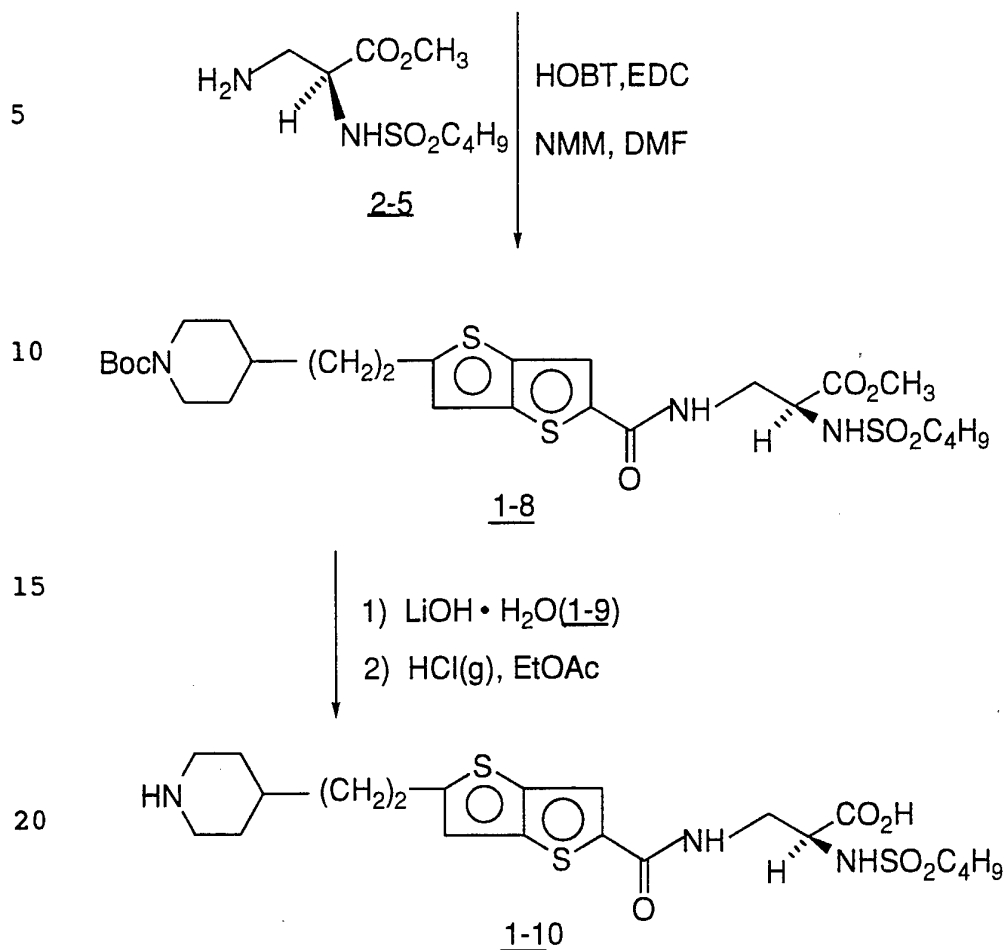
30

- 23 -

SCHEME 1

30

- 24 -

SCHEME I CONT'D2(N-t-Butyloxycarbonylpiperidin-4-yl)ethanol (1-2)

25 To a stirred solution of 4-piperidineethanol 8 (Aldrich) (18.7 g, 0.14 mol) and DMF (200 mL) at 0°C was added N-tert-butoxycarbonyl anhydride (31 g, 0.14 mol). After 1 hr the cooling bath was removed and the reaction mixture stirred for 20 hr. The reaction mixture was diluted with ether and then washed with water (2x) and brine, dried (MgSO₄), and concentrated to furnish 1-2 as a colorless oil.

30 TLC R_f = 0.25 (40% ethyl acetate/hexanes);

¹H NMR (300 MHz, CDCl₃) δ 4.09 (bs, 2H), 3.72 (t, J=7 Hz, 2H), 2.70 (m, 2H), 1.75-1.10 (m, 7H), 1.46 (s, 9H).

- 26 -

promptly diluted with EtOAc (100 ml). This was extracted with saturated Na₂CO₃ solution (25 ml), H₂O, dried (MgSO₄) and concentrated to give 1-6.

- 5 ¹H NMR (300 MHz, CDCl₃) δ 1.15 (2H, m), 1.45 (9H, s), 1.71 (4H, m), 2.69 (2H, t), 2.96 (2H, t), 4.10 (4H, m), 7.03 (1H, s), 7.86 (1H, s), 9.93 (1H, s).

10 5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-carboxylic acid (1-7)

- A solution of 1-6 (0.046 g, 0.1 mmol) in t-butanol (3 ml) at room temperature was treated with a solution of NaClO₂ (0.1 g, 1.1 mmol) and NaH₂PO₄•H₂O (0.10 g, 0.72 mmol) in 1 ml H₂O and 1 ml of 2-methyl-2-butene with stirring at room temperature for 16 hrs. The reaction mixture was concentrated and partitioned between EtOAc (10 ml) and 3 ml of 1N NaHSO₄. The organic phase was dried (MgSO₄), concentrated and the solvent was removed. The residue was triturated with hexane to give pure 1-7.

- 20 ¹H NMR (300 MHz, CDCl₃) δ 1.18 (2H, m), 1.46 (9H, s), 1.70 (3H, m), 2.69 (2H, t), 2.93 (2H, t), 4.10 (2H, bd), 7.00 (1H, s), 7.99 (1H, s).

25 5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]-thiophene-2-N-[3-(methyl 2(S)-n-butylsulfonylamino)propionate]-carboxamide (1-8)

- A solution of 1-7 (0.2 g, 0.5 mmol), methyl 2(S)-n-butylsulfonylamino-3-aminopropionate (2-5) (synthesis is described in Scheme 2) (0.14 g, 0.5 mmol), HOBT (0.07 g, 0.55 mmol), EDC (0.11 g, 0.58 mmol) in DMF (10 ml) was treated at room temperature with N-methylmorpholine (NMM) (0.15 g, 1.5 mmol) and the resulting solution was stirred for 18 hrs. The reaction mixture was poured into H₂O (200 ml) and extracted with EtOAc. The organic extract was washed with 1N KHSO₄ solution, saturated

- 25 -

2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl iodide (1-3)

To a stirring solution of 1-2 (18.0 g, 77 mmol), triphenylphosphine (22.2 g, 85 mmol), imidazole (7.9 g, 115 mmol), and benzene (800 mL) at ambient temperature was added iodine
5 (22.0 g, 85 mmol). After 5 min the heterogeneous reaction mixture was filtered and the filtrate concentrated. Flash chromatography (silica gel, 10% ethyl acetate/hexanes) gave 1-3 as an oil. TLC R_f = 0.95 (50% ethyl acetate/hexanes);

10 ¹H NMR (300 MHz, CDCl₃) δ 4.11 (m, 2H), 3.24 (t, J=6 Hz, 2H), 2.72 (m, 2H), 1.82 (dt, J=7, 7 Hz, 2H), 1.75-1.55 (m, 5H), 1.48 (s, 9H), 1.12 (m, 2H).

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-carboxaldehyde ethylene glycol acetal (1-5)

A solution of thieno [3,2-b] thiophene-2-carboxaldehyde ethylene glycol acetal (1-4) (J. D. Prugh, et al. *J. Med. Chem.* 1991, 34, 1805-1818) (0.212 g, 1.0 mmol) in THF (10 ml) cooled to -78° was treated with *n*-BuLi (1.1 mmol in hexane) with stirring for 2 hrs.
20 Then, a solution of 1-3 (0.339 g) in 2 ml THF was added and the resulting solution was allowed to slowly warm to room temperature over 16 hrs. The solvent was removed and the residue quenched with Ether/H₂O and the organic phase was separated, dried (MgSO₄) and concentrated. The residue was purified by flash
25 chromatography on silica gel eluting with 10-20% EtOAc/hexane to give pure 1-5.

¹H NMR (300 MHz, CDCl₃) δ 1.14 (2H, m), 1.46 (9H, s), 1.70 (5H, m), 2.65 (2H, t), 2.90 (2H, t), 4.08 (8H, m), 6.14 (1H, s), 6.91 (1H, s), 7.26 (1H, s).
30

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-carboxaldehyde (1-6)

A solution of 1-5 (0.458 g, 1.08 mmol) in acetone (20 ml) was treated with 2.2 g of trifluoroacetic acid for 5 minutes, then

- 27 -

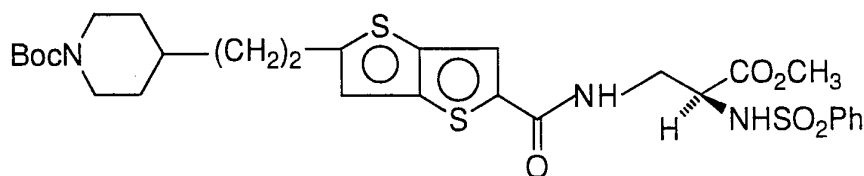
NaHCO₃ solution, brine, and then dried (MgSO₄). The solvent was removed and the residue purified by flash chromatography on silica gel eluting with 55% EtOAc/hexane to give pure 1-8.

¹H NMR (300 MHz, CDCl₃) δ 0.90 (3H, t), 1.15 (2H, m), 1.27 (2H, m), 1.46 (9H, s), 1.72 (5H, m), 2.78 (2H, t), 2.91 (2H, t), 3.05 (2H, t), 4.10 (2H, m), 4.39 (1H, bs), 6.00 (1H, bd), 6.92 (1H, s), 7.18 (1H, m), 7.72 (1H, s).

5-[2-(Piperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-N-[3-(2(S)-n-butyl-sulfonylamino)propionic acid]carboxamide (1-10)

A solution of 1-8 (0.28 g) in CH₃OH (20 ml)/THF (20 ml) was treated with LiOH·H₂O (excess) in H₂O (20 ml) with stirring at room temperature for 4 hrs. The reaction mixture was concentrated and the residue was acidified with 1N KHSO₄ solution and extracted with EtOAc. The organic phase was dried (MgSO₄) and concentrated to give the desired acid 1-9. This was dissolved in EtOAc (20 ml), cooled to -30°C and HCl (gas) was bubbled into this solution for 1 hr. This was allowed to warm to room temperature with stirring for 2 hrs. The solvent was then removed and the residue collected to provide pure 1-10.

¹H NMR (300 MHz, CD₃OD) δ 0.86 (3H, t), 1.30 (6H, m), 1.72 (5H, m), 2.00 (3H, m), 3.00 (6H, m), 3.32 (2H, m), 3.58 (1H, dd), 3.82 (1H, dd), 4.32 (1H, m), 7.13 (1H, s), 7.86 (1H, s).

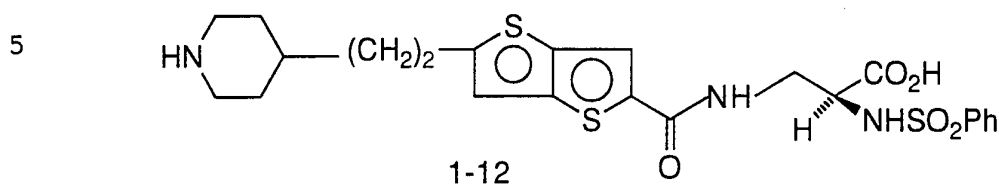


1-11

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]-thiophene-2-N-[3-(methyl 2(S)-phenylsulfonylamino)propionate]-carboxamide (1-11)

- 28 -

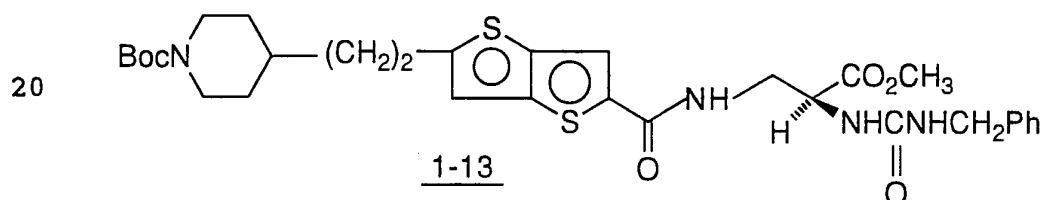
1-7 was treated with 2-7 as described for 1-8 to provide 1-11.



10 5-[2-(Piperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-N-[3-(2(S)-phenylsulfonylamino)propionic acid]carboxamide (1-12)

1-11 was treated with HCl gas in EtOAc as described for 1-10 to provide pure 1-12.

15 ¹H NMR (300 MHz, CD₃OD) δ 1.42 (3H, m), 1.72 (3H, m), 2.00 (3H, m), 2.98 (7H, m), 3.36 (3H, m), 3.71 (1H, dd), 4.15 (2H, m), 7.12 (1H, s), 7.40 (3H, m), 7.69 (1H, s), 7.81 (2H, m).

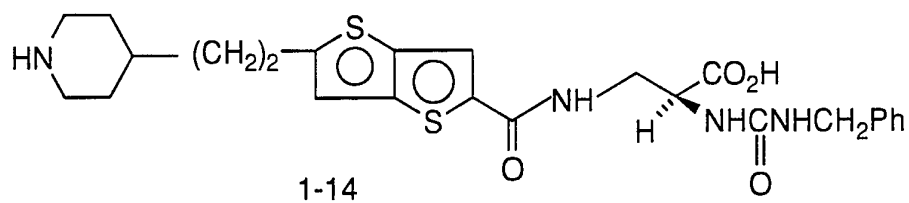


25 5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-N-[3-(methyl 2(S)-benzylureido)propionate]-carboxamide (1-13)

1-7 was treated with 2-9 as described for 1-9 to provide pure 1-13.

30 ¹H NMR (300 MHz, CDCl₃) δ 1.15 (2H, m), 1.45 (9H, s), 1.70 (3H, m), 2.65 (2H, t), 2.92 (2H, t), 3.75 (3H, s), 3.79 (2H, m), 4.10 (2H, bd), 4.32 (2H, m), 4.70 (1H, m), 6.93 (1H, s), 7.20 (5H, m), 7.61 (1H, s).

- 29 -

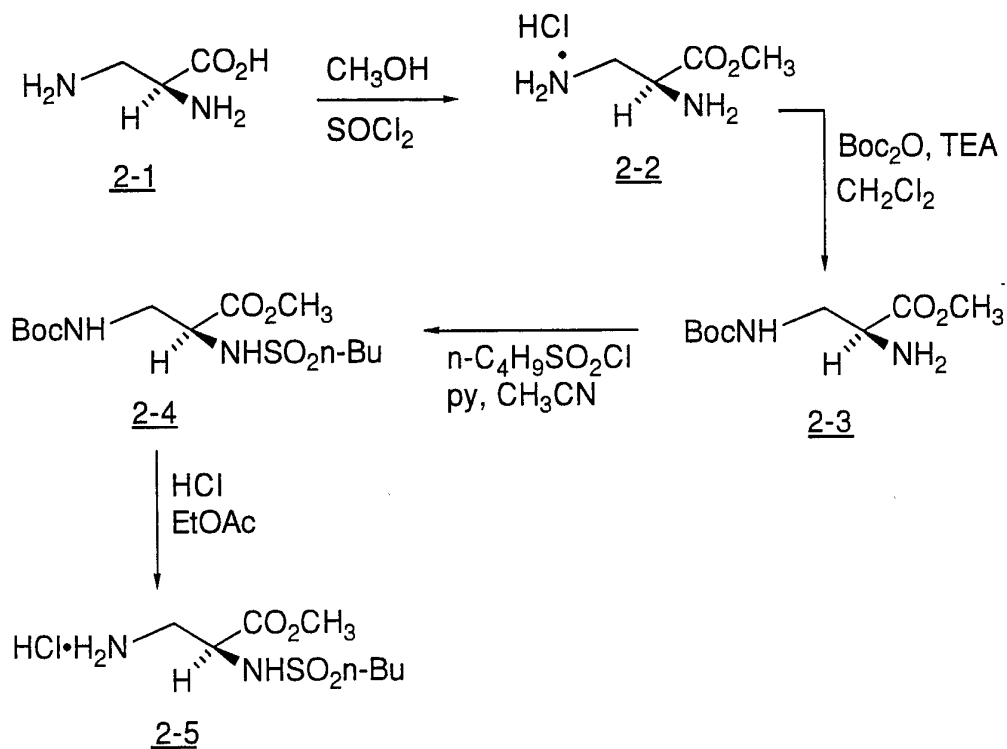


5-[2-(Piperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-N-[3-(2(S)-benzylureido)propionic acid]carboxamide (1-14)

1-13 was treated with HCl gas in EtOAc as described for 1-10 to provide pure 1-14.

¹H NMR (300 MHz, CD₃OD) δ 1.41 (2H, m), 1.70 (3H, m), 2.00 (2H, m), 2.98 (4H, m), 3.65 (2H, m), 4.38 (2H, m), 4.55 (1H, m), 7.16 (6H, m), 7.79 (1H, s).

SCHEME 2



- 30 -

Methyl 2(S),3-diaminopropionate hydrochloride (2-2)

Methanol (400 mL) was cooled to 0°C and thionyl chloride (217 mL, 3.0 moles, 20 eq) was added dropwise under argon. After addition was completed, the solution was warmed to
5 RT for 20 min. 2(S),3-Diaminopropanoic acid (20 g, 0.143 mole) (Schweizerhall Chemicals) was crushed to a fine powder and added to the solution. The reaction was heated to reflux for 48 hrs, at which time TLC showed a small amount of starting material remaining. An additional portion of methanol (100 mL) and thionyl
10 chloride (72 mL) was prepared as before and added to the reaction at RT; the reaction was then stirred overnight at RT. The reaction was worked up by removal of solvent at 40°C in vacuo to give 2-2 as foam.
R_f 0.72 (9:1:1 EtOH/H₂O/NH₄OH).

15 ¹H NMR (400 MHz, D₂O) δ 4.55 (dd, J=5.4 8.2 Hz, 1H), 3.92 (s, 3H), 3.64 (dd, J=8.2, 13.8 Hz, 1H), 3.55 (dd, J=5.4, 13.8 Hz, 1H).

Methyl [2(S)-amino-3-(N-t-Butyloxycarbonylamino)]propionate (2-3)

20 2-2 (6.0 g, 31.5 mmole) was crushed to a fine powder, suspended in 1L of CH₂Cl₂ and cooled to -78°C under argon. Triethylamine (17.5 mL, 0.126 mole, 4 eq) was added dropwise as the solution gradually became homogenous. Di-t-butylidicarbonate (6.18 g, 2.83 mmole, 0.9 eq) was dissolved in 50 mL CH₂Cl₂ and
25 added dropwise to the solution. After the addition was completed, the reaction was placed in an ice bath and stirred for 1 1/2 hours. The reaction was transferred to a separatory funnel and extracted with 3 X 50 mL of 10% KHSO₄ solution. The aqueous layer was washed with 3 X 10 mL of CH₂Cl₂, then basified with sat. NaHCO₃
30 and 3N NaOH solution to pH10 and extracted with 10 X 100 mL of CH₂Cl₂. The organic layer was dried with Na₂SO₄, filtered and evaporated to give of a pale yellow oil. Column chromatography on silica gel with 2.5% MeOH/EtOAc gave 4.22 g (68%) of the pure product as an oil.

- 31 -

R_f 0.39 (5% MeOH/EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 5.0 (bs, 1H), 3.72 (s, 3H), 3.56 (t, J=5.7 Hz, 1H), 3.46 (m, 1H), 3.23 (m, 1H), 1.55 (bs, 2H), 1.42 (s, 9H).

Methyl [2(S)-(n-Butylsulfonylamino)-3-(t-butyloxycarbonylamino)]-propionate (2-4)

2-3 (2.5 g, 11.4 mmole) was dissolved in acetonitrile (100 mL) and three portions of n-butylsulfonyl chloride (1.62 mL, 12.5 mmole, 1.1 eq each) and pyridine (1.0 mL, 12.5 mmole, 1.1 eq each) were added over a period of three hours. The reaction was allowed to stir overnight, concentrated to 1/4 its original volume, then diluted with 100 mL EtOAc and washed with 10% KHSO₄ (5 X 20 mL), dried with brine and MgSO₄, filtered and evaporated. Column chromatography on silica gel eluting with 20%-40% EtOAc/Hexanes gave the pure product as an oil.

R_f 0.6 (5% MeOH/CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.48 (bd, 1H), 4.9 (bs, 1H), 4.22 (m, 1H), 3.8 (s, 3H), 3.53 (m, 2H), 3.02 (m, 2H), 1.80 (m, 2H), 1.46 (m, 2H), 1.43 (s, 9H), 0.94 (t, J=7.4 Hz, 3H).

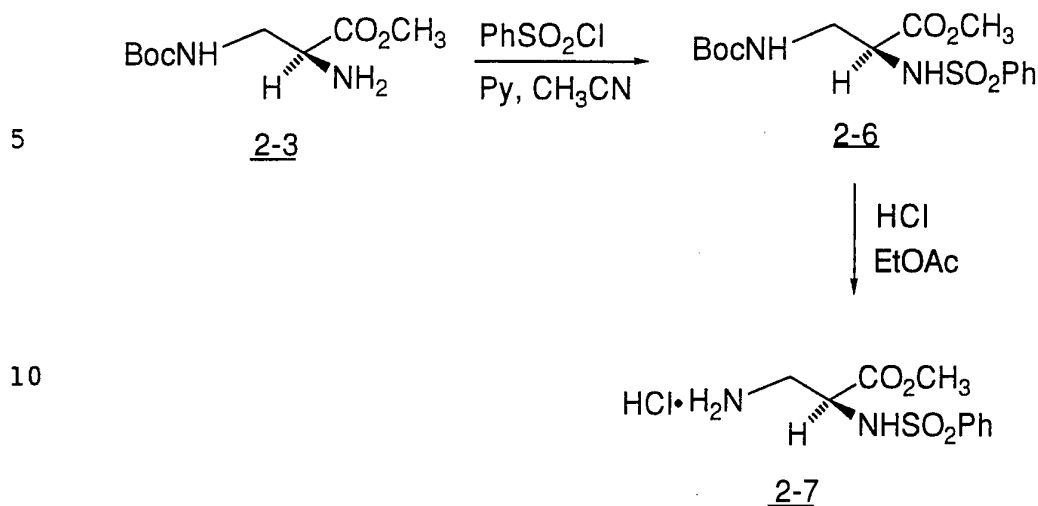
Methyl [2(S)-(n-Butylsulfonylamino)-3-amino]propionate (2-5)

2-4 (2.0 g, 5.9 mmole) was dissolved in 30 mL of EtOAc and cooled to -40°C. HCl gas was bubbled through the solution until it was saturated, then the reaction was warmed to 0°C and stirred for 1 hr. The excess HCl was removed under vacuum at room temperature and the reaction was concentrated at 35°C to give pure product as a foam.

R_f 0.6 (9:1 EtOH/H₂O).

¹H NMR (400 MHz, CDCl₃) δ 8.1 (bs, 2H), 7.2 (m, 1H), 4.65 (m, 1H), 3.82 (s, 3H), 3.65 (m, 1H), 3.54 (m, 1H), 3.20 (bs, 2H), 1.8 (m, 2H), 1.45 (m, 2H), 0.95 (t, J=7.3 Hz).

- 32 -



Methyl [2(S)-(Phenylsulfonylamino)-3-(t-butyloxycarbonylamino)]
propionate (2-6)

Treatment of 2-3 (0.58 g, 2.67 mmol) in CHCl_3 (10 ml) with PhSO_2Cl (9.15 mmol) as described for 2-4 gave 2-6 following purification on silica gel eluting with 30% EtOAc/hexane (R_f 0.4).

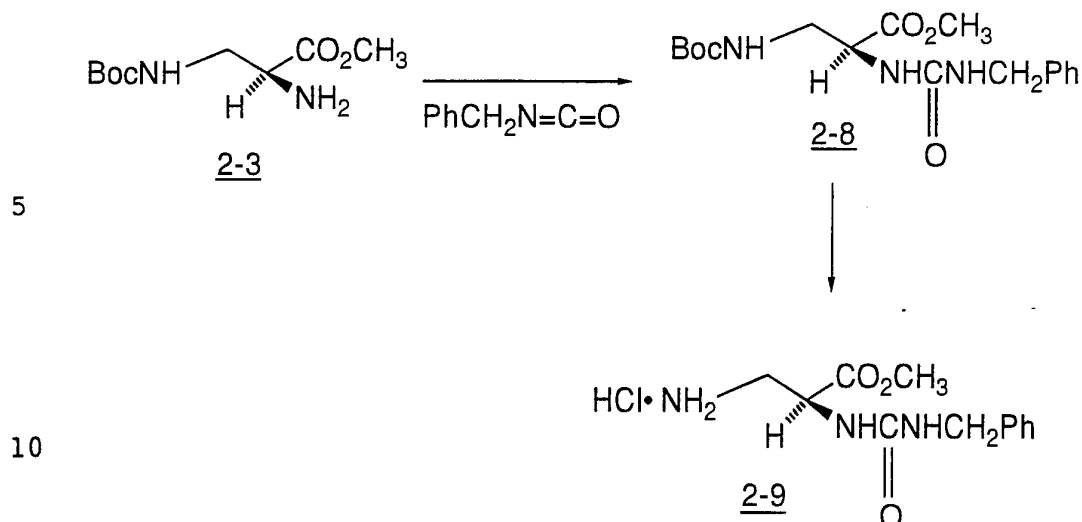
^1H NMR (300 MHz, CDCl_3) δ 1.45 (9H, s), 3.60 (3H, s), 4.03 (1H, m), 4.98 (1H, m), 6.70 (1H, bd), 7.58 (3H, m), 7.89 (2H, d).

Methyl [2(S)-(Phenylsulfonylamino)-3-amino]propionate
hydrochloride (2-7)

2-6 (0.8 g, 2.2 mmol) was dissolved on EtOAc (10 ml) and treated with HCl gas as described for 2-5 to afford pure 2-7. R_f 0.4 [silica, 10% MeOH/ CHCl_3 (saturated NH_4OH)].

^1H NMR (300 MHz, CD_3OD) δ 3.09 (1H m), 3.30 (2H, m), 3.36 (1H, m), 3.40 (3H, s), 4.24 (1H, m), 7.60 (3H, m), 7.88 (2H, m).

- 33 -



15 Methyl [2(S)-(Benzylureido)-3-(t-butyloxycarbonyl-
amino)]propionate(2-8)

2-3 (1.29 g, 5.91 mmol) in THF (35 ml) at room temperature was treated with benzyl isocyanate (6.5 mmol) with stirring for 16 hrs. The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with 5% MeOH/EtOAc to give pure 2-8.

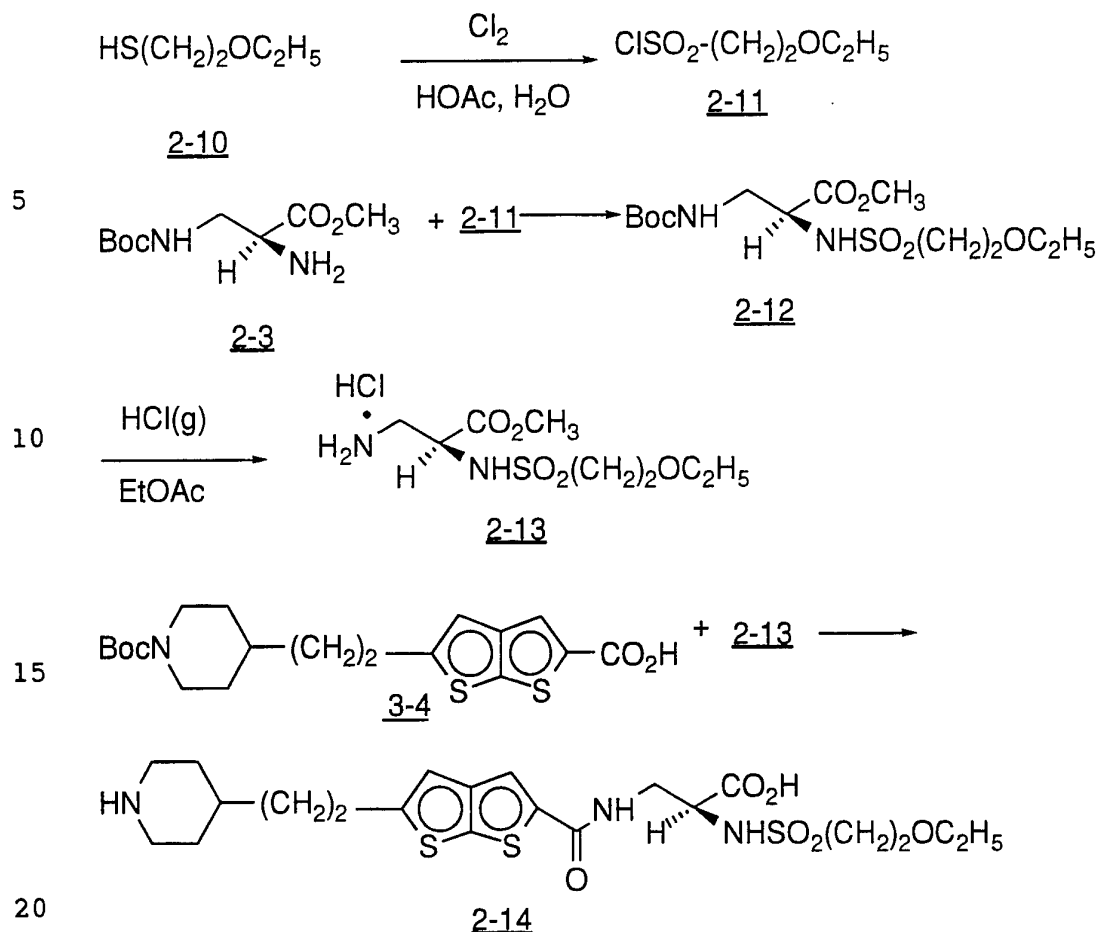
¹H NMR (300 MHz, CDCl₃) δ 1.43 (9H, s), 1.48 (2H, m), 3.40 (1H, m), 3.58 (1H, m), 3.63 (3H, s), 4.34 (3H, m), 4.57 (1H, m), 5.28 (1H, m), 5.47 (1H, m), 5.80 (1H, d), 7.26 (5H, m).

Methyl 2(S)-(Benzylureido)-3-aminopropionate hydrochloride (2-9)

2-8 (1.19 g) was dissolved in EtOAc and treated with HCl gas as described for 1-10 to provide pure 2-9.

¹H NMR (300 MHz, CD₃OD) δ 3.25 (2H, m), 3.39 (2H, dd), 3.77 (3H, s), 4.35 (2H, s), 4.55 (1H, m), 7.35 (5H, m).

- 34 -



2-Ethoxyethanesulfonyl Chloride (2-11)

A solution of HOAc (25 ml) and H₂O (2 ml) was cooled to 0° and treated with 2-mercaptoethyl ethyl ether (2-10) (4.5 ml, 47 mmol). A stream of chlorine gas was then bubbled into this solution for 2 minutes which turned from colorless to bright yellow. This solution was stirred at 0° for 3.5 hours, diluted with H₂O and extracted with CH₂Cl₂. The organic phase was washed with H₂O, 5% NaOH, H₂O, brine and dried (MgSO₄). Solvent removal gave 2-11 as a clear oil.

¹H NMR (300 MHz, CDCl₃) δ 1.22 (3H, t), 3.78 (2H, q), 3.98 (4H, m).

- 35 -

Methyl [2(S)-(2-Ethoxyethanesulfonylamino)-3-(t-butyloxycarbonyl-amino)] propionate (2-12)

2-3 was treated with 2-11 as described for 2-4 to provide 2-12.

5

¹H NMR (300 MHz, CDCl₃) δ 1.25 (3H, t), 1.45 (9H, s), 3.32 (2H, m), 3.5 (4H, m), 3.80 (3H, s), 3.84 (2H, m), 4.24 (1H, m).

Methyl [2(S)-(2-Ethoxyethanesulfonylamino)-3-amino]propionate (2-13)

10

2-12 was treated with HCl gas as described for 2-5 to give pure 2-13.

¹H NMR (300 MHz, CD₃OD) δ 1.19 (3H, t), 3.65-3.76 (6H, m), 3.89 (5H, m).

15

5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-2(S)-(2-ethoxyethanesulfonylamino)propionic acid] carboxamide (2-14)

3-4 was treated with 2-13 and this intermediate was deprotected as described for 1-10 to give pure 2-14.

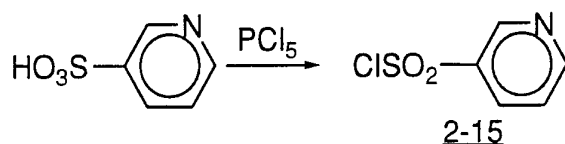
20

¹H NMR (300 MHz, D₂O) δ 1.03 (3H, t), 1.20-1.53 (5H, m), 1.75 (2H, bd), 2.60 (2H, bs), 2.73 (2H, bt), 3.34 (6H, m), 3.50 (1H, m), 3.75 (4H, m), 4.27 (1H, m), 6.80 (1H, s), 7.62 (1H, s).

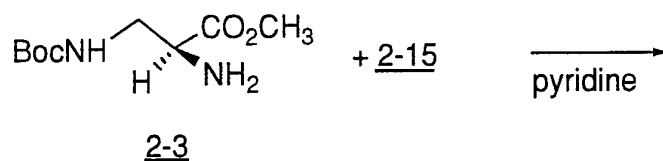
25

30

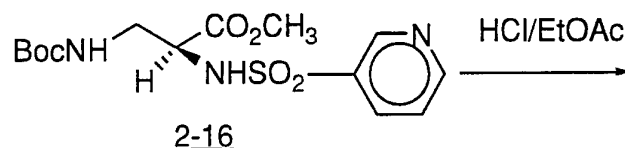
- 36 -



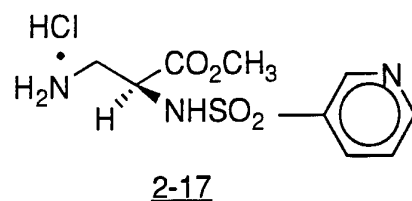
5



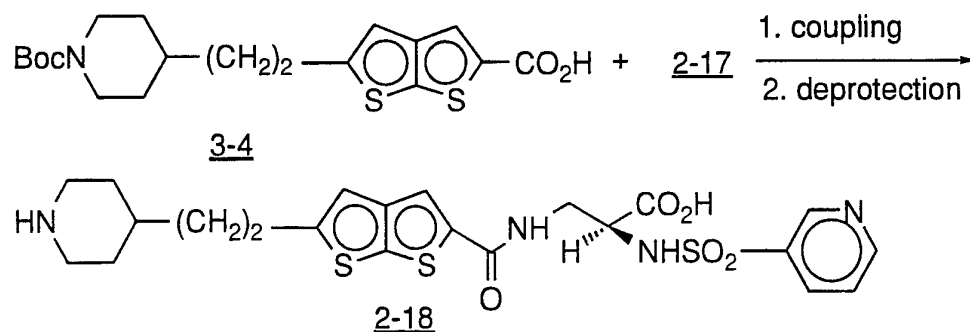
10



15



20



25

3-Pyridylsulfonyl chloride (2-15)

3-pyridylsulfonic acid (30 g, 0.188 mole) was added to PCl_5 (46.8 g, 0.225 mole), suspended in 150 mL toluene and heated to reflux overnight. The suspension was cooled and concentrated to yield a yellow oil, which was diluted with benzene, filtered through a pad of celite and concentrated to give 30.7 g (92%) of 2-15 as a yellow oil, which was used in the next step without purification.

- 37 -

^1H NMR (300 MHz, CDCl_3) δ 9.27 (1H, s), 8.98 (1H, d), 8.35 (1H, d), 7.62 (1H, dd).

5 Methyl [2(S)-(3-Pyridylsulfonylamino)-3-(N-t-butyloxycarbonyl)amino] propionate (2-16)

Methyl 2(S)-amino-3-(N-t-butyloxycarbonyl)amino-propionate 2-3 (16.8 g, 0.077 mole) dissolved in 330 mL methylene chloride was treated with sulfonyl chloride 2-15 (20.6 g, 0.116 mole) and pyridine (12.5 mL, 0.154 mole) and the reaction was
10 stirred for 21 hours. The reaction was concentrated, absorbed to silica and chromatographed with a gradient of 30% - 70% acetone/hexanes to give crude 2-16 which was swished with hot EtOAc, cooled and filtered to give 2-16 as a pale yellow solid. Rf
15 0.29 (30% acetone/hexanes).

^1H NMR (300 MHz, CDCl_3) δ 9.0 (1H, s), 8.8 (1H, d), 8.6 (1H, d), 8.1 (1H, d), 7.45 (1H, dd), 7.3 (1H, m), 4.1 (1H, m), 4.1 (3H, s), 3.4-3.5 (2H, m), 1.4 (9H, s).

20 Methyl [2(S)-(3-Pyridylsulfonylamino)-3-amino]propionate (2-17)

Methyl 2(S)-(3-pyridylsulfonyl)amino-3-(N-t-butyloxycarbonyl) aminopropionate 2-16 (17.5 g, 0.049 mole) was suspended in 200 mL EtOAc and cooled to -78°C . HCl gas was
25 bubbled through the solution for ten minutes and the solution was then placed in an ice bath. After stirring for 40 minutes at 0°C , no starting material could be detected by TLC. The solution was concentrated, first at room temperature, then at 40°C to yield 2-17 as an off-white solid. Rf 0.34 (9:1:1 EtOH/ H_2O / NH_4OH).

30 ^1H NMR (300 MHz, CD_3OD) δ 9.3 (1H, s), 9.0 (1H, dd), 8.9 (1H, d), 8.2 (1H, dd), 4.6 (1H, dd), 3.6 (3H, s), 3.5 (1H, dd), 3.3 (1H, dd).

- 38 -

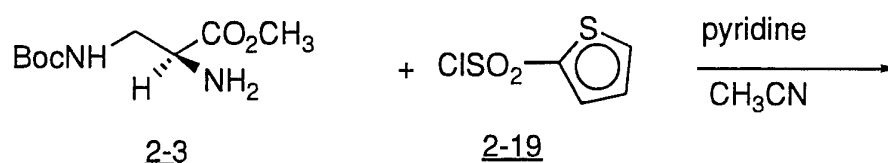
5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-2(S)-(3-pyridylsulfonylamino) propionic acid] carboxamide (2-18)

3-4 was treated with 2-17 and the resulting intermediate was deprotected as described for 1-10 to provide 2-18.

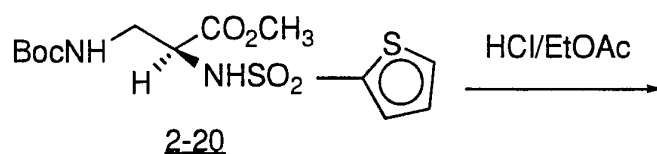
5

^1H NMR (300 MHz, D_2O) δ 0.85 (2H, m), 1.07 (1H, m), 1.34 (4H, m), 2.22 (2H, t), 2.35 (2H, m), 2.38 (2H, bd), 3.06 (1H, t), 3.62 (2H, m), 6.80 (1H, s) 6.92 (1H, m), 7.24 (1H, s), 7.79 (1H, d), 7.97 (1H, dd), 8.70 (1H, d).

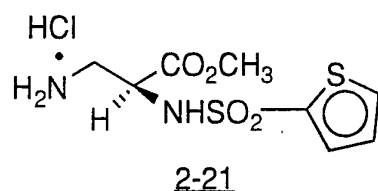
10



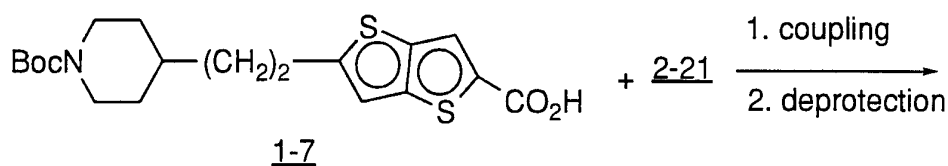
15



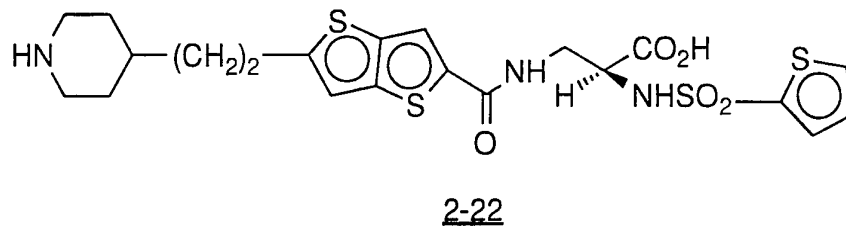
20



25



30



- 39 -

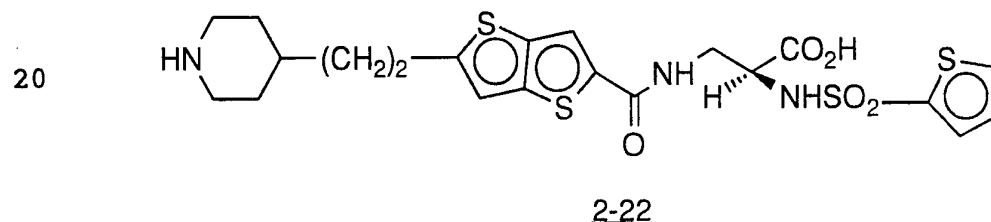
Methyl [2(S)-(2-Thienylsulfonylamino-3-(N-t-butyloxycarbonyl)amino)]-
propionate (2-20)

A solution of 2-3 (1.76 g, 5 mmol) in CH₃CN (15 ml) was treated at room temperature with pyridine (6 mmol) and 2-thiophenesulfonyl chloride (1.0 g, 5.5 mmol) (Aldrich) and this was stirred for 4 hours. The reaction mixture was concentrated, taken up in H₂O/EtOAc and the organic phase was washed with 10% KHSO₄, brine and dried. Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with hexane (7)-EtOAc (3) to give pure 2-20.

R_f 0.25 [silica, hexane (7)-EtOAc(3)].

Methyl [2(S)-(2-Thienylsulfonylamino)-3-amino]propionate (2-21)

2-20 was dissolved in EtOAc and treated with HCl gas as described for 2-17 to provide pure 2-21.

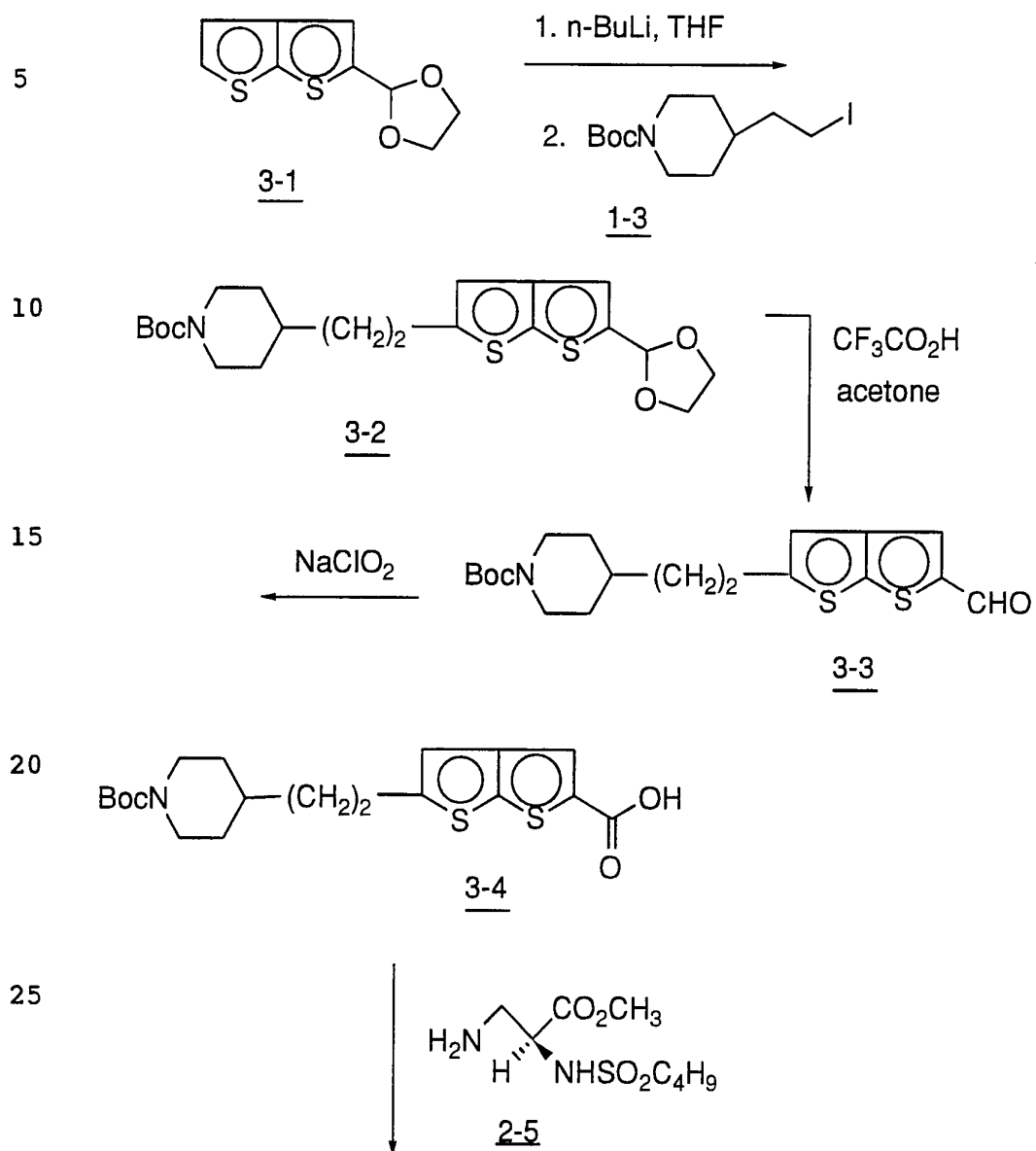


5-[2-(Piperidin-4-yl)ethyl]thieno[3,2-b]thiophene-2-N-[3-(2(S)-(2-thienylsulfonylamino) propionic acid)] carboxamide (2-22)

1-7 was treated with 2-21 as described for 1-8 and this intermediate was deprotected sequentially with LiOH and HCl/EtOAc, as described for 1-10, to provide 2-22.

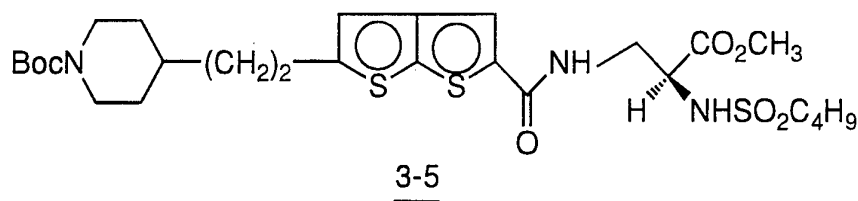
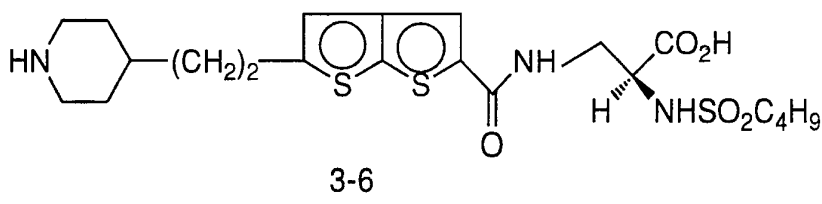
¹H NMR (300 MHz, CD₃OD) δ 1.45 (2H, m), 1.75 (3H, m), 2.08 (3H, m), 2.95 (4H, m), 3.37 (3H, m), 3.52 (1H, dd), 3.75 (1H, dd), 4.24 (1H, m), 6.98 (1H, m), 7.13 (1H, s), 7.58 (2H, m), 7.76 (1H, s).

- 40 -

SCHEME 3

30

- 41 -

1.) LiOH · H₂O2.) HCl (g)
EtOAc

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-
b]thiophene-2-carboxaldehyde ethylene glycol acetal (3-2)

15 Treatment of 3-1 (J.D. Prugh, et al. *J. Med. Chem.* 1991, 34, 1805-1818) (0.212 g, 1.0 mmol) with *n*-BuLi (1.0 mmol) followed by 1-3 (0.34 g, 1.0 mmol) as described for 1-5 provided crude 3-2. This was purified by flash chromatography on silica gel eluting with 10% EtOAc/hexanes to give pure 3-2.

20 ¹H NMR (300 MHz, CD₃OD) δ 1.15 (2H, m), 1.45 (9H, s), 1.68 (4H, m), 2.67 (2H, t), 2.90 (2H, t), 4.10 (4H, m), 6.14 (1H, s), 6.87 (1H, s), 7.21 (1H, s).

25 5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-
b]thiophene-2-carboxaldehyde (3-3)

3-2 (2.36 g, 5.57 mmol) was treated with trifluoroacetic acid (6.6 ml) in acetone (60 ml) at room temp as described for 1-6 to provide 3-3 as an oil.

30 ¹H NMR (300 MHz, CD₃OD) δ 1.15 (2H, m), 1.45 (9H, s), 1.68 (4H, m), 2.68 (2H, t), 2.93 (2H, t), 4.10 (2H, bd), 7.00 (1H, s), 7.77 (1H, s), 9.90 (1H, s).

- 42 -

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-carboxylic acid (3-4)

3-3 (2.0 g, 5.27 mmol) was treated with NaClO₂ (5.27 g, 58.3 mmol) as described for 1-7 to provide 3-4 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 1.17 (2H, m), 1.46 (9H, s), 1.70 (4H, m), 2.68 (2H, t), 2.92 (2H, t), 4.10 (2H, bd), 6.95 (1H, s), 7.94 (1H, s).

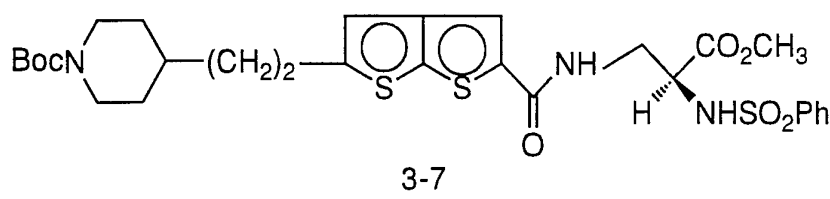
5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-(methyl 2(S)-n-butylsulfonylamino)propionate]-carboxamide (3-5)

3-4 (0.20 g, 0.5 mmol) was treated with 2-5 (0.14 g, 0.5 mmol), HOBT (0.07 g, 0.55 mmol), EDC (0.11 g, 0.58 mmol), and NMM (0.15 g, 1.5 mmol) in DMF (10 ml) as described for 1-8 to provide 3-5 after chromatography on silica gel eluting with 55% EtOAc/hexane (R_f 0.3).

5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]-thiophene-2-N-[3-(2(S)-n-butylsulfonylamino)propionic acid]carboxamide (3-6)

3-5 was treated with LiOH·H₂O as described for 1-8 to provide the desired acid. This was dissolved in EtOAc and treated with HCl gas as described for 1-10 to provide pure 3-6.

¹H NMR (300 MHz, CD₃OD) δ 0.85 (3H, t), 1.48 (4H, m), 1.72 (4H, m), 2.00 (2H, bd), 3.00 (3H, m), 3.56 (1H, m), 3.82 (1H, m), 4.30 (1H, m), 7.05 (1H, s), 7.76 (1H, s).



- 43 -

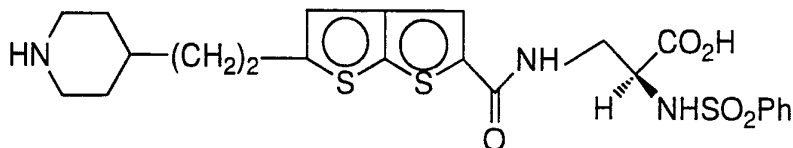
5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-(methyl-2(S)-phenylsulfonylamino)-propionate]carboxamide (3-7)

5 3-4 (0.2 g, 0.5 mmol) was treated with methyl 2(S)-phenylsulfonylamino-3-diaminopropionate (2-7) (0.15 g, 0.5 mmol), HOBT (0.074 g, 0.55 mmol), EDC (0.11 g, 0.58 mmol), and NMM (0.15 mmol as described for 1-8 to provide crude 3-7. This was purified by flash chromatography on silica gel eluting with 55% EtOAc/hexanes to give pure 3-7.

10

¹H NMR (300 MHz, CD₃OD) δ 1.15 (2H, m), 1.45 (9H, s), 1.69 (4H, m), 2.69 (2H, t), 2.90 (2H, t), 3.62 (3H, s), 3.91 (1H, m), 4.10 (3H, m), 5.81 (1H, d), 6.70 (1H, m), 6.90 (1H, s), 7.50 (4H, m), 7.85 (2H, dd).

15



20

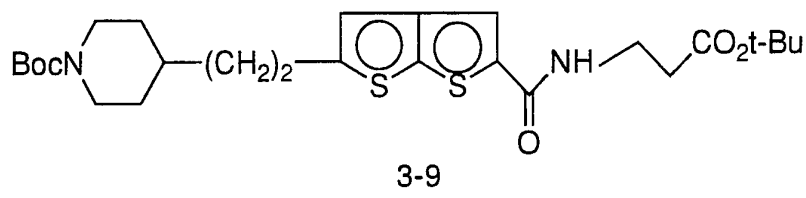
3-8

5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-(2(S)-phenylsulfonylamino)propionic acid]carboxamide (3-8)

25 3-7 was treated with LiOH·H₂O in CH₃OH/H₂O as described for 1-8 to provide the derived acid. This was dissolved in EtOAc, cooled to 10° and treated with HCl (gas) as described for 1-10 to provide pure 3-8 after trituration with water.

30 ¹H NMR (300 MHz, DMSO-d) δ 1.30 (2H, m), 1.58 (3H, m), 1.82 (2H, d), 2.80 (4H, m), 3.20 (3H, m), 7.14 (1H, s), 7.49 (3H, m), 7.79 (3H, m), 8.61 (2H, m).

- 44 -



5

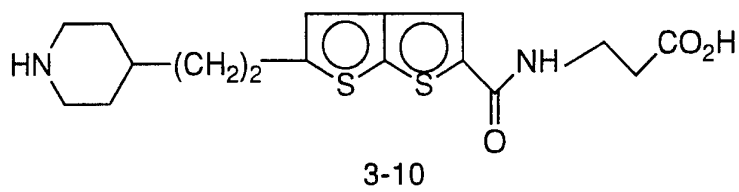
5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]-
thiophene-2-N-[3-(t-butyl propionate)]carboxamide (3-9)

3-9 (0.1 g, 0.25 mmol) was treated with t-butyl β-
alanine (0.045 g, 0.25 mmol), HOBT (0.037 g, 0.275 mmol), EDC
(0.056 g, 0.29 mmol), and NMM (0.076 g, 0.75 mmol) in DMF (5
ml) as described for 1-8 to provide crude 3-9. This was purified by
flash chromatography on silica gel eluting with 40% EtOAc/hexane
to give pure 3-9.

15

¹H NMR (300 MHz, CDCl₃) δ 1.17 (2H, m), 1.45 (9H, s), 1.47 (9H,
s), 1.67 (4H, m), 2.55 (2H, t), 2.68 (2H, t), 2.91 (2H, t), 3.68 (2H,
q), 4.10 (2H, bd), 6.72 (1H, m), 6.96 (1H, s), 7.60 (1H, s).

20



25

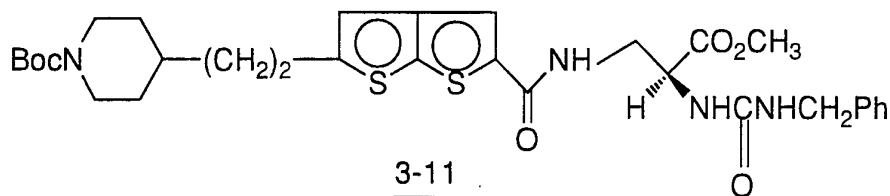
5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-propionic
acid]carboxamide (3-10)

3-9 was treated with HCl gas in EtOAc as described for
1-10 to provide pure 3-10.

30

¹H NMR (300 MHz, CD₃OD) δ 1.42 (2H, m), 1.73 (2H, m), 2.0
(2H, m), 2.62 (2H, t), 2.92 (4H, m), 3.48 (2H, bd), 3.60 (2H, t), 7.13
(1H, s), 7.82 (1H, s).

- 45 -



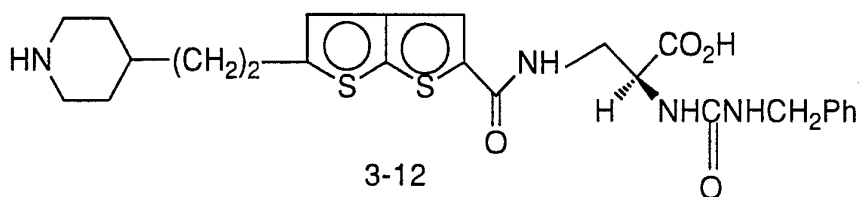
5

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]-
thiophene-2-N-[3-(2(S)-benzylureido)propionate]carboxamide (3-11)

10 3-4 was treated with 2-9 as described for 1-8 to provide
pure 3-11.

¹H NMR (300 MHz, CDCl₃) δ 1.13 (2H, m), 1.45 (9H, s), 1.68 (3H,
m), 2.68 (2H, t), 2.90 (2H, t), 4.10 (2H, bd), 4.30 (2H, m), 4.71 (1H,
m), 6.86 (1H, s), 7.22 (5H, s), 7.55 (1H, s).

15



20

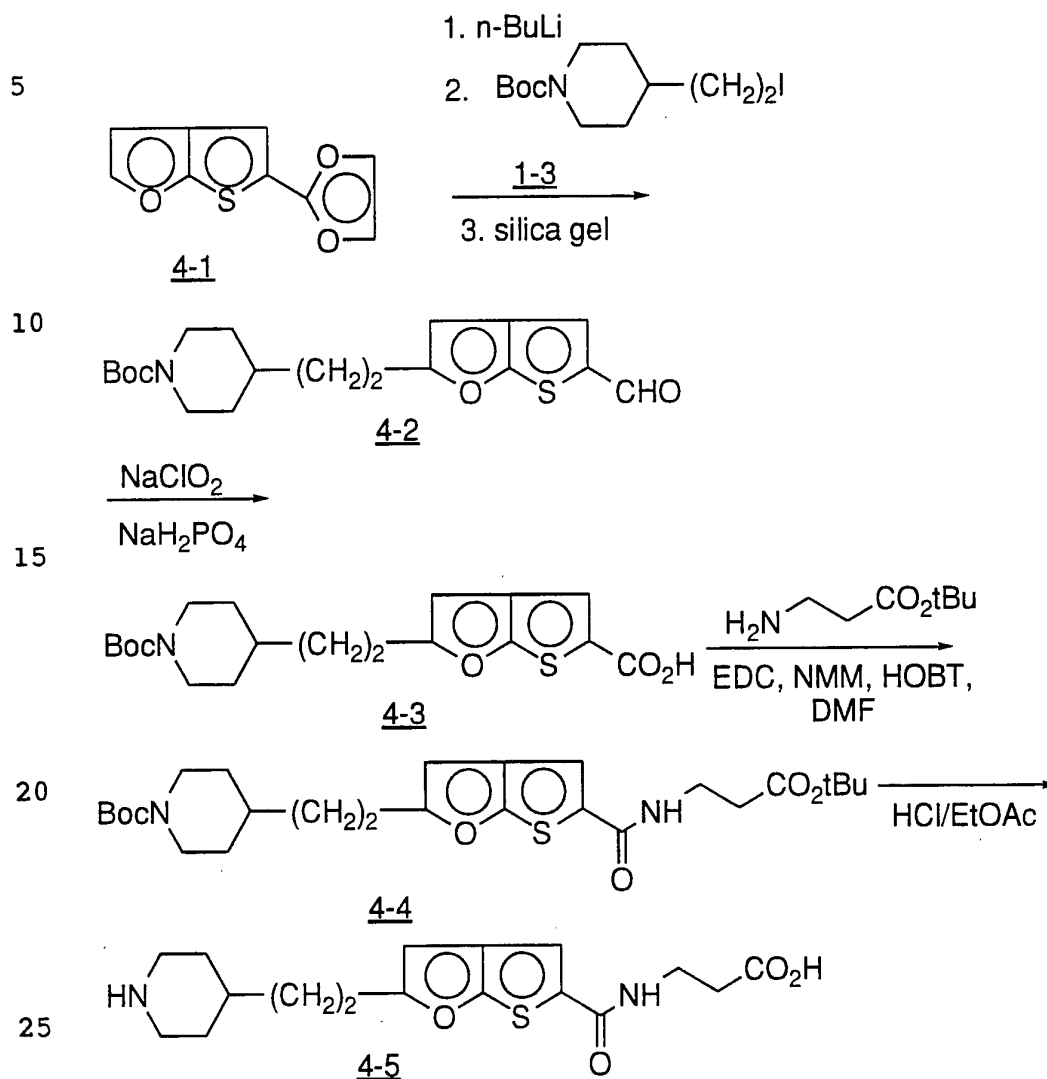
5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-(2(S)-
benzylureido)propionate]carboxamide (3-12)

25 3-11 was dissolved in EtOAc and treated with HCl gas as
described for 1-10 to provide pure 3-12.

¹H NMR (300 MHz, CD₃OD) δ 1.40 (2H, m), 1.72 (3H, m), 2.00
(3H, m), 2.96 (2H, m), 3.45 (2H, bd), 3.71 (2H, m), 7.03 (1H, s),
7.18 (5H, m), 7.71 (1H, s).

30

- 46 -

SCHEME 4

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]furan-5-carboxaldehyde (4-2)

30 A solution of thieno[2,3-b]furan autal (4-1), (G.D. Hartman, et al. *J. Med. Chem.* 1992, 35, 3027) (3.92 g, 20 mmol) in THF (140 ml) was cooled to -75° and treated with n-BuLi (20 mmol). After stirring for 1 hour at -70° this was treated with HMPA (3.5 ml), followed by 1-3 (6.79 g, 20 mmol) with stirring at -70° for 3 hours and then at ambient temperature overnight. The

- 47 -

reaction mixture was quenched with 10% KHSO₄ solution and the reaction mixture was concentrated. The residue was taken up in Et₂O, washed with H₂O, brine, dried (Na₂SO₄) and concentrated. This oil was purified by flash chromatography on silica gel eluting
5 with hexane (88%) - EtOAc (12%) to give an oil which was triturated with hexane (9)-EtOAc(1) to give pure 4-2.

¹H NMR (300 MHz, CDCl₃) δ 1.06 - 1.30 (2H, m), 1.45 (9H, s),
1.50 - 1.80 (5H, m) 2.60 - 2.75 (2H, dt), 2.75 - 2.83 (2H, t), 4.02 -
10 4.18 (2H, bd), 6.39 (1H, s), 7.59 (1H, s), 9.86 (1H, s).

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]furan-5-carboxylic acid (4-3)

A solution of 4-2 (2.5 g, 6.9 mmol) in t-BuOH (200 ml)
15 was treated with a solution of NaClO₂ (7.00 g, 77.4 mmol) and NaH₂PO₄•H₂O (7.0 g, 50.7 mmol) in H₂O (70 ml), followed by 30 ml of 2-methyl-2-butene. This 2-phase mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with EtOAc (250 ml) and the organic phase was separated and
20 washed with 10% KHSO₄ solution, brine, dried and concentrated. The resulting residue was triturated with hexane to give 4-3.

¹H NMR (300 MHz, CDCl₃) δ 1.06 - 1.29 (2H, m), 1.46 (9H, s),
1.46 - 1.8 (5H, m), 2.6 - 2.75 (2H, bt), 2.75 - 2.83 (2H, t), 4.01 -
25 4.20 (2H, bd), 6.36 (1H, s), 7.73 (1H, s), 8.8 (1H, vb).

2-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno-[2,3-b]furan-5-N-(3-t-butyl propionate)carboxamide (4-4)

4-3 was treated with β-alanine methyl ester as described
30 for 1-8 to give pure 4-4 after chromatography on silica gel eluting with hexane (7)-EtOAc (3).

¹H NMR (300 MHz, CDCl₃) δ 1.06 - 1.25 (2H, m), 1.47 (1H, s),
1.47 - 1.75 (5H, m), 2.50 - 2.60 (2H, t), 2.60 - 2.75 (2H, bt), 2.75 -

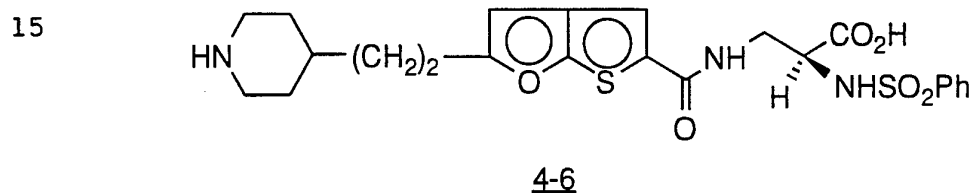
- 48 -

2.81 (2H, t), 3.61 - 3.71 (2H, q), 4.02 - 4.18 (2H, bd), 6.31 (1H, s),
6.68 (1H, bt), 7.29 (1H, s).

5 2-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]furan-5-N-(3-propionic acid)-
carboxamide (4-5)

4-4 was treated with HCl gas in EtOAc as described for
1-10 to provide 4-5.

¹H NMR (300 MHz, CD₃OD) δ 1.35 - 1.52 (2H, m), 1.59 - 1.82
10 (3H, m), 1.95 - 2.07 (2H, bd), 2.58 - 2.65 (2H, t), 2.80 - 2.88 (2H,
t), 2.88 - 3.13 (2H, dt), 3.32 - 3.45 (2H, bd), 3.55 - 3.65 (2H, m),
6.49 (1H, s), 7.52 (1H, s), 8.48 (<1H, bt).

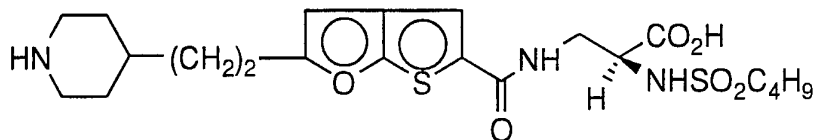


20 2-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]furan-5-N-[3-(25)-
phenylsulfonyl-aminopropionic acid]carboxamide (4-6)

4-6 was prepared from 4-3 and 2-6 in analogous fashion
to 4-5.

25 ¹H NMR (300 MHz, CD₃OD) δ 1.30 - 1.51 (2H, m), 1.60 - 1.80
(3H, m), 1.95 - 2.07 (2H, bd), 2.80 - 2.90 (2H, t), 2.90 - 3.02 (2H,
dt), 3.33 - 3.53 (3H, m), 3.66 - 3.75 (1H, m), 4.12 - 4.21 (1H, m),
6.50 (1H, s), 7.34 - 7.52 (4H, m), 7.79 - 7.87 (2H, d), 8.38 - 8.46
30 (>1H, bt)

- 49 -

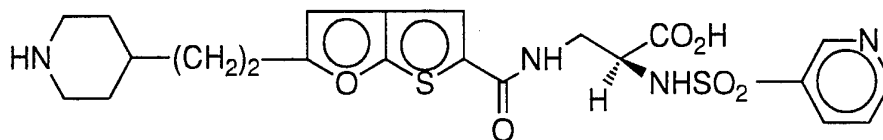
4-7

5

2-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]furan-5-N-[3-2(S)-butylsulfonyl-aminopropionic acid]carboxamide (4-7)

4-7 was prepared from 4-3 and 2-5 in analogous fashion
10 to 4-5.

¹H NMR (300 MHz, CD₃OD) δ 0.82 - 0.92 (3H, t), 1.27 - 1.50 (4H, m), 1.60 - 1.90 (5H, m), 1.94 - 2.05 (2H, bd), 2.80 - 2.88 (2H, t), 2.88 - 3.10 (4H, m), 3.32 - 3.42 (2H, bd), 3.50 - 3.61 (1H, m), 3.75
15 - 3.85 (1H, m), 4.23 - 4.31 (1H, m), 6.50 (1H, s), 7.58 (1H, s), 8.46 - 8.53 (>1H, bt).



20

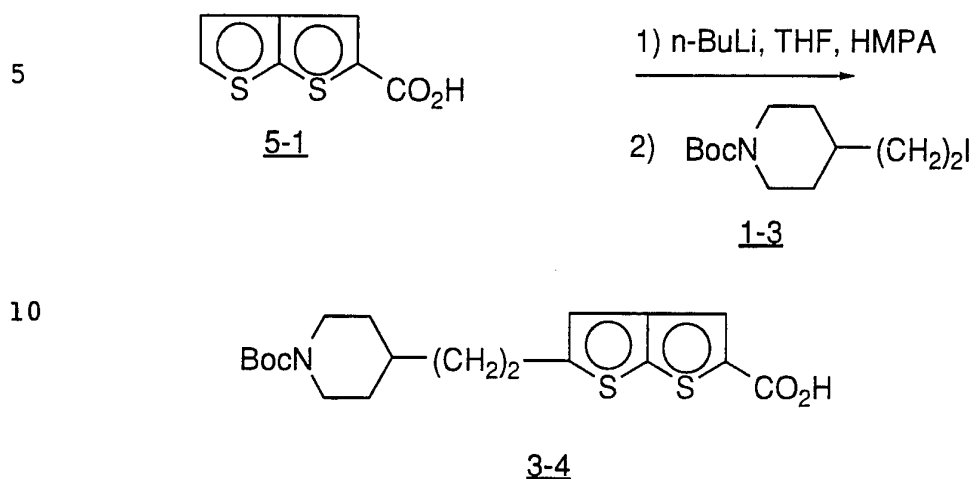
4-8

25 2-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]furan-5-N-[3-(2(S)-3-pyridylsulfonylaminopropionic acid)]carboxamide (4-8)

4-8 was prepared from 4-3 and 2-17 in analogous fashion to 4-5.

¹H NMR (300 MHz, CD₃OD) δ 1.31 - 1.41 (2H, m), 1.60 - 1.81 (3H, m), 1.96 - 2.10 (2H, bd), 2.80 - 2.90 (2H, t), 2.90 - 3.03 (2H, dt), 3.33 - 3.43 (2H, bd) 3.47 - 3.56 (1H, dd), 4.74 - 4.83 (1H, dd), 4.35 - 4.42 (1H, m), 6.50 (1H, s), 7.49 (1H, s), 7.89 - 7.98 (1H, bt), 8.68 - 8.78 (1H, bd), 8.78 - 8.85 (1H, d), 9.19 (1H, bd).
30

- 50 -

SCHEME 5

15

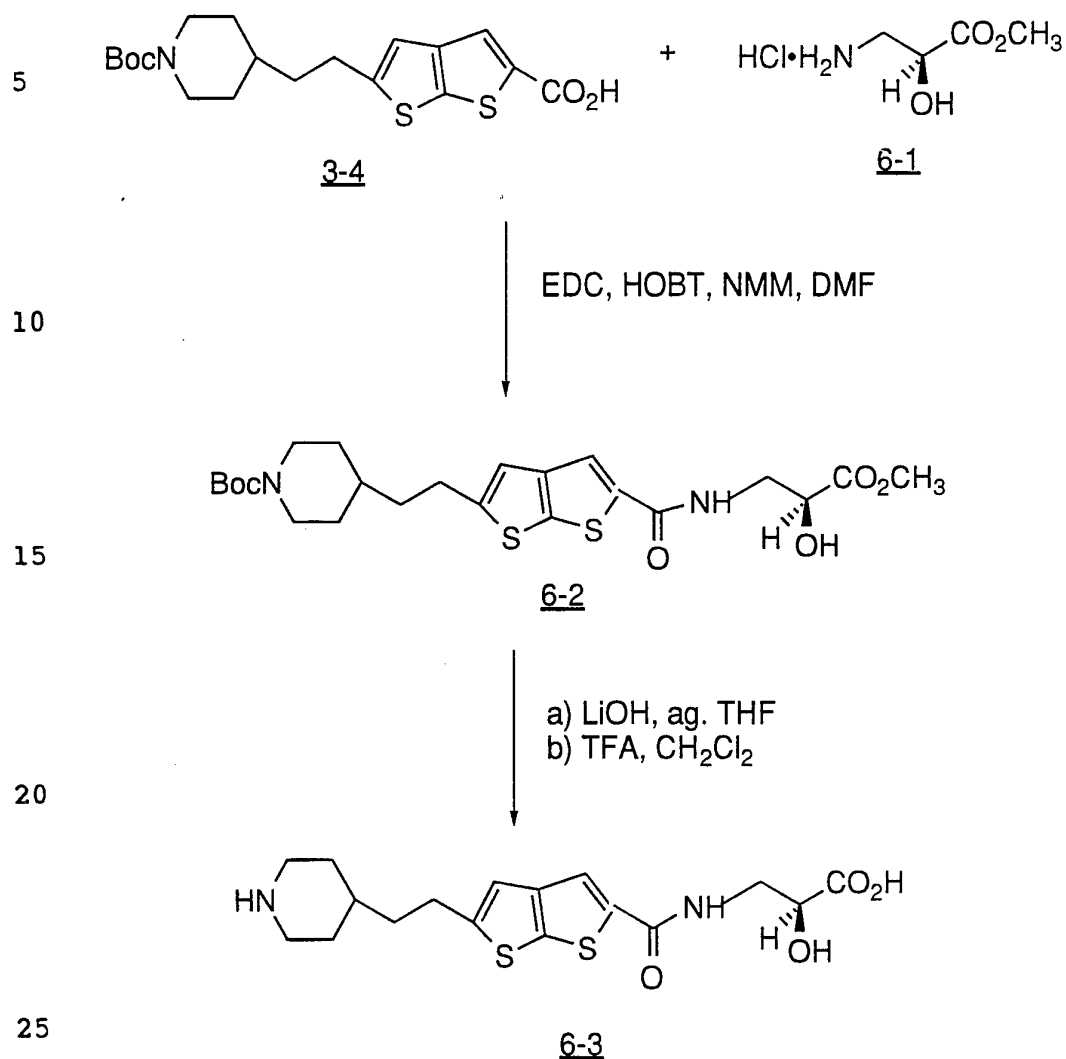
5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-carboxylic acid (3-4)

A solution of 5-1 (0.184 g, 1 mmol) (J.D. Prugh, et al. *J. Med. Chem.* 1991, 34, 1805-18) in THF (7 ml) was treated with HMPA (0.72 g, 4 mmol), cooled to -78° for 0.5 hr., and then treated with a solution of 1-3 (0.34 g, 1.0 mmol) in THF (2 ml). The resulting solution was stirred at -70° for 3 hours and then at ambient temperature overnight. The reaction mixture was concentrated and the residue was partitioned between EtOAc and 1N KHSO₄ solution.

25 The organic phase was separated, washed with water, brine, dried (MgSO₄) and concentrated. The residue was triturated with hexane to provide 3-4.

30

- 51 -

SCHEME 6

5-[2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]-
thiophene-2-N-[3-(methyl 2(S)-hydroxypropionate)carboxamide] (6-2)

30 A stirred solution of 3-4 (80 mg, 0.20 mmol), 6-1 (for preparation see *Pol. J. Chem.* 53 (7-8), 1533, 1993) (38 mg, 0.24 mmol), HOBT (35 mg, 0.25 mmol), NMM (77 μ L, 0.70 mmol), and DMF (2 mL) at -15° was treated with EDC (50 mg, 0.25 mmol) in a single portion followed by removal of the cooling bath. After 20 hours the reaction mixture was diluted with EtOAc and then washed

- 52 -

with 10% KHSO₄, saturated NaHCO₃, H₂O, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 80% EtOAc/hexanes) gave 6-2 as a white solid.

5 ¹H NMR (400 MHz, CDCl₃) δ 1.14 (m, 2H), 1.46 (9H, s), 1.45 - 1.74 (5H, m), 2.67 (2H, m), 2.91 (2H, bt), 3.92 (1H, m), 3.80 (2H, m), 3.83 (3H, s), 4.09 (2H, m), 4.40 (1H, m), 6.38 (1H, m), 6.91 (1H, s), 7.53 (1H, s).

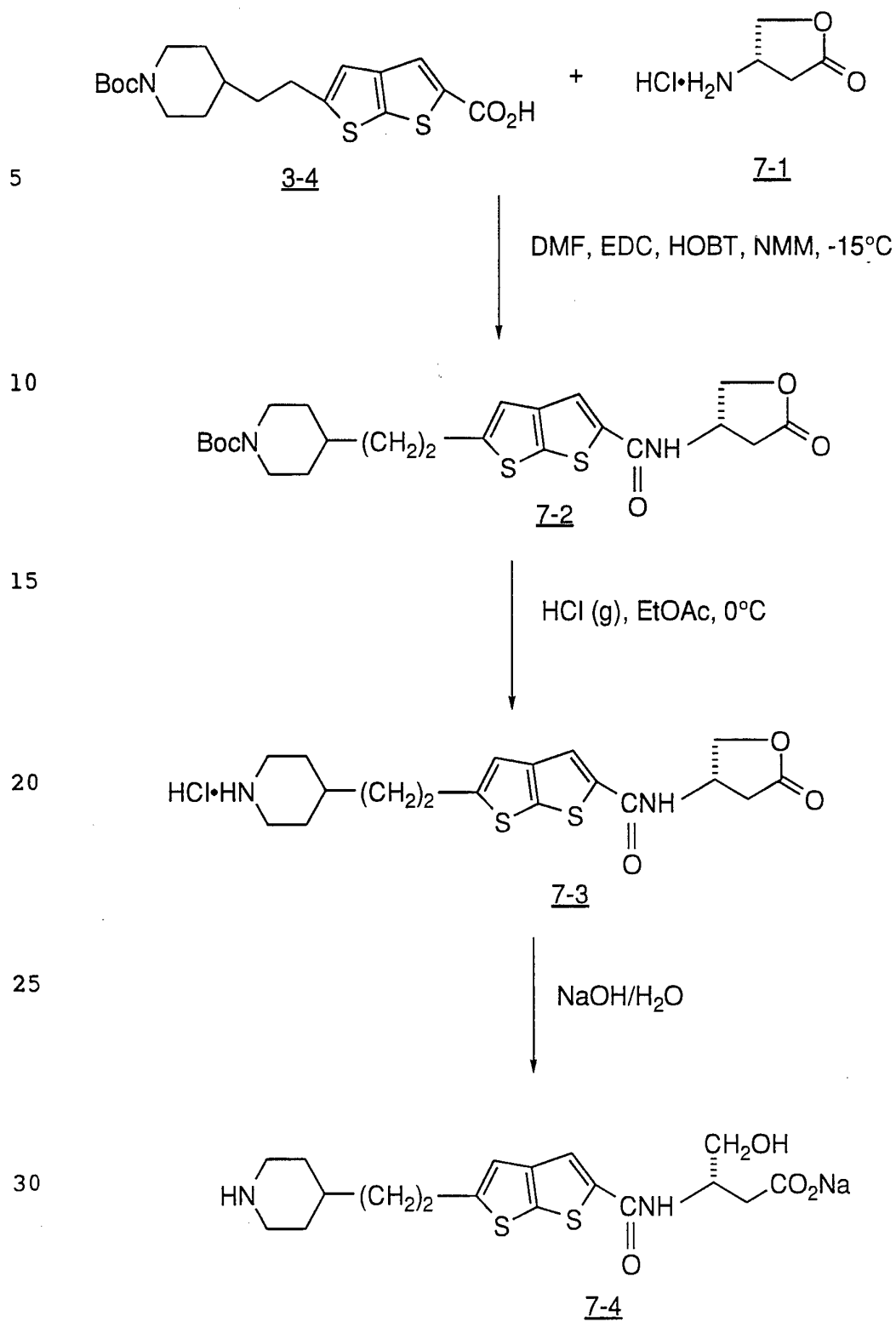
10 5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3-(2(S)-hydroxy-propionic acid)] carboxamide (6-3)

To a stirred solution of 6-2 (78 mg, 0.16 mmol) in THF (1.6 ml) was added 1N LiOH (0.4 ml, 0.4 mmol). After 2.5 hours the reaction mixture was diluted with EtOAc and washed sequentially
15 with 10% KHSO₄, and brine, and then concentrated. The resulting white solid was dissolved in CH₂Cl₂ (0.8 ml) and then treated with TFA (0.8 ml). After 1 hour the reaction was concentrated and the residual TFA removed with toluene. Trituration of the resulting oil
20 with 10:1:1 ethanol/NH₄OH/H₂O gave 6-3 as a colorless solid after filtration.

25 ¹H NMR (400 MHz, D₂O) δ 1.23 (2H, m), 1.47 (1H, m), 1.53 (2H, m), 1.70 (2H, m), 2.73 (4H, m), 3.22 (2H, m), 3.57 (2H, d), 4.32 (1H, t), 6.80 (1H, s), 7.58 (1H, s).

30

- 53 -



- 54 -

5-[2-(N-t-Butoxycarbonylpiperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[4(S)-furanone]carboxamide (7-2)

Utilizing the procedure for converting 3-4 to 6-2, 3-4 (100 mg, 0.25 mmol) was coupled to 7-1 (for preparation see: Hvidt, T. et al., *Can. J. Chem.*, 66(4), 779, 1988; 41 mg, 0.30 mmol) to afford 7-2 (120 mg) as a white solid after flash chromatography (silica, 75% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 1.13 (2H, m), 1.46 (9H, s), 1.45-1.70 (5H, m), 2.64 (3H, m), 2.86 (2H, m), 2.95 (1H, m), 4.08 (2H, m), 4.40 (1H, m), 4.59 (1H, m), 4.92 (1H, m), 6.88 (1H, s), 7.41 (1H, bd), 7.64 (1H, s).

5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[4(S)-furanone]carboxamide (7-3)

7-2 (119 mg, 0.25 mmol) was dissolved in EtOAc and treated with HCl gas as described for 2-17 to provide 7-3 (93 mg) as a colorless solid.

¹H NMR (400 MHz, D₂O) δ 1.27 (2H, m), 1.50 (1H, m), 1.57 (2H, m), 1.83 (2H, m), 2.58 (1H, dd), 2.79 (4H, m), 2.97 (1H, dd), 3.26 (2H, m), 4.30 (1H, dd), 6.92 (1H, s), 7.60 (1H, s).

5-[2-(Piperidin-4-yl)ethyl]thieno[2,3-b]thiophene-2-N-[3(S)-hydroxy-methyl(sodium)propionate]carboxamide (7-4)

7-3 (21 mg, 45 μg) was dissolved in 50 mM NaOH (4.55 ml). After 1 hour the solution was concentrated to dryness to give 7-4 as a solid.

¹H NMR (400 MHz, D₂O) δ 0.90 (2H, m), 1.13 (1H, m), 1.36 (2H, m), 1.45 (2H, m), 2.32 (4H, m), 2.60 (2H, m), 2.80 (2H, m), 3.54 (2H, m), 4.28 (1H, m), 6.82 (1H, s)

- 55 -

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

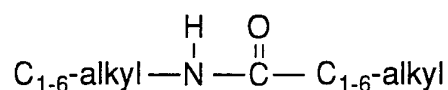
5 Acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, 10 hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, 15 subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

The term "pharmaceutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that 20 is being sought by a researcher or clinician. The term "anti-coagulant" shall include heparin, and warfarin. The term "thrombolytic agent" includes agents such as streptokinase and tissue plasminogen activator. The term "platelet anti-aggregation agent" includes such as aspirin and dipyridamole.

25 The term "alkyl" means straight or branched alkane, alkene or alkyne. The term "alkoxy" includes an alkyl portion where alkyl is as defined above. The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The 30 C_{0-n} or C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit. The term "halogen" includes fluorine, chlorine, iodine and bromine. The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. Under standard

- 56 -

nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₆ alkyl substituted with C₁₋₆ alkylcarbonylamino is equivalent to



10

In the schemes and examples below, various reagent symbols have the following meanings:

- BOC
 (or Boc): t-butyloxycarbonyl.
 Pd-C: Palladium on activated carbon catalyst.
 DMF: Dimethylformamide.
 DMSO: Dimethylsulfoxide.
 TFA: trifluoroacetic acid.
 CBZ: Carbobenzyloxy.
 CH₂Cl₂: Methylene chloride.
 CHCl₃: chloroform.
 EtOH: ethanol.
 MeOH: methanol.
 EtOAc: ethyl acetate.
 HOAc: acetic acid.
 BOP: Benzotriazol-1-yloxytris(dimethylamino)-phosphonium, hexafluorophosphate.
 EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide.
 Oxone: potassium peroxyxymonosulfate.
 LDA: Lithium diisopropylamide.

The compounds of the present invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills,

- 57 -

powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the
5 compound desired can be employed as an anti-aggregation agent.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa
10 receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may
15 form thrombi and thromboemboli. The compounds of the present invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere
20 to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between gpIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko et al., Amer. J. Physiol., 252(H), 615-621 (1987)). Platelets released from artificial surfaces show impaired hemostatic function. Compounds
25 of the invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or
30 coronary artery bypass procedures. They may also be used to prevent myocardial infarction.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the

- 58 -

patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe
5 the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably
10 0.1-100 mg/kg/day and most preferably 0.1-20 mg/kg/day.

Intravenously, the most preferred doses will range from about 1 to about 100 µg/kg/minute during a constant rate infusion.

Advantageously, compounds of the present invention may be administered in divided doses of two, three, or four times daily.
15 Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the
20 dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical
25 diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

30 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and

- 59 -

the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

- 60 -

The compounds of the present invention can also be co-administered with suitable anticoagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies.

5 They may also be combined with heparin, aspirin, or warfarin.

Preferred compounds of the invention are selected from the group consisting of:

10

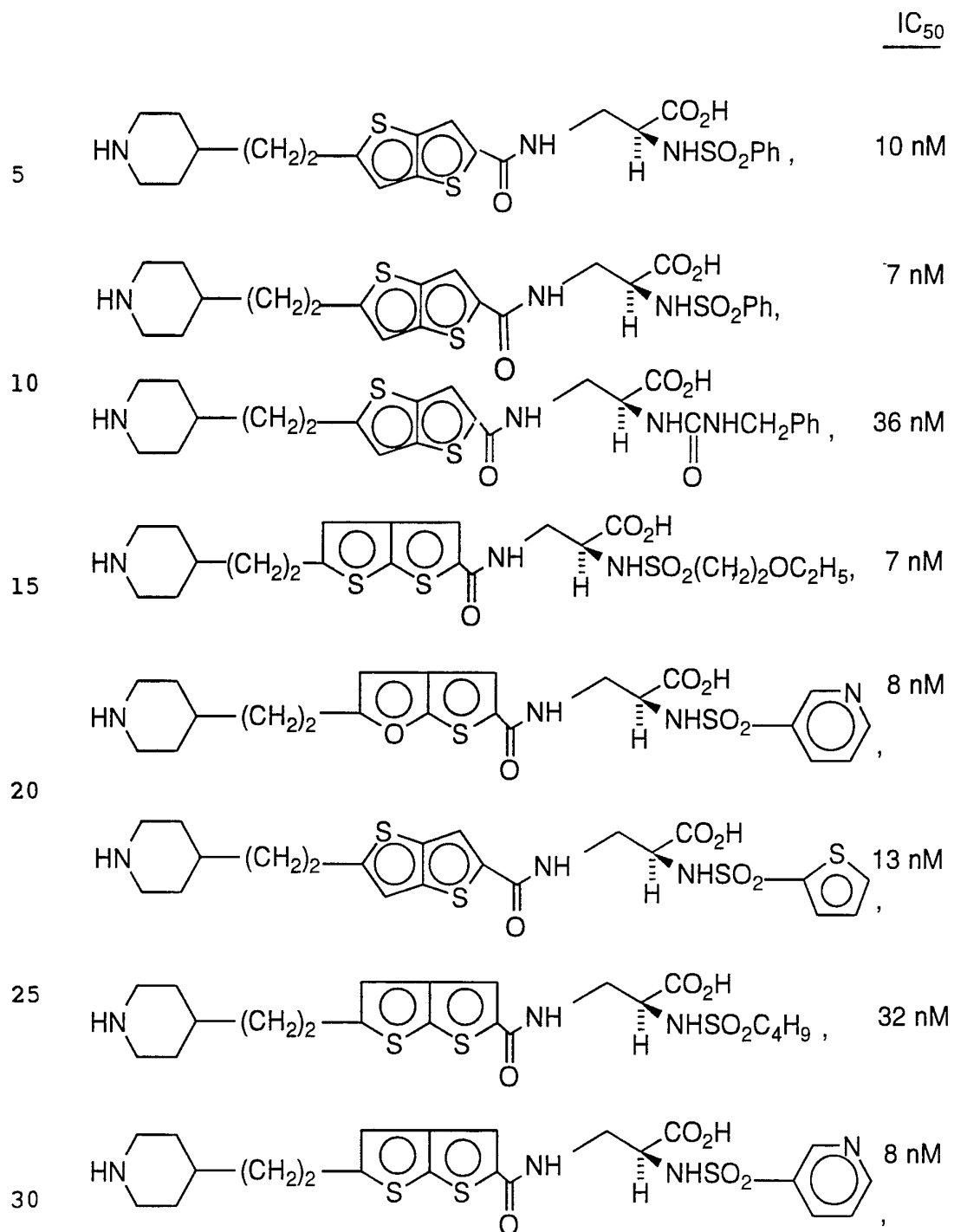
15

20

25

30

- 61 -



- 62 -

		<u>IC₅₀</u>
5		8 nM
10		410 nM
15		76 nM
20		8 nM
25		5 nM
30		42 nM
		800 nM

Platelet aggregation is measured at 37° C in a Chronolog aggregometer. The reaction mixture contains gel-filtered human

- 63 -

platelets (2×10^8 per ml), fibrinogen (100 micrograms per ml (ug/ml)), Ca^{2+} (1mM), and the compound to be tested. The aggregation is initiated by adding 10mM ADP 1 minute after the other components are added. The reaction is then allowed to
5 proceed for at least 2 minutes. The extent of inhibition of aggregation is expressed as the percentage of the rate of aggregation observed in the absence of inhibitor. The IC_{50} is the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

10 The novel compounds of the present invention were prepared according to the procedure of the following examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is
15 considered as the invention, and any combination of the compounds or their moieties may itself form a genus.

In addition to the following preparative procedures, several examples of in-vitro bioactivity of compounds within the scope of the present invention are indicated. To illustrate, one test
20 which is used to evaluate fibrinogen receptor antagonist activity is based on evaluation of the inhibition of ADP-stimulated platelet aggregation. Aggregation requires that fibrinogen bind to and occupy the platelet fibrinogen receptor site. Inhibitors of fibrinogen binding inhibit platelet aggregation. In the ADP-stimulated platelet
25 aggregation assay used to determine inhibition associated with the compounds claimed in the instant invention, human platelets are isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine
30 serum albumin.

Therapeutic Treatment

Compounds of the invention may be used for inhibiting integrin protein-complex function relating to cell attachment activity.

- 64 -

They may be administered to patients where inhibition of human or mammalian platelet aggregation or adhesion is desired.

Compounds of the invention may find utility in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in
5 cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of the invention may
10 be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

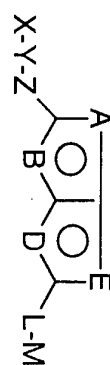
The following table exemplifies additional compounds falling within the scope of the present invention.

15

20

25

30



X	Y	Z	A	B	E	D	L	M
H ₂ N	CH ₂	CH ₂	CH	O	CH	S		
CH ₃ NH	CH ₂	O	CH	S	CH	O		
		NH	CH	S	CH	S		
	(CH ₂) ₆	N(CH ₃)	CH	S	CH	S		

5

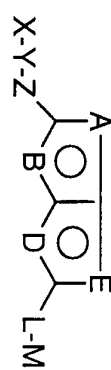
10

15

20

25

30



X	Y	Z	A	B	E	D	L	M
	$-\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)-\text{CH}_2-$	$\text{N}(\text{CH}_2\text{Ph})_2$	CH	NH	CH	S	CH_2SOCH_2	$\text{CH}_2\text{COCH}_2\text{OC}(=\text{O})-$
	$-\text{CH}_2\text{N}(\text{CH}_2\text{O})-\text{C}-\text{CH}_2-$	$(\text{CH}_2)_2$	CH	NH	CH	O	$\text{CH}_2\text{SO}_2\text{CH}_2$	$-\text{CH}_2\text{CONH}-\text{CH}(\text{Ph})-\text{CO}_2\text{H}$
	$-\text{CH}_2\text{CN}-\text{C}(=\text{O})-\text{CH}_2-$	$(\text{CH}_2)_3$	CH	O	CH	S	$-\text{CH}=\text{CH}-$	$\text{CH}_2\text{CNH}-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)-\text{CO}_2\text{H}$

5

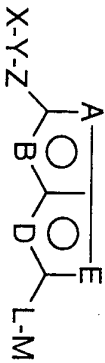
10

15

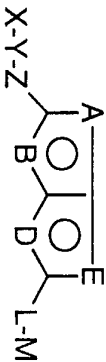
20

25

30



X	Y	Z	A	B	E	D	L	M
	$(CH_2)_3O(CH_2)_2$	$\begin{array}{c} O \\ \\ CNH \end{array}$	CH	O	CH	NH	$-C\equiv C-$	$\begin{array}{c} O \\ \\ CH_2CH-COH \\ \\ CH_2Ph \end{array}$
	$O(CH_2)_4$	$\begin{array}{c} CH_3 \\ \\ -N-C- \\ \\ O \end{array}$	O	CH	CH	S	SO_2NH	$(CH_2)_2-CH_2-COH$
	$(CH_2)_5O$	$\begin{array}{c} O \\ \\ CH_2CCH_2 \end{array}$	O	CH	S	CH	SO_2N	$\begin{array}{c} CH_2-CH-CO_2H \\ \\ NH \\ \\ O \end{array}$
	$H_2N-C-NH-$	$\begin{array}{c} HN \\ \\ CCH_2 \end{array}$	O	CH	CH	S	$\begin{array}{c} O \\ \\ CNH \end{array}$	$\begin{array}{c} CH_2-CH-CO_2H \\ \\ O=CNC_2H_5 \end{array}$



X	Y	Z	A	B	E	D	L	M
	CH_2SO_2	NH	CH	NH	CH	$\text{N}(\text{CH}_3)$	$\text{C}=\text{O}$	
	$(\text{CH}_2)_2\text{NHSO}_2$	$\text{N}(\text{CH}_3)$	O	CH	O	CH	SO_2	
	$\text{NHSO}_2(\text{CH}_2)_2$	$(\text{CH}_2)_2$	S	CH	O	CH	$\text{C}=\text{O}$ $\text{N}(\text{CH}_3)$	
	$(\text{CH}_2)_3\text{C}(=\text{O})\text{CH}_2$	CH_2	O	CH	S	CH	CH_2	

5

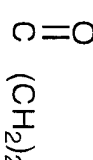
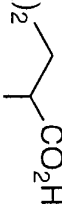
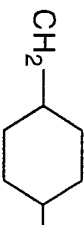

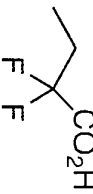
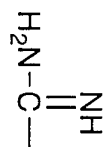
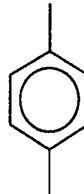
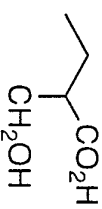
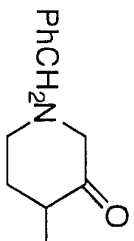
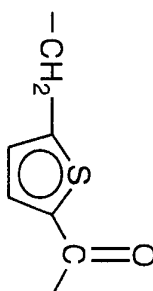
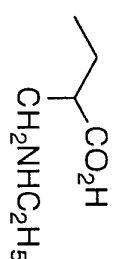
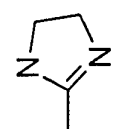

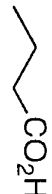
10

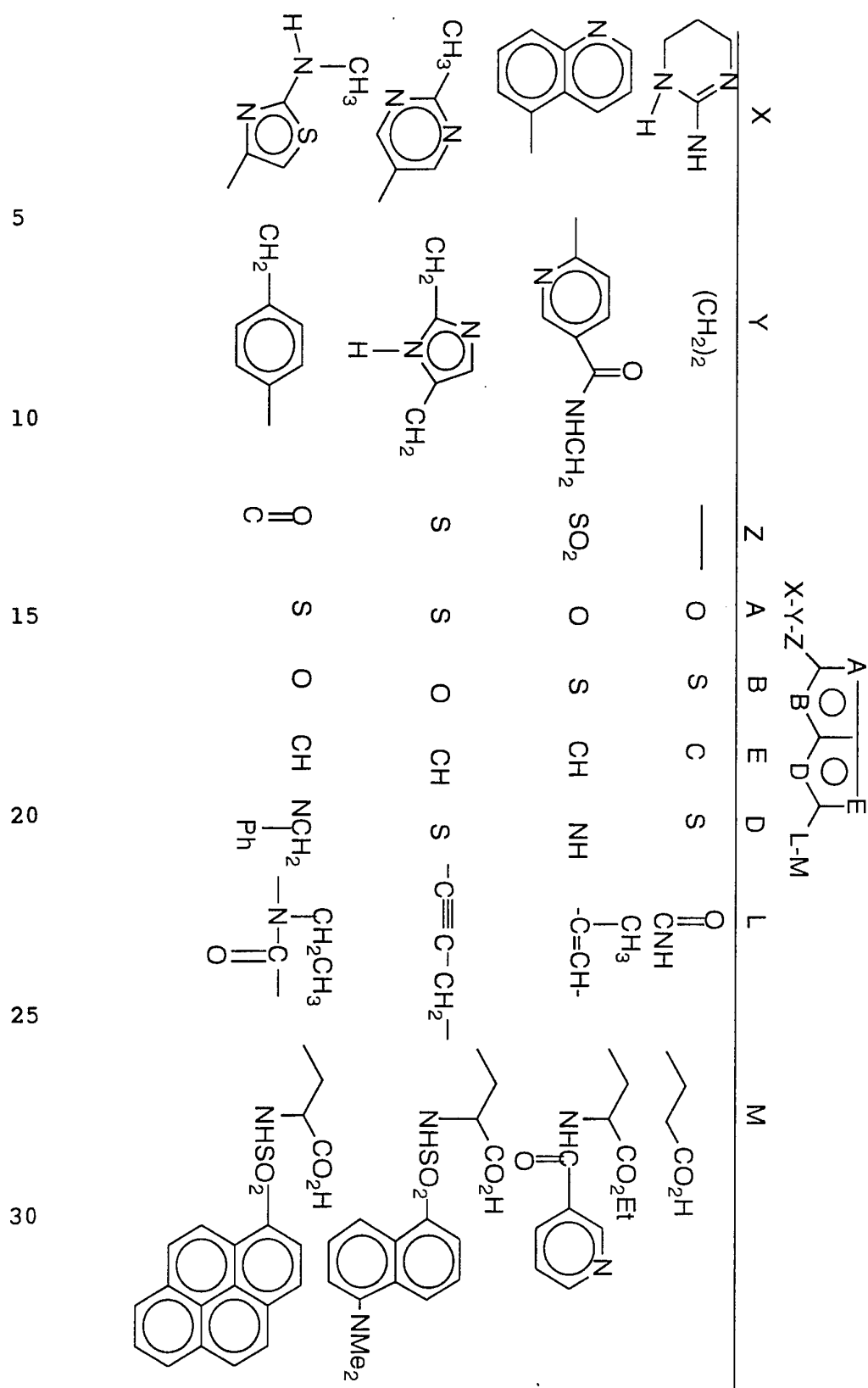
15

20

25

30

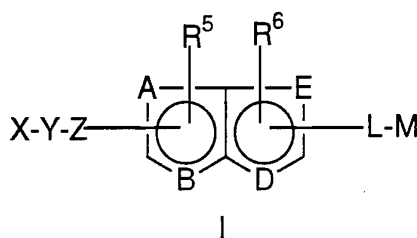
<div><div>X</div><div>Y</div><div>Z</div><div><div>X-Y-Z</div><div><div>A</div><div>B</div><div>C</div><div>D</div><div>E</div><div>L-M</div></div></div><div>M</div></div>										
CH ₃ O(CH ₂) ₃ NH-		O	S	CH	S	CH	C=C	(CH ₂) ₂		NHSO ₂ NHCH ₃
HO ₂ C(CH ₂) ₂ N		NH	S	NH	NH	S				
		—	O	NH	N	O	O			
		CH ₂	O	S	C	S	-NH-			
		—	O	S	C	S	NHCH ₂			



- 71 -

WHAT IS CLAIMED IS:

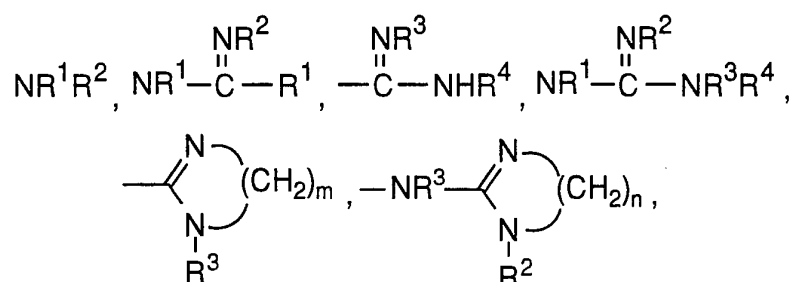
1. A compound of the general formula I



10 and the pharmaceutically acceptable salts thereof wherein:

A, B, D and E are independently selected from C, N, O and S;

15 X is



or a 4- to 10- membered mono- or
 25 polycyclic aromatic or nonaromatic ring system containing
 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and
 either unsubstituted or substituted with R^1 , R^2 , R^3 or R^4 ,
 wherein R^1 , R^2 , R^3 and R^4 are independently selected
 from the group consisting of hydrogen,
 30 C1-10 alkyl,
 aryl C0-8 alkyl,
 oxo,
 thio,
 amino C0-8 alkyl, C1-3 acylamino C0-8 alkyl,
 C1-6 alkylamino C0-8 alkyl,

- 72 -

C₁₋₆ dialkylamino C₀₋₈ alkyl,
 C₁₋₄ alkoxy C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyl, C₁₋₃ alkoxy carbonyl C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy, or
 5 hydroxy C₀₋₆ alkyl, where m and n are integers
 independently chosen from 2-5;

Y is C₀₋₈ alkyl, C₀₋₈ alkyl (C₄₋₁₀ cycloalkyl),
 C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
 10 C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-O-C₀₋₈ alkyl,
 C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl, or
 C₀₋₈ alkyl-SO₂-NR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-NR³-SO₂-C₀₋₈ alkyl,
 15 C₀₋₈ alkyl-CO-C₀₋₈ alkyl,
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,

(CH₂)₀₋₆ aryl-C(=O)-(CH₂)₀₋₆, or

20 (CH₂)₀₋₆ aryl-C(=O)-NH-(CH₂)₀₋₆ ;

Z and L are independently chosen from

25 (CH₂)_mC(=O)NR³(CH₂)_n, (CH₂)_mNR³C(=O)(CH₂)_n, (CH₂)_mNR³(CH₂)_n,
 (CH₂)_mC(=O)(CH₂)_n, (CH₂)_mC(S)(CH₂)_n, (CH₂)_mSO₂(CH₂)_n,
 (CH₂)_mS(CH₂)_n, (CH₂)_mSO(CH₂)_n,
 30 (CH₂)_mSO₂NR³(CH₂)_n,
 (CH₂)_mNR³SO₂(CH₂)_n, (CH₂)_mCR³=CR⁴(CH₂)_n,
 (CH₂)_mC≡C(CH₂)_n, (CH₂)_m, and (CH₂)_mO(CH₂)_n,

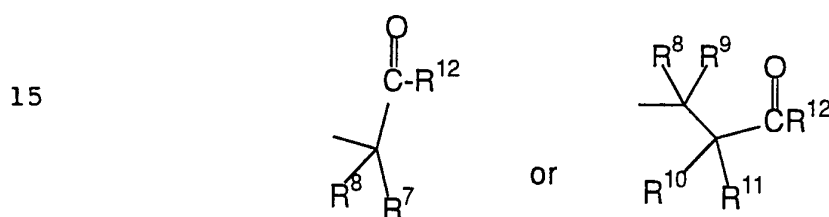
where m and n are integers independently chosen from 0-6;

- 73 -

R^5 and R^6 are independently chosen from:

hydrogen,
 C1-6 alkyl,
 C0-6 alkylcarboxy C0-6 alkyl,
 C0-6 alkyloxy C0-6 alkyl,
 hydroxy C0-6 alkyl,
 aryl C0-6 alkyl, and
 halogen;

10 M is:



wherein R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from:

20

hydrogen, fluorine,
 C1-8 alkyl, hydroxyl, hydroxy C1-6 alkyl, carboxy C0-6
 alkyl, C1-6 alkyloxy, aryl C0-6 alkyloxy, C1-6
 alkylcarbonyl, aryl C0-6
 alkylcarbonyl, C1-6 alkylcarbonyloxy, aryl C0-6
 alkylcarbonyloxy, C1-6 alkylaminocarbonyloxy C0-6
 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8-alkyl,
 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,

30

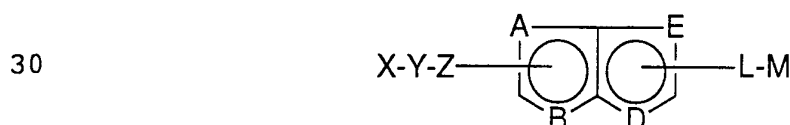
- 74 -

C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, and
 aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, and
 wherein groups may be unsubstituted or substituted with
 one or more substituents selected from R¹ and R²; and

R¹² is chosen from

hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, and
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, or
 an L- or D-amino acid joined by an amide linkage and
 wherein the carboxylic acid moiety of said amino acid is
 as the free acid or is esterified by C₁₋₆ alkyl.

2. A compound of Claim 1 having the formula



A, B, D and E are independently chosen from C, N, O and S;

X is $-\text{NR}^1\text{R}^2$, $\text{NR}^1 - \overset{\text{NR}^2}{\underset{\parallel}{\text{C}}} - \text{R}^1$, $-\overset{\text{NR}^3}{\underset{\parallel}{\text{C}}} - \text{NHR}^4$,

- 75 -

$$-NR^1-\overset{\overset{NR^2}{\parallel}}{C}NR^3R^4$$
, or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^1 , R^2 , R^3 or R^4 , wherein R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

Y is C₀₋₈ alkyl,
 C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
 C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-O-C₀₋₈ alkyl,
 C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl,
 C₀₋₈ alkyl-SO₂-NR³-C₀₋₈ alkyl, or
 (CH₂)₀₋₆ aryl (CH₂)₀₋₆;

Z and L are independently chosen from:

$$(CH_2)_m \overset{\overset{O}{\parallel}}{C} NR^3 (CH_2)_n, (CH_2)_m NR^3 \overset{\overset{O}{\parallel}}{C} (CH_2)_n,$$

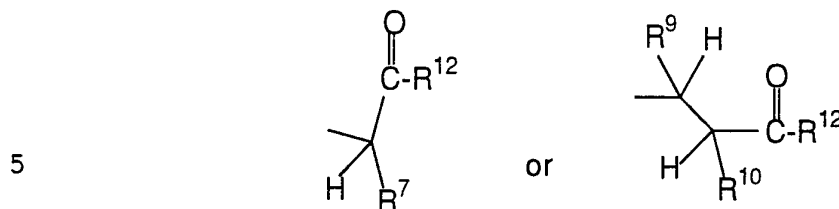
$$(CH_2)_m \overset{\overset{O}{\parallel}}{C} (CH_2)_n, (CH_2)_m SO_2 (CH_2)_n,$$

$$(CH_2)_m SO_2 NR^3 (CH_2)_n, (CH_2)_m NR^3 SO_2 (CH_2)_n, \text{ or } (CH_2)_m,$$

where m and n are integers independently chosen from 0-6;

- 76 -

M is:



wherein R⁷, R⁹, and R¹⁰ are independently chosen from:

hydrogen, fluorine, hydroxyl,
 C₁₋₈ alkyl,
 C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,
 aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl, and
 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl;

30 R¹² is chosen from

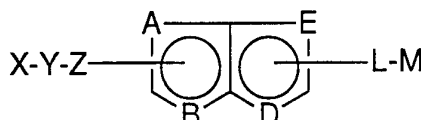
hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, and
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,

- 77 -

and the pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 having the formula

5



10 and the pharmaceutically acceptable salts, wherein:

A, B, D and E are independently chosen from C, N, O and S;

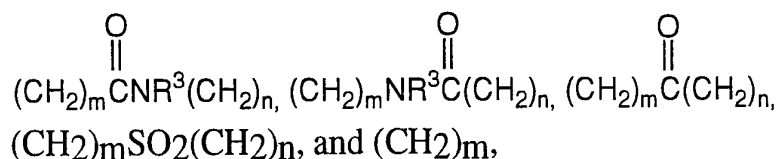
15 X is $\text{-NR}^1\text{R}^2$, $\text{-}\overset{\text{NR}^3}{\underset{\text{||}}{\text{C}}}\text{-NHR}^4$ or a 4- to 8- membered nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and O wherein R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of hydrogen,

20 C1-10 alkyl, or aryl C0-8 alkyl;

Y is C0-8 alkyl,
C0-8 alkyl- NR^3 -CO-C0-8 alkyl,
25 C0-8 alkyl-CONR³-C0-8 alkyl,
C0-8 alkyl-O-C0-8 alkyl, or
C0-8 alkyl-S(O_n)-C0-8 alkyl;

Z and L are independently chosen from:

30



where m and n are integers independently chosen from 0-6;

- 78 -

M is:



wherein R^9 and R^{10} are independently chosen from:

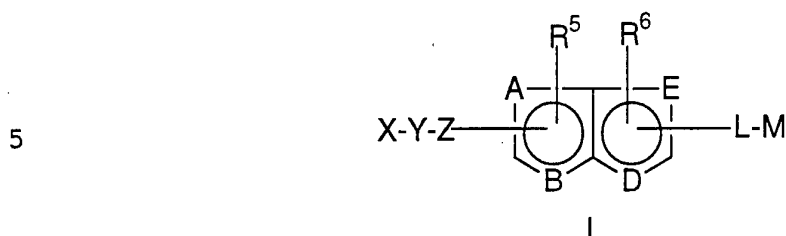
- 10 hydrogen, fluorine,
C1-8 alkyl,
C3-8 cycloalkyl,
aryl C0-6 alkyl,
C0-6 alkylamino C0-6 alkyl,
C0-6 dialkylamino C0-6 alkyl,
15 C1-8 alkylsulfonylamino C0-6 alkyl,
aryl C0-6 alkylsulfonylamino C0-6 alkyl,
C1-8 alkyloxycarbonylamino C0-8-alkyl,
aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
C1-8 alkylcarbonylamino C0-6 alkyl,
20 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminocarbonylamino C0-8 alkyl,
C0-8 alkylaminocarbonylamino C0-6 alkyl,
aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
25 C1-6 alkylsulfonyl C0-6 alkyl,
aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl, or
aryl C0-6 alkylcarbonyl C0-6 alkyl; and

30 R^{12} is chosen from

- hydroxy,
C1-8 alkyloxy, and
aryl C0-6 alkyloxy.

- 79 -

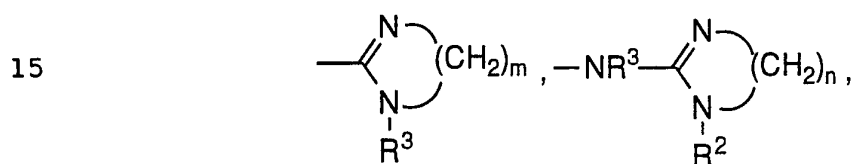
4. A compound of the general formula I



and the pharmaceutically acceptable salts thereof wherein:

10 A, B, D and E are independently selected from C, N, O and S;

X is



20 or a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with R² or R³ wherein R² and R³ are independently selected

25 from the group consisting of hydrogen, C₁-10 alkyl, aryl C₀-8 alkyl, oxo, thio,

30 amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl, C₁-6 alkylamino C₀-8 alkyl, C₁-6 dialkylamino C₀-8 alkyl, C₁-4 alkoxy C₀-6 alkyl, carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6 alkyl, carboxy C₀-6 alkyloxy, or

- 80 -

hydroxy C₀₋₆ alkyl, where m and n are integers independently chosen from 2-5;

Y is C₀₋₈ alkyl, C₀₋₈ alkyl (C₄₋₁₀ cycloalkyl),
 C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
 C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-O-C₀₋₈ alkyl,
 C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl, or
 C₀₋₈ alkyl-SO₂-NR³-C₀₋₈ alkyl-,
 C₀₋₈ alkyl-NR³-SO₂-C₀₋₈ alkyl-,
 C₀₋₈ alkyl-CO-C₀₋₈ alkyl,
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,

(CH₂)₀₋₆ aryl-C(=O)-(CH₂)₀₋₆, or

(CH₂)₀₋₆ aryl-C(=O)-NH-(CH₂)₀₋₆;

Z and L are independently chosen from

(CH₂)_mC(=O)NR³(CH₂)_n, (CH₂)_mNR³C(=O)(CH₂)_n, (CH₂)_mNR³(CH₂)_n,

(CH₂)_mC(=O)(CH₂)_n, (CH₂)_mC(=S)(CH₂)_n, (CH₂)_mSO₂(CH₂)_n,

(CH₂)_mS(CH₂)_n, (CH₂)_mSO(CH₂)_n,
 (CH₂)_mSO₂NR³(CH₂)_n,
 (CH₂)_mNR³SO₂(CH₂)_n, (CH₂)_mCR³=CR²(CH₂)_n,
 (CH₂)_mC≡C(CH₂)_n, (CH₂)_m, and (CH₂)_mO(CH₂)_n,

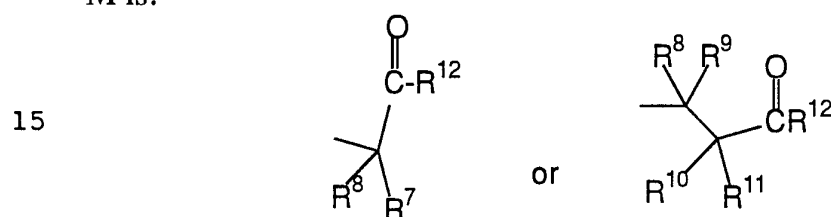
- 81 -

where m and n are integers independently chosen from 0-6;

R⁵ and R⁶ are independently chosen from:

- 5
hydrogen,
C₁₋₆ alkyl,
C₀₋₆ alkylcarboxy C₀₋₆ alkyl,
C₀₋₆ alkyloxy C₀₋₆ alkyl,
hydroxy C₀₋₆ alkyl,
aryl C₀₋₆ alkyl, and
10 halogen;

M is:



wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from:

- 20 hydrogen, fluorine,
C₁₋₈ alkyl, hydroxyl, hydroxy C₁₋₆ alkyl, carboxy C₀₋₆
alkyl, C₁₋₆ alkyloxy, aryl C₀₋₆ alkyloxy, C₁₋₆
alkylcarbonyl, aryl C₀₋₆
25 alkylcarbonyl, C₁₋₆ alkylcarbonyloxy, aryl C₀₋₆
alkylcarbonyloxy, C₁₋₆ alkylaminocarbonyloxy C₀₋₆
alkyl,
C₃₋₈ cycloalkyl,
aryl C₀₋₆ alkyl,
30 C₀₋₆ alkylamino C₀₋₆ alkyl,
C₀₋₆ dialkylamino C₀₋₆ alkyl,
C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,
aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,

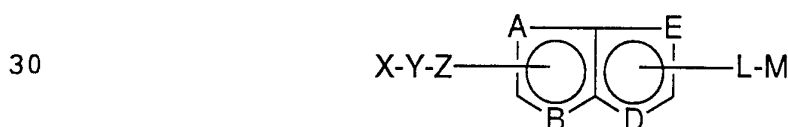
- 82 -

C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, and
 aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, and
 wherein groups may be unsubstituted or substituted with
 one or more substituents selected from R² and R³; and

R¹² is chosen from

hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, and
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, or
 an L- or D-amino acid joined by an amide linkage and
 wherein the carboxylic acid moiety of said amino acid is
 as the free acid or is esterified by C₁₋₆ alkyl.

5. A compound of Claim 4 having the formula



wherein A, B, D and E are independently chosen from C, N, O and S;

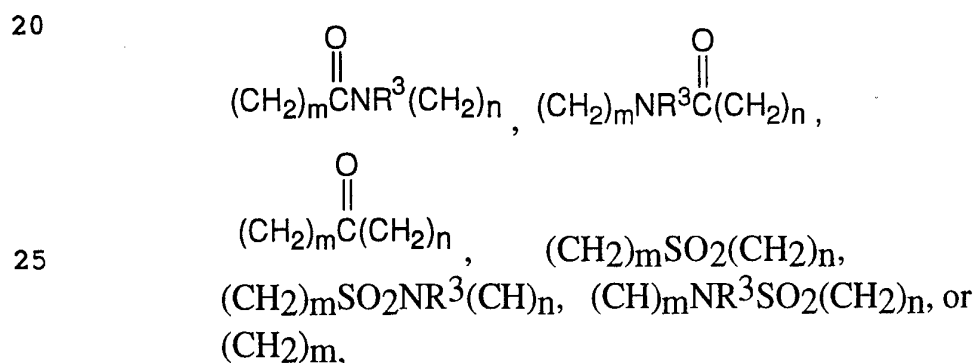
- 83 -

X is a 4- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either unsubstituted or substituted with hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

Y is C₀₋₈ alkyl, C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl, C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl, C₀₋₈ alkyl-O-C₀₋₈ alkyl, C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl, C₀₋₈ alkyl-SO₂-NR³-C₀₋₈ alkyl, or (CH₂)₀₋₆ aryl, (CH₂)₀₋₆;

R³ is selected from hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

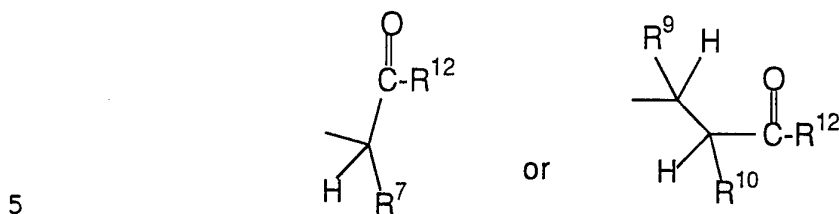
Z and L are independently chosen from:



where m and n are integers independently chosen from 0-6;

M is:

- 84 -



wherein R⁷, R⁹, and R¹⁰ are independently chosen from:

hydrogen, fluorine, hydroxyl,
 C₁₋₈ alkyl,
 10 C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₀₋₆ alkylamino C₀₋₆ alkyl,
 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 15 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 C₁₋₈ alkyloxycarbonylamino C₀₋₈-alkyl,
 aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 20 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 25 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl, and
 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl; and

R¹² is chosen from

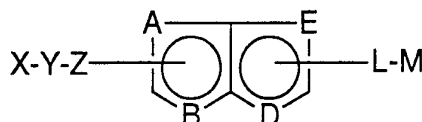
30 hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy, and
 aryl C₀₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,

- 85 -

and the pharmaceutically acceptable salts thereof.

6. A compound of Claim 5 having the formula

5



10 and the pharmaceutically acceptable salts, wherein:

A, B, D and E are independently chosen from C, N, O and S;

15 X is a 4- to 8- membered nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N and O;

Y is C₀₋₈ alkyl,
 20 C₀₋₈ alkyl-NR³-CO-C₀₋₈ alkyl,
 C₀₋₈ alkyl-CONR³-C₀₋₈ alkyl,
 C₀₋₈ alkyl-O-C₀₋₈ alkyl, or
 C₀₋₈ alkyl-S(O_n)-C₀₋₈ alkyl;

25 R³ is hydrogen, C₁₋₁₀ alkyl, or aryl C₀₋₈ alkyl;

Z and L are independently chosen from:

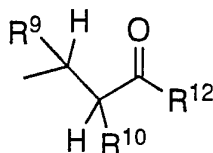
30 $(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{CNR}^3 (\text{CH}_2)_n$, $(\text{CH}_2)_m \text{NR}^3 \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$, $(\text{CH}_2)_m \overset{\text{O}}{\parallel} \text{C} (\text{CH}_2)_n$,
 $(\text{CH}_2)_m \text{SO}_2 (\text{CH}_2)_n$, and $(\text{CH}_2)_m$,

where m and n are integers independently chosen from 0-6;

- 86 -

M is:

5



wherein R^9 and R^{10} are independently chosen from:

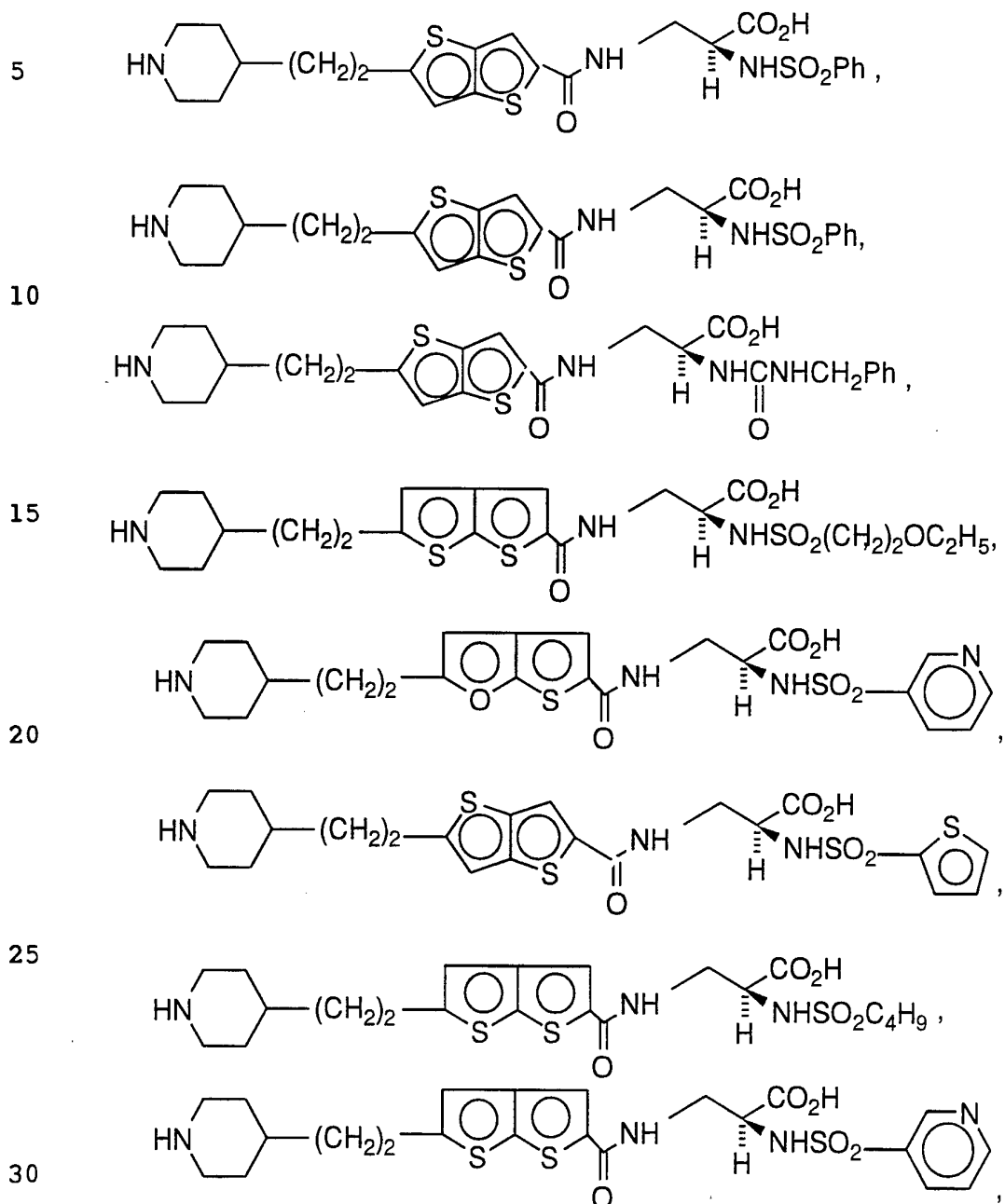
- hydrogen, fluorine,
 10 C1-8 alkyl,
 C3-8 cycloalkyl,
 aryl C0-6 alkyl,
 C0-6 alkylamino C0-6 alkyl,
 C0-6 dialkylamino C0-6 alkyl,
 15 C1-8 alkylsulfonylamino C0-6 alkyl,
 aryl C0-6 alkylsulfonylamino C0-6 alkyl,
 C1-8 alkyloxycarbonylamino C0-8-alkyl,
 aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 20 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 aryl C0-8 alkylaminocarbonyl C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 25 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 C1-6 alkylcarbonyl C0-6 alkyl, or
 aryl C0-6 alkylcarbonyl C0-6 alkyl; and

30 R^{12} is chosen from

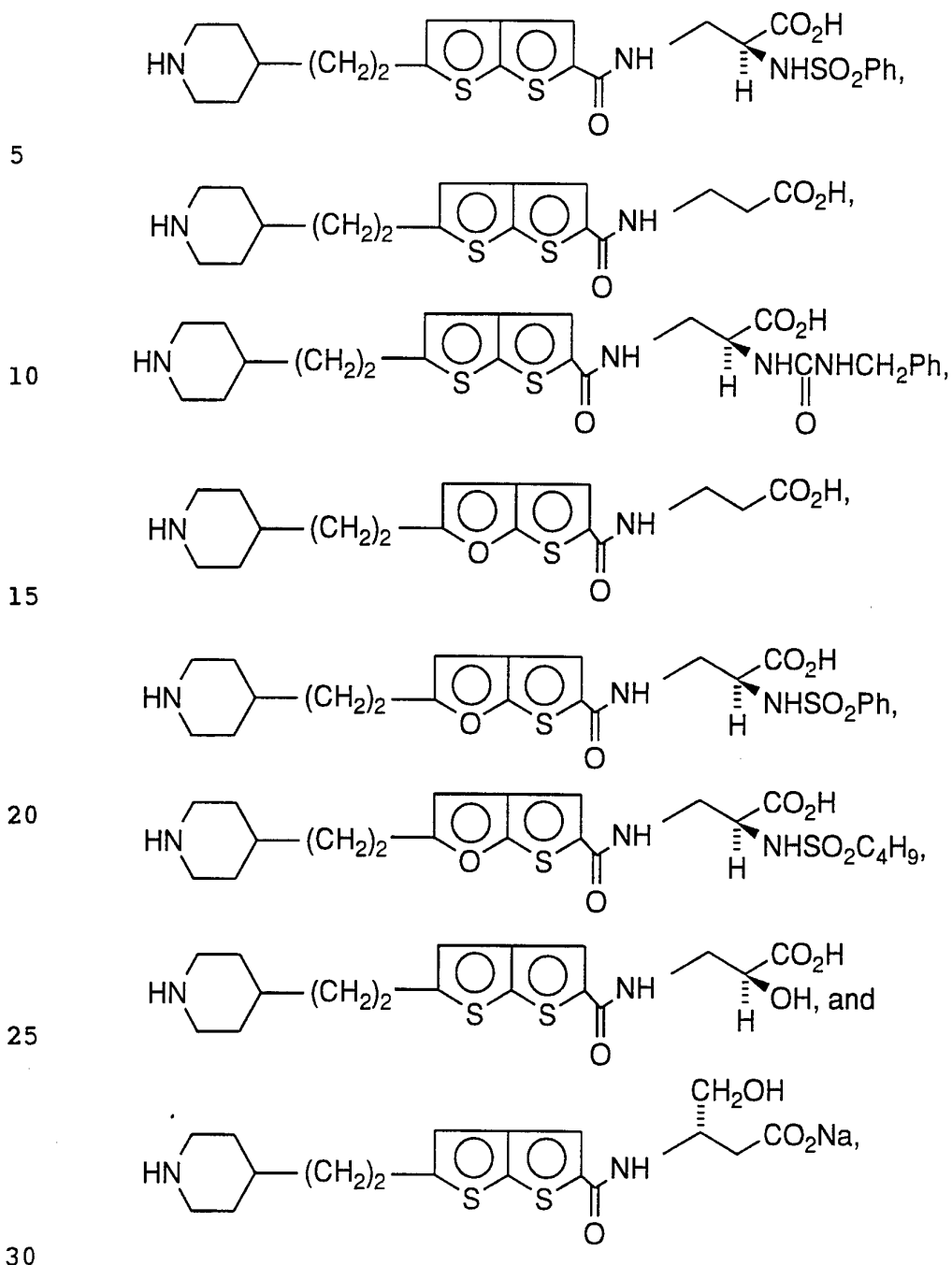
hydroxy,
 C1-8 alkyloxy, and
 aryl C0-6 alkyloxy.

- 87 -

7. A compound of Claim 6 selected from the group consisting of:



- 88 -



and pharmaceutically acceptable salts thereof.

- 89 -

8. A compound of Claim 1 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

5

9. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10

10. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

15

11. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

20

12. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with an anticoagulant agent and pharmaceutically acceptable carrier.

25

13. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

30

14. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and pharmaceutically acceptable carrier.

15. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in

- 90 -

combination with an anticoagulant and pharmaceutically acceptable carrier.

5 16. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 17. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with a thrombolytic agent and a pharmaceutically acceptable carrier.

15 18. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with an anticoagulant agent and pharmaceutically acceptable carrier.

20 19. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with an antiplatelet agent and a pharmaceutically acceptable carrier.

25 20. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 10.

30 21. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal a composition of Claim 10.

 22. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal a composition of Claim 11.

- 91 -

23. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal a composition of Claim 12.

5 24. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 13.

10 25. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 14.

15 26. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 15.

20 27. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 16.

28. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 17.

25 29. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 18.

30 30. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 19.

31. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in

- 92 -

combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

5 32. A composition for preventing or treating thrombus or embolus formation in a mammal, comprising a compound of Claim 1 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

10 33. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 31.

15 34. A method for preventing or treating thrombus or embolus formation in a mammal, comprising administering to the mammal the composition of Claim 32.

20 35. A compound of Claim 7 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

25 36. A composition for inhibiting the binding of fibrinogen to blood platelets, in a mammal, comprising a compound of Claim 7 and a pharmaceutically acceptable carrier.

30 37. A composition for inhibiting the aggregation of blood platelets, in a mammal, comprising a compound of Claim 7 and a pharmaceutically acceptable carrier.

38. A composition for preventing thrombus or embolus formation in a mammal, comprising a compound of Claim 7 and a pharmaceutically acceptable carrier.

- 93 -

- 5 39. A composition for treating thrombus or embolus formation in a mammal, comprising a compound of Claim 7 and a pharmaceutically acceptable carrier.
40. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 37.
- 10 41. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal a composition of Claim 37.
42. A method for preventing thrombus or embolus formation in a mammal, comprising administering to the mammal a composition of Claim 38.
- 15 43. A method for treating thrombus or embolus formation in a mammal, comprising administering to the mammal a composition of Claim 39.
- 20 44. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 7 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.
- 25 45. A composition for preventing or treating thrombus or embolus formation in a mammal, comprising a compound of Claim 7 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.
- 30

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/08865

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

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

INDEX MEDICUS

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

APS, DIALOG, CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,084,466 (ALIG ET AL) 28 January 1992.	1-45
A,P	US, A, 5,256,812 (ALIG ET AL) 26 October, 1993.	1-45
A,P	US, A, 5,273,982 (ALIG ET AL.) 28 December 1993.	1-45
A	EP, A, 0,372,486 (ALIG ET AL.) 13 June 1990.	1-45
A	JOURNAL OF MEDICINAL CHEMISTRY, Volume 35, No. 24, issued August 1992, G.D. Hartman et al. "Nonpeptide fibrinogen receptor antagonists. 1. Discovery and design of exosite inhibitors," pages 4640-4642.	1-45

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 02 NOVEMBER 1994	Date of mailing of the international search report 17 NOV 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CELIA CHANG Jella Collier for Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08865

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/33, 31/395, 31/445, 31/495, 31/505, 31/535; C07D 205/08, 211/32, 401/10, 401/12, 403/10, 403/12, 405/10, 405/12, 409/10, 409/12, 411/10, 411/12, 413/10, 413/12

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/183, 514/210, 514/233.5, 514/234.5, 514/235.2, 514/237.2, 514/255, 514/256, 514/314, 514/318, 514/320, 514/321, 514/322, 514/323, 514/324, 540/362, 540/480, 540/481, 544/111, 544/143, 544/145, 544/153, 544/333, 544/368, 544/376, 544/377, 546/167, 546/175, 546/193, 546/196, 546/197, 546/498, 546/199, 546/200, 546/202.

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/183, 514/210, 514/233.5, 514/234.5, 514/235.2, 514/237.2, 514/255, 514/256, 514/314, 514/318, 514/320, 514/321, 514/322, 514/323, 514/324, 540/362, 540/480, 540/481, 544/111, 544/143, 544/145, 544/153, 544/333, 544/368, 544/376, 544/377, 546/167, 546/175, 546/193, 546/196, 546/197, 546/498, 546/199, 546/200, 546/202.