PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 413/06, 401/06, 401/14, 209/14, 209/34, A61K 31/405, 31/415, 31/44, 31/445, 31/535

A1

(11) International Publication Number: **WO 95/17397**

(43) International Publication Date: 29 June 1995 (29.06.95)

(21) International Application Number: PCT/US94/14706

(22) International Filing Date: 19 December 1994 (19.12.94)

(30) Priority Data:
169,904 20 December 1993 (20.12.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 169,904 (CON)
Filed on 20 December 1993 (20.12.93)

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

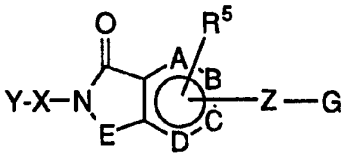
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HARTMAN, George, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). EGBERTSON, Melissa [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VASSALLO, Laura, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). BIRCHENOUGH, Laura, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

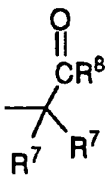
(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.

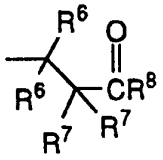
(54) Title: FIBRINOGEN RECEPTOR ANTAGONISTS



I (I)



(a)



(b)

(57) Abstract

Fibrinogen receptor antagonists of formula (I) are disclosed for use in inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets, wherein G is (a) or (b).

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**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

TITLE OF THE INVENTION
FIBRINOGEN RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part patent application of United States Serial No. 07/821,116, filed January 15, 1992, which is a continuation-in-part patent application of United States Serial No. 07/784,484, filed October 29, 1991.

FIELD OF THE INVENTION

This invention relates to the discovery of fibrinogen receptor antagonists of Formula I for use in inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets when administered to mammals, preferably humans.

BACKGROUND OF THE INVENTION

The interaction of platelets with the coagulation and fibrinolytic systems in the maintenance of hemostasis may become pathogenic, requiring prevention and treatment. The fibrinogen receptor antagonists of Formula I are useful in treating various diseases related to platelet aggregation and fibrin formation.

An interest in platelet inhibitors has reemerged as a result of a better understanding of the role of platelets and thrombosis in the pathogenesis of vascular disease, including unstable angina, acute myocardial infarction and stroke.

Platelets are cell-like anucleated fragments, found in the blood of all mammals which participate in blood coagulation. Fibrinogen is a glycoprotein present as a normal component of blood plasma. Fibrinogen participates in platelet aggregation and fibrin formation in the blood clotting mechanism. Platelets are deposited at sites of vascular injury where multiple physiological agonists act to initiate platelet aggregation culminating in the formation of a platelet plug to minimize blood loss. If the platelet plug occurs in the lumen of a blood vessel, normal blood flow is impaired.

Platelet membrane receptors are essential in the process of platelet adhesion and aggregation. Interaction of fibrinogen with a receptor on the platelet membrane complex IIb/IIIa is known to be essential for normal platelet function.

Zimmerman et al., U.S. Patent No. 4,683,291, describes peptides having utility in the study of fibrinogen-platelet, platelet-platelet, and cell-cell interactions. The peptides are described as having utility where it is desirable to retard or prevent formation of a thrombus or clot in the blood.

Pierschbacher et al., U.S. Patent No. 4,589,881, describes the sequence of an 11.5 kDal polypeptide fragment of fibronectin which embodies the cell-attachment-promoting activity of fibronectin.

Ruoslahti et al., U.S. Patent No. 4,614,517, describes tetrapeptides which alter cell-attachment activity of cells to various substrates.

Pierschbacher et al., Proc. Natl. Acad. Sci. USA, Vol. 81, pp. 5985-5988, October, 1984, describe variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Pierschbacher et. al. further assayed the cell attachment-promoting activities of a number of structures closely resembling the Arg-Gly-Asp-Ser peptide, and found "that the arginine, glycine, and aspartate residues cannot be replaced even with closely related amino acids, but that several amino acids can replace serine without loss of activity."

Ruoslahti et al., Science, Vol. 238, pp. 491-497, October 23, 1987, discuss cell adhesion proteins. They specifically state that "elucidation of the amino acid sequence of the cell-attachment domain in fibronectin and its duplication with synthetic peptides establish the sequence Arg-Gly-Asp (RGD) as the essential structure recognized by cells in fibronectin."

Cheresh, Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 6471-6475, September 1987, describes the Arg-Gly-Asp-directed adhesion receptor involved in attachment to fibrinogen and the von Willebrand Factor.

Adams et al., U. S. Patent No. 4,857,508, describes tetrapeptides which inhibit platelet aggregation and the formation of a thrombus.

Tjoeng et al., EP 352,249, describe platelet aggregation inhibitors which antagonize interactions between fibrinogen and/or extracellular matrix proteins and the platelet gpIIb/IIIa receptor.

Alig et al., EP 372,486, describe N-aryl beta-amino acids which inhibit fibrinogen, fibronectin and von Willebrand factor to the blood platelet fibrinogen receptor (glyco-protein IIb/IIIa).

Alig et al., EP 381,033, describe di-aryl or heteroaryl substituted alkanoic acid derivatives of a defined formula which inhibit binding of proteins to their specific receptors on cell surfaces, including fibrinogen.

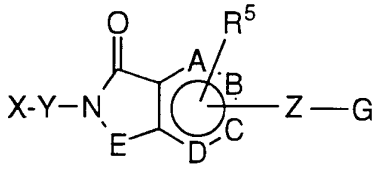
Alig et al., EP 384,362, describe glycine peptides of a specified formula containing an amidine group which inhibit binding of fibrinogen to platelet fibrinogen receptors.

Horwell et al., EP 405,537, describe N-substituted cycloalkyl and polycycloalkyl alpha-substituted Trp-Phe- and phenethylamine derivatives which are useful for treating obesity, hypersecretion of gastric acid in the gut, gastrin-dependent tumors, or as antipsychotics.

It is an object of the present invention to provide fibrinogen receptor antagonists for use in inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets. Another aspect of the present invention is to provide novel fibrinogen receptor antagonist compounds. Other objects of the present invention are to provide methods of inhibiting the binding of fibrinogen to blood platelets and inhibiting the aggregation of blood platelets, through the administration of novel fibrinogen receptor antagonist compounds. The above and other objects are accomplished by the present invention in the manner described below.

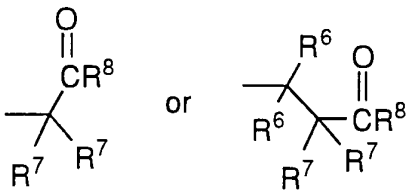
SUMMARY OF THE INVENTION

The present invention provides fibrinogen receptor antagonist compounds of the formula:



I

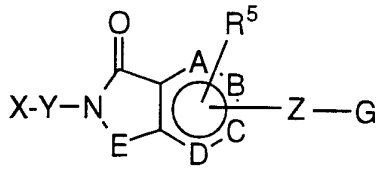
wherein G is



for use in inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. The above-mentioned compounds can be used in a method of acting upon a fibrinogen receptor which comprises administering a therapeutically effective but non-toxic amount of such compound to a mammal, preferably a human. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, dispersed therein, an effective but non-toxic amount of such compound is another feature of this invention.

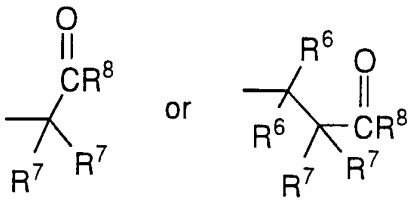
DETAILED DESCRIPTION OF THE INVENTION

Fibrinogen receptor antagonist compounds of Formula I are useful in a method of inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. Fibrinogen receptor antagonists of this invention are illustrated by compounds having the formula:



I

wherein G is



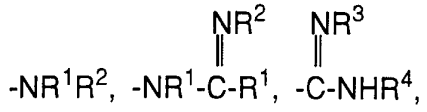
wherein:

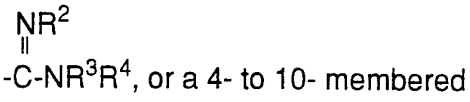
A, B, C and D independently represent a carbon atom or a nitrogen atom;

E is -$(CH_2)_n$-;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

X is



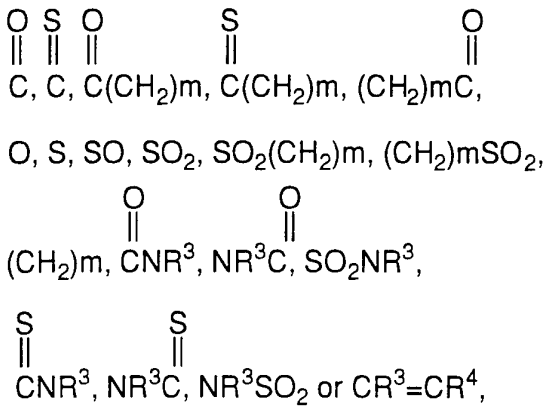


mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, 0 and S and either unsubstituted or substituted with R^1, R^2, R^3 or

R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

Y is C_{0-8} alkyl,
C_{0-8} alkyl-NR^3-CO-C_{0-8} alkyl,
C_{0-8} alkyl-$CONR^3$-C_{0-8} alkyl,
C_{0-8} alkyl-O-C_{0-8} alkyl,
C_{0-8} alkyl-$S(O_n)$-C_{0-8} alkyl, or
C_{0-8} alkyl-SO_2-NR^3-C_{0-8} alkyl-,
C_{0-8} alkyl-NR^3-SO_2-C_{0-8} alkyl-,
C_{1-8} alkyl-CO-C_{0-8} alkyl;

Z is



wherein m is 0-6;

R^5 is

hydrogen,
C_{1-6} alkyl,
C_{0-6} alkylcarboxy C_{0-6} alkyl,
C_{0-6} alkyloxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
aryl C_{0-6} alkyl, or
halogen;

R^6 is

hydrogen,
C_{1-8} alkyl,
aryl C_{0-6} alkyl,
C_{3-8} cycloalkyl C_{0-6} alkyl,
C_{0-6} alkylcarboxy C_{0-6} alkyl, carboxy C_{0-6} alkyl,
C_{1-4} alkyloxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,

provided that any of which R^6 groups may be substituted or unsubstituted independently with R^1 or R^2, and provided that, when two R^6 groups are attached to the same carbon, they may be the same or different;

R^7 is

hydrogen, fluorine,
C_{1-8} alkyl,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,

C_{1-8} alkyloxycarbonylamino C_{0-8}-alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C0-6 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-6 alkylaminosulfonylamino C0-6 alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl

wherein groups may be unsubstituted or substituted with one or more substituents selected from R^1 and R^2, and provided that when two R^7 groups are attached to the same carbon atom, they may be the same or different;

R^8 is

hydroxy,
C_{1-8} alkyloxy,
aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} 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 C_{1-6} alkyl.

When substituent R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 or Y includes the definition C_0, (e.g. aryl C_0 alkyl), the group modified by C_0 is not present in the substituent.

"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 R^1.

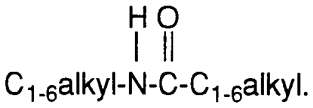
"Alkyl" means straight or branched chain alkane, alkene or alkyne.

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

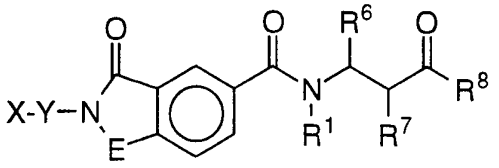
"Oxo" means =O.

"Thio" means =S.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionallity toward the point of attachment. For example, a C_{1-6}alkyl substituted with C_{1-6}alkyl-carbonylamino is equivalent to



A preferred embodiment of the present invention is



II

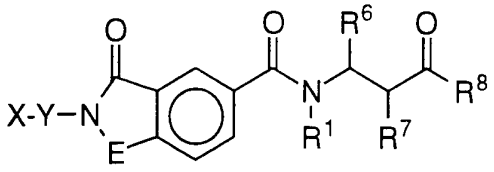
II wherein:

E is -$(CH_2)_n$-;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

X, Y, R^1, R^2, R^3, R^4, R^6, R^7 and R^8 are as previously defined.

A more preferred embodiment of the present invention is III wherein:



II

E is $-(CH_2)_n-$;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

X is

$-NR^1R^2$ or a 4- to 10-membered mono- or polycyclic aromatic or non-aromatic ring system containing 0, 1 or 2 heteroatoms chosen from N or O and either unsubstituted or substituted with R^1 and R^2, wherein

R^1 and R^2 are independently chosen from:
hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

Y is

C_{0-6} alkyl,

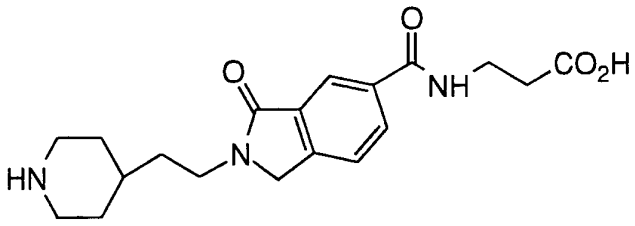
C_{1-6} alkyl-CO-C_{0-6} alkyl, or
C_{0-6} alkyl-NR^3-CO-C_{0-6} alkyl;

R^6 and R^7 are as previously defined and

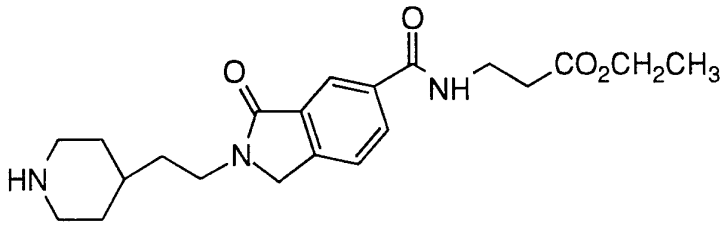
R^8 is

hydroxy,
C_{1-6} alkyloxy,
aryl C_{1-4} alkyloxy, or
C_{1-6} alkylcarbonyloxy C_{1-4} alkyloxy.

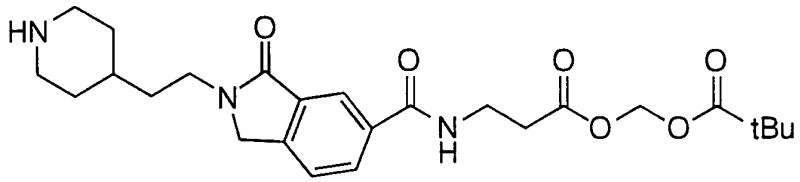
Preferred compounds of the invention are:



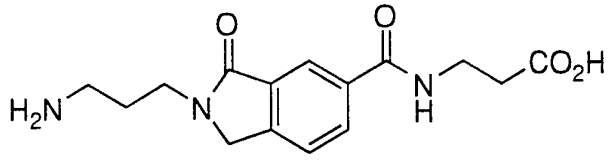
,



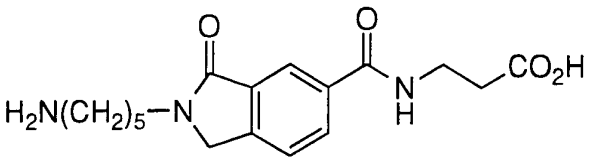
,



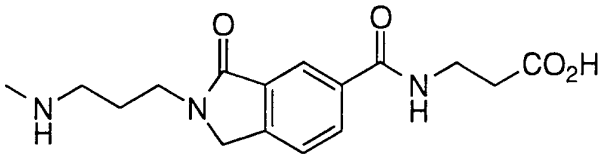
,



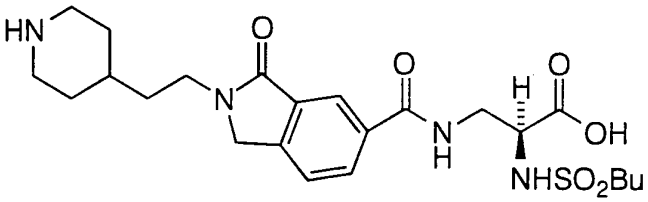
,



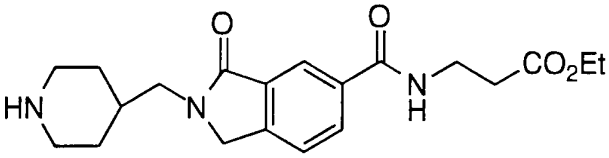
,



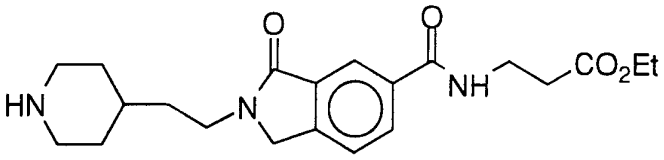
,



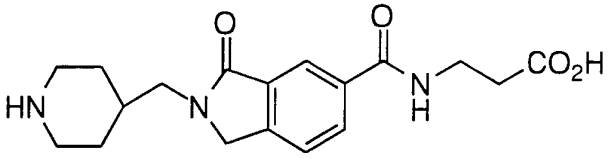
,



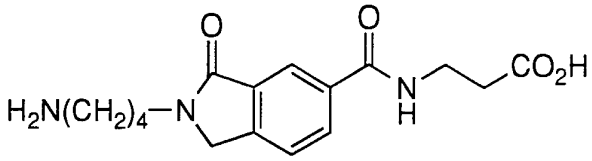
,



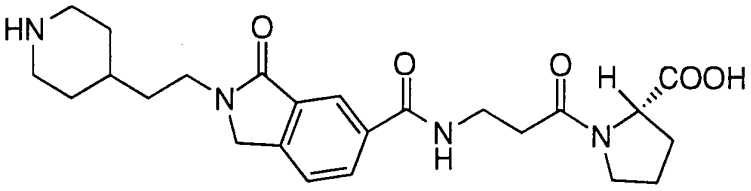
,



,

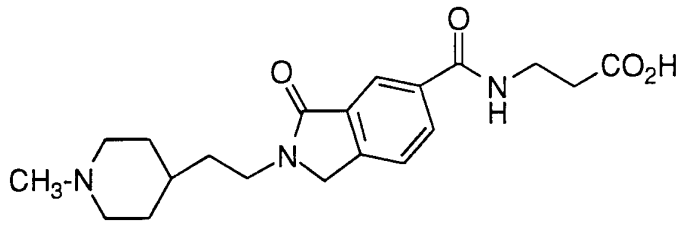


, and

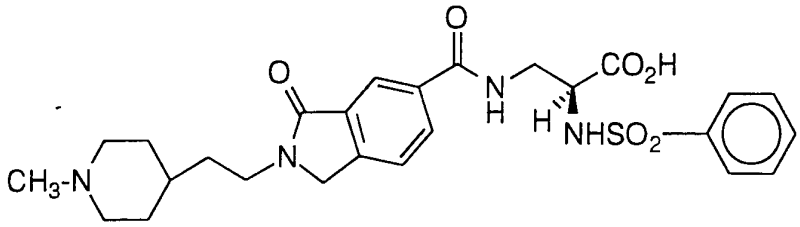


,

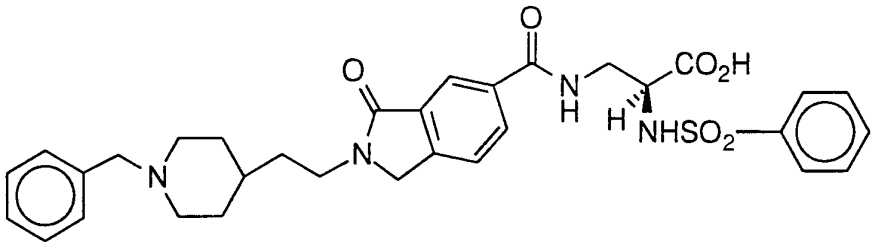
Other preferred compounds of the invention are:



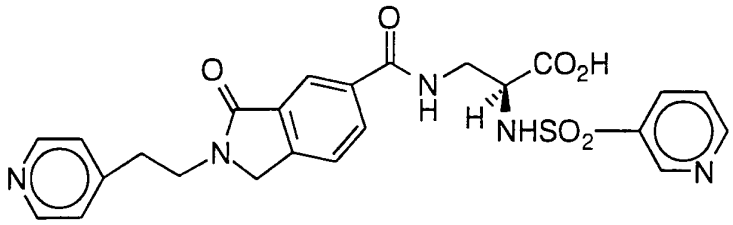
,



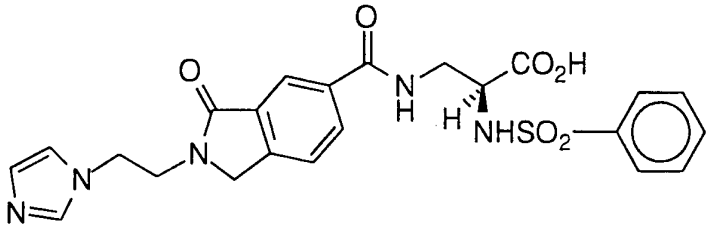
,



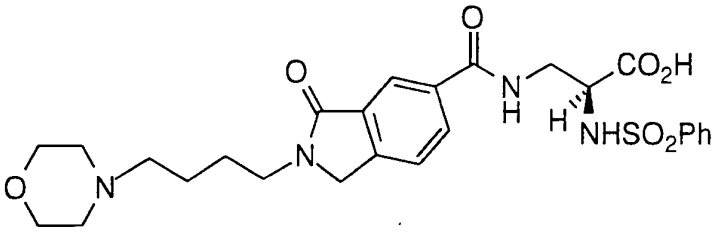
,



,



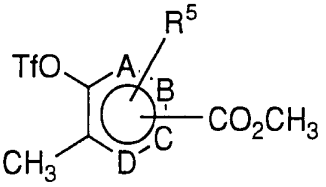
, and



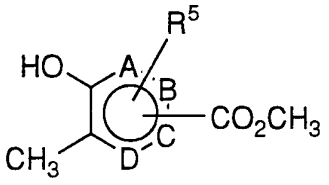
.

Generally, compounds of the present invention can be made according to a procedure including the following steps:

a) preparing a triflate activated aromatic group of the following general formula:

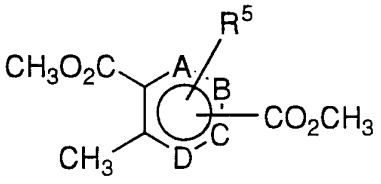


using



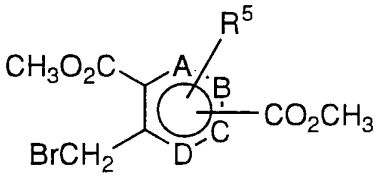
and Tf_2O;

b) inserting a carbonyl group for the triflate group using metal catalyzed carbonyl insertion, followed by trapping with methanol, to form



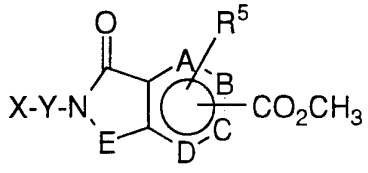
;

c) brominating the heterocyclic methyl group to form



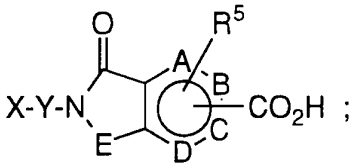
;

d) cyclizing with a primary amine to form

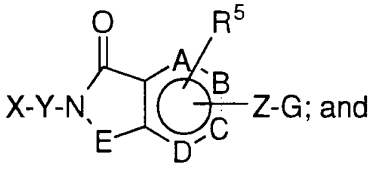


wherein X is an N-terminus protected primary amine, or a primary amine protected directly following this cyclization step;

e) converting the C-terminus ester, via hydrolysis, to an acid



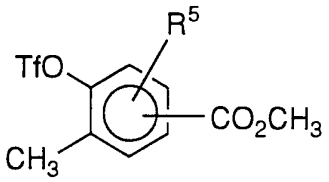
f) coupling the acid with an unsubstituted or substituted amino acid or C-terminus protected analog, or diamino acid or C-terminus protected analog, and optionally functionalizing the amino acid at the alpha- or beta-position, to form



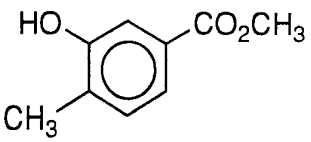
g) deprotecting the protected C-terminus and N-terminus.

Preferably the procedure involves

a) preparing an activated aryl group:

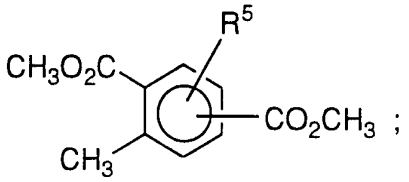


using

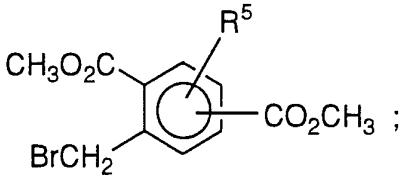


and T_2O;

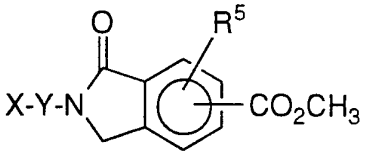
b) inserting a carbonyl group for the triflate group using metal catalyzed carbonyl insertion followed by trapping with methanol to form



c) brominating the aryl methyl group to form

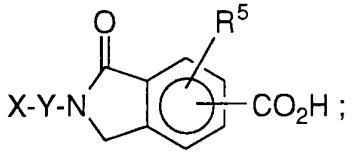


d) cyclizing with a primary amine to form

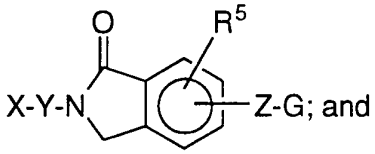


wherein X is an N-terminus protected primary amine, or a primary amine protected directly following this cyclization step;

e) converting the C-terminus ester, via hydrolysis, to an acid



f) coupling the acid with an unsubstituted or substituted amino acid or C-terminus protected analog, or diamino acid or C-terminus protected analog, and optionally functionalizing the amino acid at the alpha- or beta-position via acylation or sulfonylation, to form

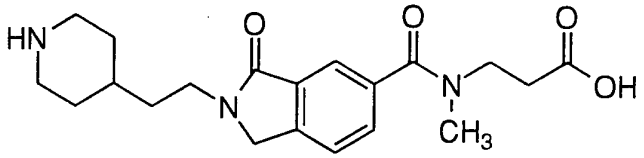
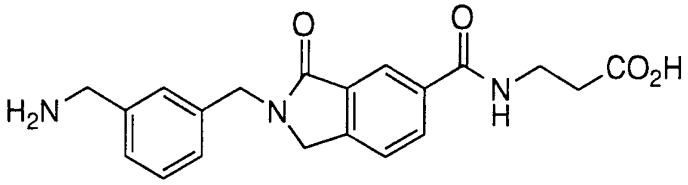
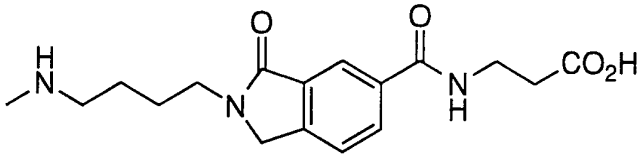
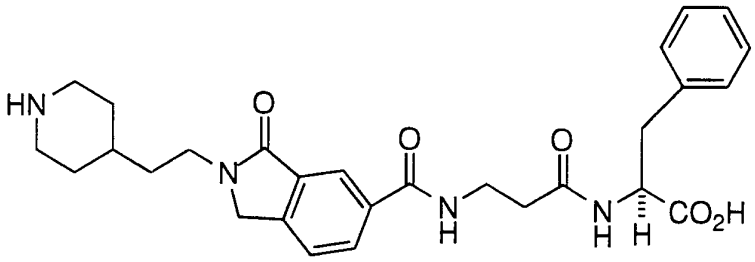


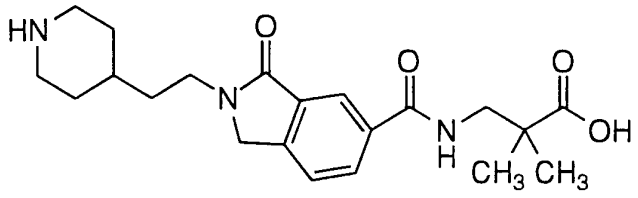
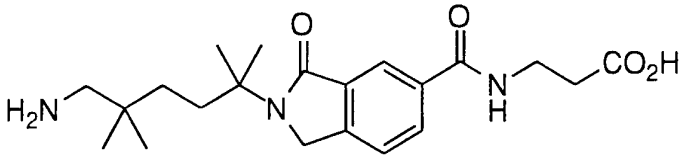
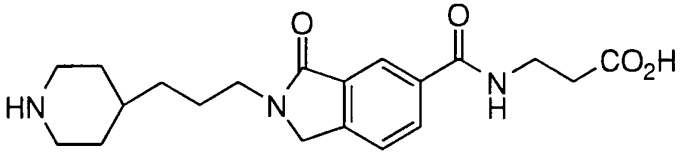
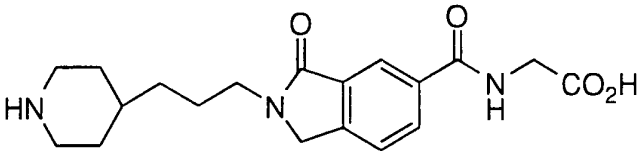
g) deprotecting the protected C-terminus and N-terminus.

An ADP-stimulated platelet aggregation assay was used to determine inhibition associated with compounds of the invention.

Human platelets were 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 serum albumin. Platelet aggregation was measured at 37°C in a a Chronolog aggregometer. The reaction mixture contained gel-filtered human platelets (2 x 10^8 per ml), fibrinogen (100 µg/ml), Ca^{2+} (1 mM), and the compound to be tested. Aggregation was initiated by adding 10 uM ADP 1 minute after the other components had been added. The reaction was allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation was 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.

Additional preferred embodiments of the invention, shown below with platelet aggregation inhibition potency data (IC_{50} μM) are:

Compound	IC_{50} μM
	0.16
	4.3
	5.7
 L-isomer	0.42

Compound	IC_{50} uM
	1.0
	21
	0.92
	14.0

The abbreviations listed below are defined as Bn, benzyl; NMM, N-methylmorpholine; HOBt, 1-hydroxybenzotriazole; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMF, dimethylformamide; Pib, 4-(4-piperidyl)butanoyl; pTSA, para-toluenesulfonic acid; DMS, dimethylsulfide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; DIBAL, diisobutylaluminum hydride; Boc (or BOC), tert-butoxycarbonyl; Cbz, benzyloxycarbonyl; Suc, succinoyl; alpine borane, β-isopinocamphenyl-9-borabicyclo[3.3.1]-nonane; TBDMS, tert-butyldimethylsilyl; Jones reagent, chromic acid; NBS, N-Bromosuccinimide; BPO, Benzoyl peroxide; PPh_3, triphenyl phosphine; DMSO, Dimethylsulfoxide; Et_3N, triethylamine; Tf_2O, triflic anhydride; DMAP, 4-dimethylaminopyridine; BOP, benzotriazol-1-

yloxytris(dimethylamino)phosphonium hexafluorophosphate; PhCHO, benzaldehyde; and Boc_2O, di-t-butyldicarbonate; dppp, 1,3-bis(diphenylphosphino)propane; ETOH, ethyl acetate; CH_2Cl_2, methylene chloride; HOAc, acetic acid; CH_3OH, methanol; $CHCl_3$, chloroform.

Unless otherwise indicated, all degree values are Celsius.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

The compounds of Formula I are useful in inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood

platelets, treatment of thrombus formation or embolus formation, and in the prevention of thrombus formation or embolus formation. These compounds are useful as pharmaceutical agents for mammals, especially for humans. The compounds of this invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. Compounds of this invention may also be used to prevent or modulate the progress of myocardial infarction, unstable angina and thrombotic stroke, in either acute or chronic settings. In addition, they may be 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 form thrombi and thromboemboli. Compounds of this invention may be administered to surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardio-vascular surgery in order to oxygenate blood. Platelets adhere 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., 1987, 252:H, pp 615-621). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of this invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, reocclusion, and restenosis during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism, reocclusion and restenosis after angioplasty of coronary and other arteries and after coronary artery bypass procedures.

The compounds of Formula I may be administered to mammals, preferably in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants such as alum, in a pharmaceutical composition which is non-toxic and in a therapeutically effective amount, according to standard pharmaceutical practice. The

compounds can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, trans-dermal, subcutaneous and topical administration.

For oral use of a fibrinogen receptor antagonist according to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added.

For intramuscular, intraperitoneal, subcutaneous, and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment and prevention of diseases related to platelet aggregation, fibrin formation, and thrombus and embolus formation, comprising the administration of a therapeutically effective but non-toxic amount of the compounds of Formula I, with or without pharmaceutically acceptable carriers or diluents.

Compositions of this invention include fibrinogen receptor antagonist compounds of this invention in combination with pharmacologically acceptable carriers, e.g. saline, at a pH level e.g. 7.4, suitable for achieving inhibition of platelet aggregation. The compositions may also be combined with anticoagulants such as heparin or warfarin. The compositions may also be combined with throm-bolytic agents such as plasminogen activators or streptokinase in order to inhibit platelet aggregation in more acute settings. The composition may further be combined with antiplatelet agents such as aspirin. The compositions are

soluble in an aqueous medium, and may therefore be effectively administered in solution.

When a compound according to Formula I is used as a fibrinogen receptor antagonist in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patients symptoms.

In one exemplary application, a suitable amount of compound is administered orally to a heart attack victim subsequent to angioplasty. Administration occurs subsequent to angioplasty, and is in an amount sufficient to inhibit platelet aggregation, e.g. an amount which achieves a steady state plasma concentration of between about 0.01-50 μM preferably between about 0.01-10 μM.

The present invention also includes a pharmaceutical composition comprising compounds of the present invention in combination with tissue type plasminogen activator or streptokinase. The invention also includes a method for promoting thrombolysis and preventing reocclusion in a patient which comprises administering to the patient an effective amount of compositions of the invention.

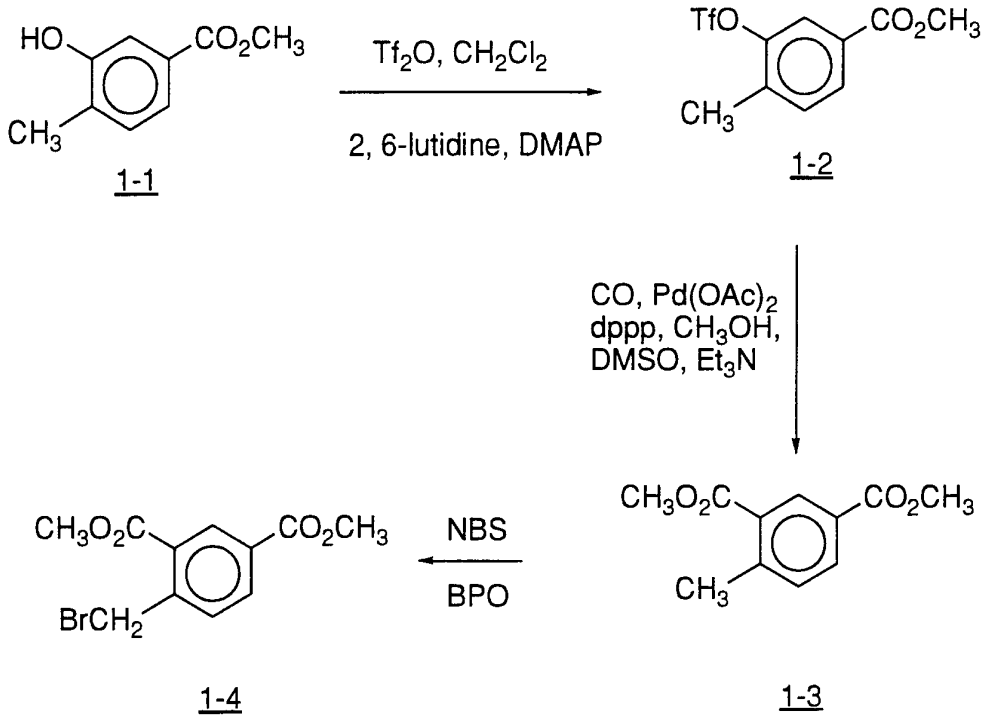
The present invention provides a method of inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, and in preventing thrombus formation or embolus formation in a mammal, comprising the administration of a therapeutically effective but non-toxic amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents.

The present invention still further provides a method of inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, and in preventing thrombus formation or embolus formation in a mammal, comprising the administration of a therapeutically effective but non-toxic amounts of the compounds of this invention in combination with thrombolytic agents, such as tissue plasminogen activators or streptokinase, anticoagulants such as heparin or warfarin, or antiplatelet

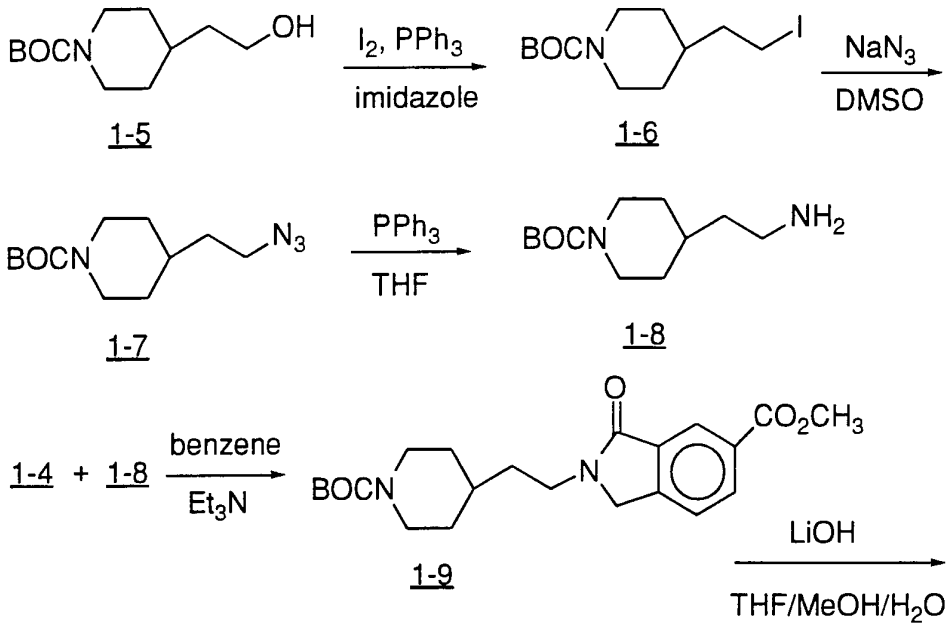
agents such as aspirin, with or without pharmaceutically acceptable carriers or diluents.

The compounds of Formula I are prepared according to the reaction schemes set forth below.

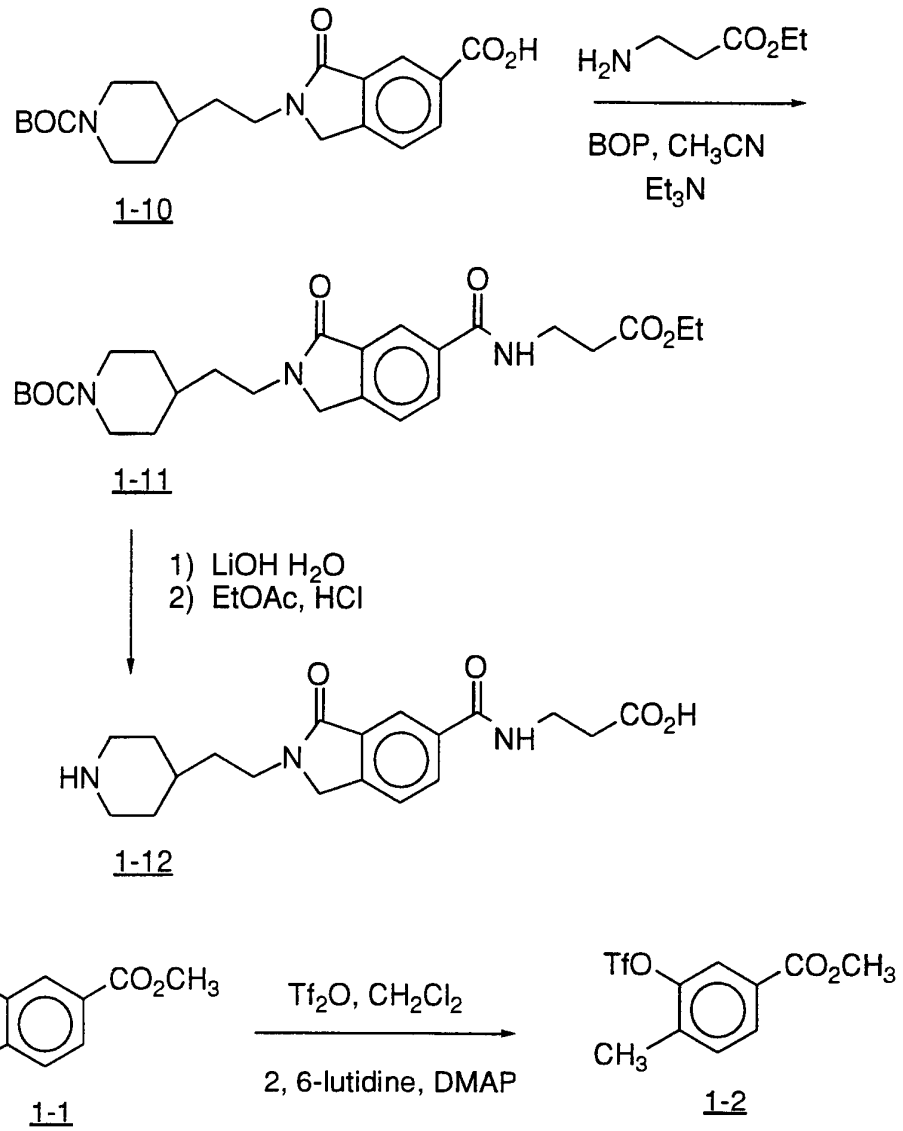
SCHEME 1



SCHEME 1 CONT'D



SCHEME 1 CONT'D

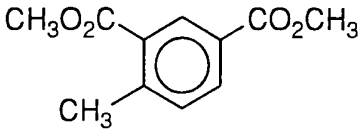


Methyl 4-methyl-3-trifluoromethanesulfonyloxybenzoate (1-2)

A solution of methyl 4-methyl-3-hydroxybenzoate (1-1) (20.0 g, 0.12 moles) [prepared from the corresponding carboxylic acid (Aldrich) by treatment with a methanolic solution of HCl gas] in CH_2Cl_2 (900 ml) was cooled to -40° and treated successively with 2,6-lutidine (0.18 moles), DMAP (2.9 g, 0.024 moles) and trifluoro-methylsulfonyl

anhydride (0.18 moles). The cooling bath was then removed and the resulting mixture was stirred at ambient temperature for 2.0 hours. The solvent was then removed and the residue was purified by flask chromatography on silica eluting with hexane(8)/EtOAc(2) to provide pure 1-2, R_f 0.35.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (3H, s), 3.85 (3H, s), 7.30 (1H, d), 7.84 (1H, s), 7.90 (1H, d).

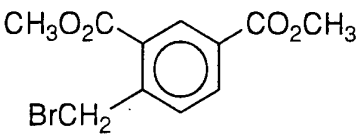


1-3

Dimethyl 4-methylbenzene-1,3-dicarboxylate (1-3)

A solution of 1-2 (30.0 g, 0.121 moles) in methanol/300 ml was treated successively with DMSO (180 ml), triethylamine (0.278 moles), palladium acetate (0.807 g, 3.6 mmoles) and dppp (1.48 g, 3.6 mmoles) as the reaction turned to a clear dark brown solution. Carbon monoxide was then bubbled through the reaction mixture for 3 minutes and the resulting mixture was heated at reflux, while continuing to bubble CO. After refluxing for 4 hours the reaction mixture was concentrated and the resulting brown oil was purified by flask chromatography on silica gel eluting with hexane(90)/EtOAc(10) to provide pure 1-3.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (3H, s), 3.95 (3H, s), 3.96 (3H, s), 7.37 (1H, d), 8.09 (1H, dd), 8.60 (1H, d).



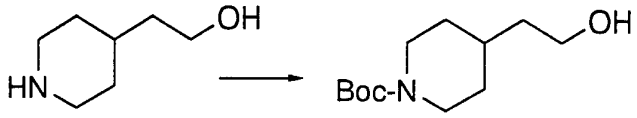
1-4

Dimethyl 4-bromomethylbenzene-1,3-dicarboxylicacid (1-4)

A solution of 1-3 (1.35 g, 6.5 mmole) in $CHCl_3$ (20 ml) was treated with dibenzoyl peroxide (0.078g, 3.5 mmol) and N-bromosuccinimide (NBS) (1.1g, 6.5 mmole) and the resulting solution was heated at reflux for 2 hours.

The cooled reaction mixture was concentrated, taken up in CCl_4, filtered and the filtrate was concentrated to give 1-4 as a tan solid. R_f 0.5 [silica gel, hexane(70)/EtOAc(30)].

Preparation of Boc-4-Piperidine-2-ethanol (1-5)



1-5

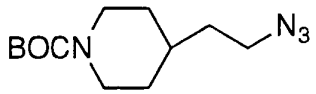
4-Piperidine-2-ethanol (Aldrich) (130 g, 1.0 mole) was dissolved in 700 mL dioxane, cooled to 0°C and treated with 3 N NaOH (336 mL, 1.0 mole), and di-t-butyldicarbonate (221.8 g, 1.0 mole). The ice bath was removed and the reaction stirred overnight. The reaction was concentrated, diluted with water and extracted with ether. The ether layers were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to give 1-5.

R_f = 0.37 in 1:1 EtOAc/Hexanes, ninhydrin stain.

^1H NMR (300MHz, $CDCl_3$) δ 4.07 (bs, 2H), 3.7 (bs, 2H), 2.7 (t, J = 12.5 Hz, 2H), 1.8-1.6 (m, 6H), 1.51 (s, 9H), 1.1 (ddd, J = 4.3, 12.5, 12 Hz, 2H).

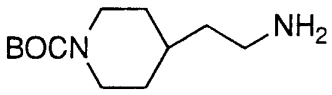
Boc-4-piperidine-2-ethyl iodide (1-6)

Boc-4-piperidine-2-ethanol (1-5) (10.42 g, 0.048 mole was dissolved in 400 ml benzene and imidazole (4.66 g, 0.068 moles) and triphenylphosphine (15.24 g, 0.05 moles) were added at room temperature. After 6 hours the reaction mixture was filtered and the filtrate was evaporated to give a dark residue. This was purified by flash chromatography on silica gel eluting with 10% EtOAc-hexanes to give 1-6 as a yellow oil.



Boc-4-piperidine-2-ethylazide (1-7)

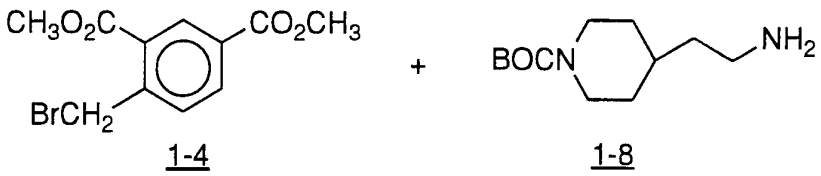
To 1-6 (27.9 g, 0.082 moles) dissolved in DMSO (400 ml) was added sodium azide (5.01 g, 0.086 moles) at room temperature and the resulting solution was heated at 65° for 2 hours. The cooled reaction mixture was diluted with 250 ml EtOAc, extracted with 2 x 100 ml portions of water 2 x 50 ml portions of brine and then dried ($MgSO_4$). Solvent removal provided 1-7 as a pale yellow oil, Rf 0.5 (silica gel, 70% acetone/hexane).



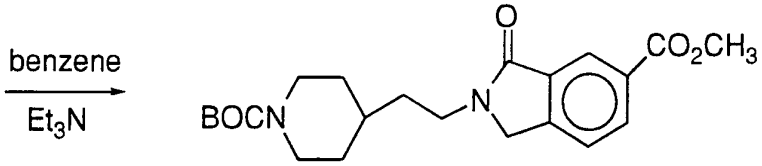
Boc-4-piperidine-2-ethylamine(1-8)

To a solution of 1-5 (19.3 g, 0.076 moles) in THF (400 ml)/H_2O (195 ml) was added triphenylphosphine (80.0g, 0.305 moles) in one portion at room temperature. This was stirred at room temperature 3 hours and the organic solvents were then removed in vacuo. The residue was acidified to pH 2 with 10% $KHSO_4$ solution and this was extracted 4 x 100 ml portions of EtOAc. The organic extract was extracted with 2 x 100 ml portions of 10% $KHSO_4$ and the aqueous phases were combined and the pH was adjusted to 10 with 2N NaOH. This solution was extracted with 4 x 200 ml portions of CH_2Cl_2. These were combined, dried ($MgSO_4$) and the solvent was removed to give 1-8 as an oil. Rf 0.3 (silica gel, eluting with 10% CH_3OH in $CHCl_3/NH_3$).

^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (broad, 2H), 2.72 (t, J=7.2Hz, 2H), 2.62 (m, 2H), 1.64 (d, J=12.2Hz, 2H), 1.43 (s, 9H), 1.42-1.32 (m, 5H), 1.09 (m, 2H).



1-4 1-8



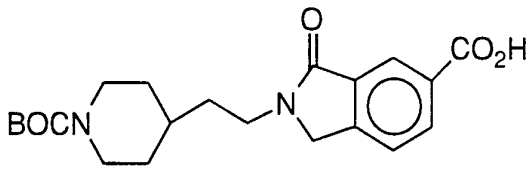
1-9

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[2(4-N-t-butyloxy-carbonylpiperidinyl)ethyl]-3-oxo (1-9)

A solution of 1-4 (1.0 g, 3.5 mmoles) in benzene (5 ml) was treated with 1-8 (0.80 g, 3.5 mmol) and triethylamine (0.49 ml, 3.5 mmol) and the reaction mixture was heated at reflux for 3 hours. The solvent was removed and the residue was taken up in EtOAc, washed in 10% $KHSO_4$ solution, H_2O, brine and dried. Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with hexane(1)/EtOAc(1) to give pure 1-9.

R_f 0.2 (silica gel, hexane(1)/EtOAc(1)).

^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (2H, m), 1.43 (9H, s) 1.61 (4H, m), 1.73 (2H, bd), 2.62 (2H, bt), 3.64 (2H, t), 3.93 (3H, s), 4.07 (2H, m), 4.40 (2H, s), 7.50 (1H, d), 8.21 (1H, dd), 8.47 (1H, d).

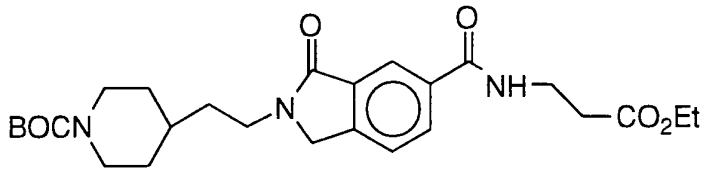


1-10

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[2-(4-N-t-butyloxy-carbonylpiperidinyl)ethyl]-3-oxo (1-10)

A solution of 1-9 (0.43 g, 1.12 mmole) in THF (1)/MeOH(1)/H_2O(1) (9 ml) was treated at room temperature with $LiOH \cdot H_2O$ (0.235 g, 5.6 mmol) and the resulting solution was stirred for 4 hours. The reaction mixture was then diluted with EtOAc (75 ml)/10% $KHSO_4$ solution (30 ml) and the organic phase was separated and dried (Na_2SO_4). Solvent removal gave the desired acid 1-10. R_f 0.5 (silica gel, CH_2Cl_2(9)/MeOH (0.5)/HOAc(0.5)).

^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (2H, m), 1.42 (9H, s), 1.60 (3H, m), 1.71 (2H, bd), 2.63 (2H, bt), 3.68 (2H, t), 4.08 (2H, m), 4.40 (2H, s), 7.03 (1H, d), 8.28 (1H, dd), 8.60 (1H, s).



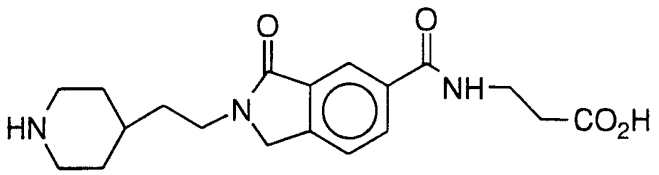
1-11

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(carboethoxy)ethyl]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)ethyl]-3-oxo (1-11)

A solution of 1-10 (0.35 g, 0.94 mmole), triethylamine (0.40 ml, 2.82 mmol), and β-alanine ethyl ester (0.22 g, 1.41 mmol) (Aldrich) in CH_3CN (5 ml) was treated at room temperature with BOP (1.2 mmoles) reagent and the resulting solution was stirred for 16 hours.

The solvent was removed and the residue was taken up in EtOAc, washed with H_2O, 10% $KHSO_4$ solution, brine and dried (Na_2SO_4). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with hexane(20)/EtOAc(80) to give pure 1-11 as a clear oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.10-1.30 (3H, m), 1.44 (9H, s), 1.60 (3H, m), 1.75 (2H, bd), 2.63 (4H, m), 3.70 (4H, m), 4.05-4.20 (4H, m), 4.38 (2H, s), 7.50 (1H, d), 8.08 (2H, m).



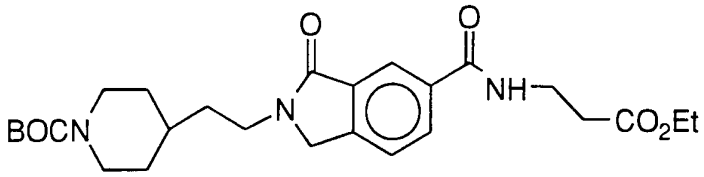
1-12

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[2-(4-piperidinyl)ethyl]-3-oxo (1-12)

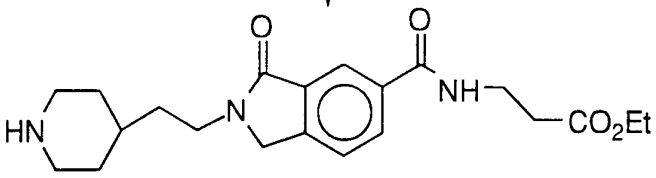
A solution of 1-11 (0.32 g, 0.68 mmol) in THF(1)/MeOH-(1)/H_2O(1) (9 ml) was treated with LiOH•H_2O (0.14 g, 3.4 mmoles) at room temperature for 1.0 hr. The solvent was then removed and the residue was taken up in EtOAc and washed with 10% $KHSO_4$ solution, brine and dried (Na_2SO_4). Solvent removal gave the desired acid. R_f 0.3 (silica gel, $CHCl_3$ (9)/MeOH (0.5)/HOAc (0.5)).

This acid (0.30 g, 0.68 mmole) was dissolved in CH_2Cl_2 and anisole (150 µl) was added. This was cooled to -15°C and trifluoroacetic acid (3 ml) was added and the resulting mix stirred for 0.5 hours. The solvent was removed and the residue purified by flash chromatography on silica gel eluting with EtOH (9)/NH_4OH (1.2)/H_2O (1.2) to provide pure 1-12.

^1H NMR (300 MH_3, D_2O) δ 1.30 (7H, m), 1.50-1.70 (3H, m), 1.83 (2H, bd), 2.38 (2H, t), 2.80 (2H, dt), 3.27 (2H, bd), 3.50 (4H, m), 4.42 (2H, s), 7.51 (1H, d), 7.83 (2H, m).



1-11

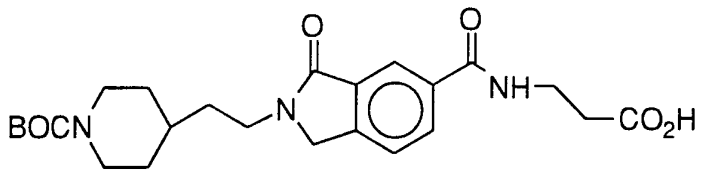


1-13

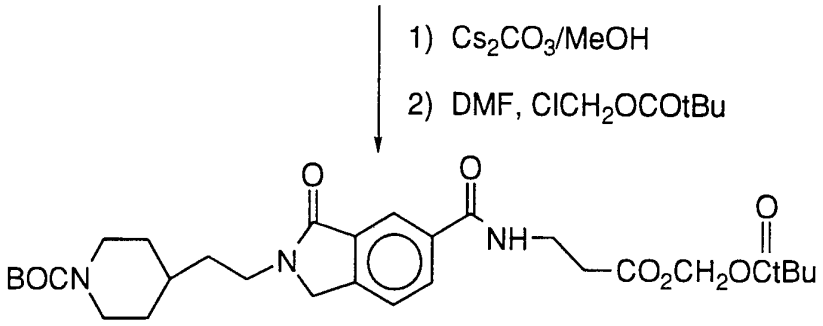
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(carboethoxy)ethyl]-2-[2-(4-piperidinyl)ethyl]-3-oxo (1-13)

A solution of 1-11 (0.72 g, 1.57 mmoles) in EtOAc (20 ml) was cooled to -78°C and HCl gas was bubbled through. This solution for 1-2 minutes and the reaction mixture was then stirred at 0°C. After a few minutes a white solid had precipitated and this mixture was stirred for 0.5 hours. The solvent was then removed and the residue was triturated with Et_2O to give pure 1-13.

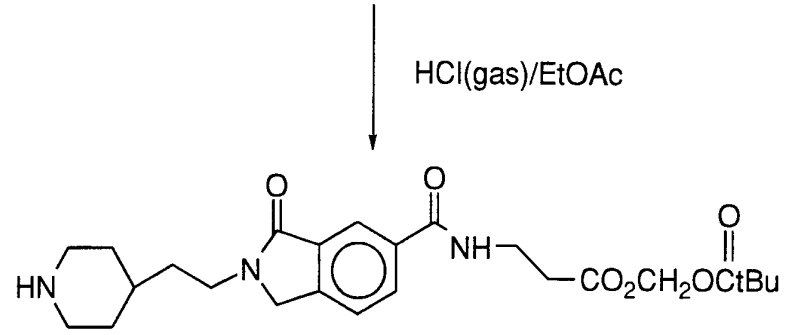
^1H NMR (300 MHz, CD_3OD) δ 1.23 (3H, t), 1.45 (2H, m), 1.66 (2H, m), 1.72 (2H, m), 2.07 (2H, m), 2.65 (2H, t), 2.94 (2H, m), 3.47 (2H, bd), 3.68 (4H, m), 4.12 (2H, q), 4.57 (2H, s), 7.67 (1H, d), 8.03 (1H, dd), 8.14 (1H, d).



1-14



1-15



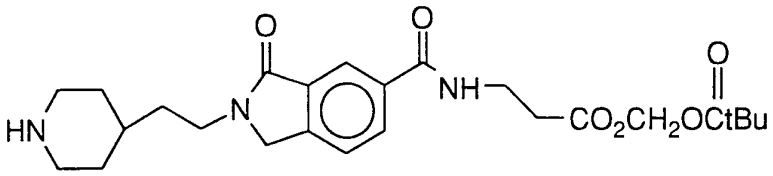
1-16

1H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butylcarbonyl-oxymethylcarboxy)ethyl]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)-ethyl]-3-oxo (1-15)

A slurry of 1-16 (0.80 g, 1.8 mmoles) in MeOH (20 ml) was treated with Cs_2CO_3 (0.24 g, 0.90 mmoles) at room temperature and the resulting mixture was stirred for 45 minutes. The solvent was then removed and the residue was slurried in DMF (20 ml) and this was treated at room temperature with chloromethyl pivalate (1.8 mmoles). The resulting mixture was stirred at room temperature for 24 hours.

The reaction mixture was then diluted with EtOAc and washed with H_2O, 10% $KHSO_4$, saturated with $NaHCO_3$ solvent and brine. The organic phase was dried ($MgSO_4$), and the solvent removed to provide 1-15 as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 1.11-1.25 (13H, m), 1.46 (9H, s), 1.63 (2H, q), 1.77 (2H, bd), 2.62-2.76 (4H, m), 3.72 (9H, m), 4.09 (2H, bd), 4.42 (2H, s), 5.80 (2H, s), 6.89 (1H, bt), 7.53 (1H, d), 8.09 (1H, d), 8.14 (1H, s).

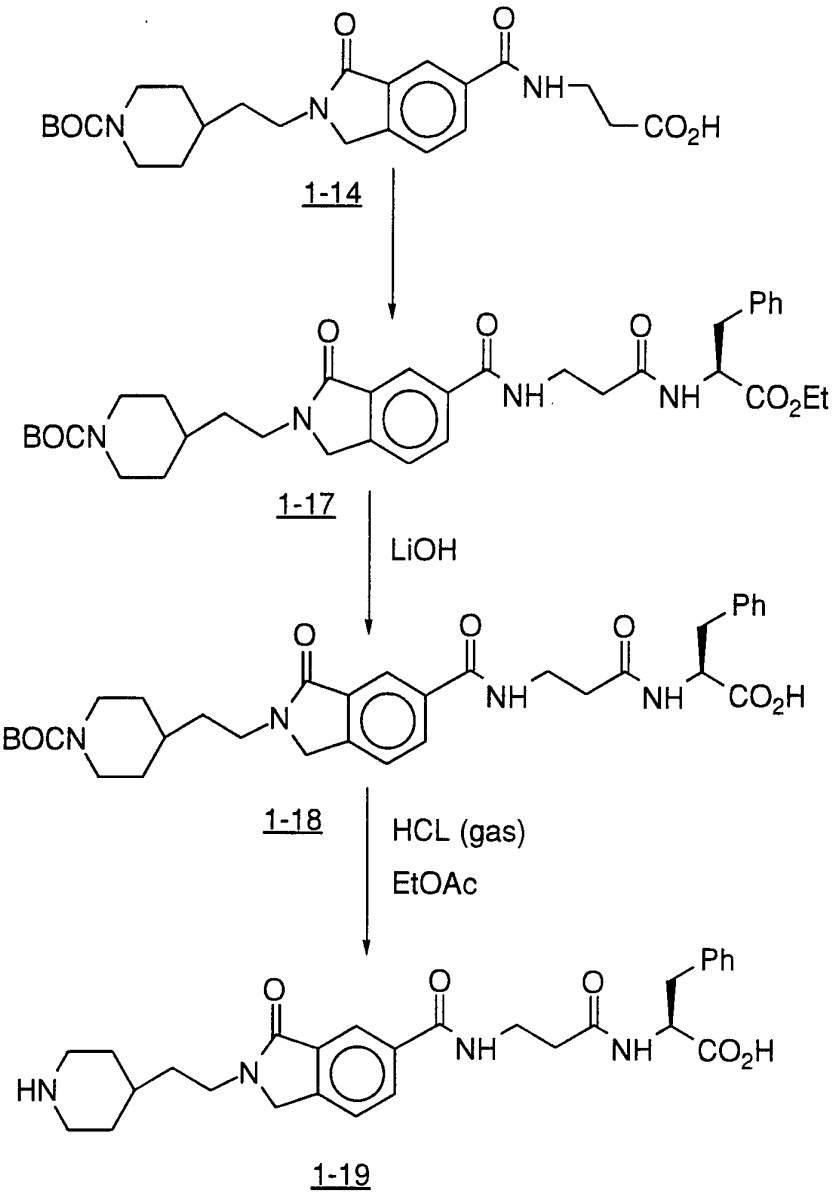


1-16

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butylcarbonyloxy-methylcarboxy)ethyl]-2-[2-(4-piperidinyl)ethyl]-3-oxo (1-16)

A solution of 1-15 (15 mg) in EtOAc (5 ml) was cooled to -78°C and treated with HCl gas for 10 minutes and the resulting solution was stirred at -10°C for 1.0 hour. The solvent was then removed to provide pure 1-16 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 1.06 (9H, s), 1.92 (1H, m), 1.70 (2H, m), 2.08 (2H, bd), 3.73 (2H, t), 2.95 (2H, dt), 3.38 (2H, bd), 3.70 (6H, m), 4.58 (2H, s), 5.86 (2H, s), 7.67 (1H, d), 8.06 (1H, d), 8.17 (1H, s).

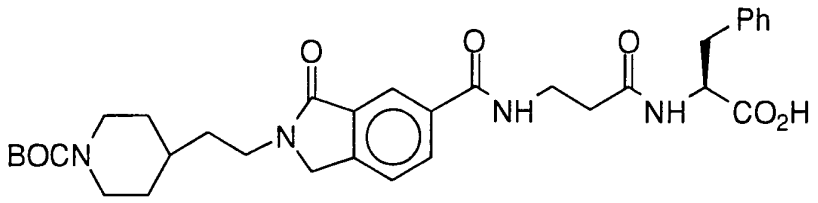


1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[L-Phe(OEt)-2-(carboxamido)ethyl]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)ethyl]-3-oxo(1-17)

1-14 (0.35 g, 0.76 mmoles) was treated with L-phenylalanine ethyl ester (2.0 mmoles), N-methylmorpholine (2.0 mmoles) and BOP (0.886 g, 2.0 mmoles), in CH_3CN (5 ml) at room temp for 24 hrs. as described for 6-3. Flash chromatography on silica gel

eluting with EtOAc (9)/MeoH (1) gave pure 1-17 as a white solid. Rf 0.3 (silica gel, $CHCl_3$(2)/acetone (1).

^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, t), 1.47 (9H,S), 1.79 (2H, bd), 2.54 (2H, t), 2.72 (2H, m), 3.15 (2H, m) 3.75 (5H, m), 4.20 (4H, m), 4.43 (2H, S), 2.90 (1H, q), 7.12 2H, m), 7.25 (5H, m), 7.54 (1H, d), 8.08 (1H, d), 8.19 (1H, S).

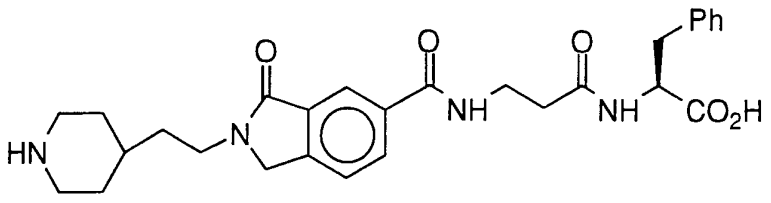


1-18

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N[L-Phe-2-(carboxamido)-ethyl]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)ethyl]-3-oxo(1-18)

1-17 (0.46 g, 0.72 mmoles) was treated with $LiOH \cdot H_2O$ (0.152 g, 3.6 mmoles) as described for 1-12 to give 1-18 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 1.13 (2H, m), 1.43 (9H, s), 1.66 (2H, q), 1.80 (2H, bd), 2.50 (2H, t), 2.70 (2N, M), 2.93 (1H, m), 3.20 (1H, dd), 3.58 (2H, q), 3.70 (2H, t), 4.04 (2H, m), 4.56 (2H, S), 4.68 (1H, m), 7.20 (5H, m), 7.56 (1H, d), 8.02 (1H, d), 8.15 (1H, s).



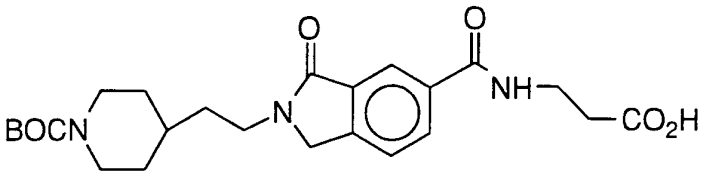
1-19

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N[L-Phe-2-(carboxamido)-ethyl]-2-[2-(4-piperidinyl)ethyl]-3-oxo (1-19)

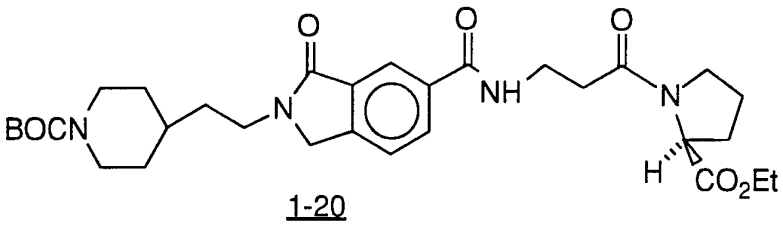
1-18 (0.35 g, 0.37 mmoles) was treated with HCl gas as described for 1-13 to give pure 1-19 as a white solid.

^1H NMR (300 MHz, D_2O) δ 1.35 (2H, m), 1.62 (2H, m), 1.93 (2H, m), 2.43 (2H, m), 2.79 (3H,m), 3.07 (1H, m), 3.28 (2H, m), 3.45(2H, m), 4.50

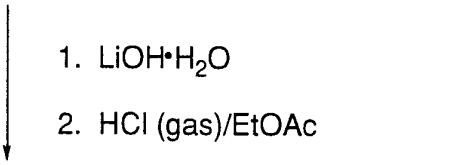
(2H,S), 6.80 (1H, m), 6.92 (2H, m), 7.00 (2H, m), 7.55 (1H, d), 7.77 (2H, bs).

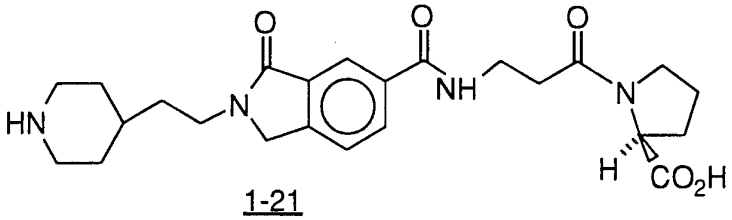


1-14



1-20





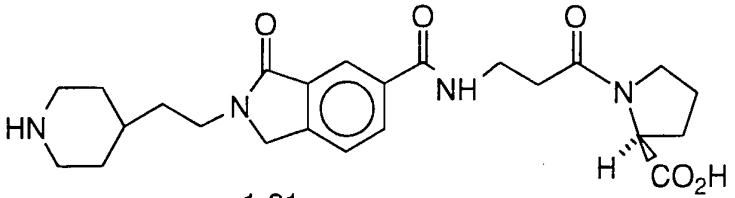
1-21

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[L-Pro(OEt)-2-(carboxamido)ethyl]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)ethyl]-3-oxo (1-20)

1-14 (0.35 g, 0.76 mmoles) was treated with L-Proline ethyl ester (0.288 g, 2.0 mmoles), N-methylmorpholine (2.0 mmoles) and BOP (0.886 g, 2.0 mmoles) in CH3CN (5 ml) as described for 1-17 to give an oily

residue. This was purified by flash chromatography on silica gel eluting with acetone (1)/$CHCl_3$(1) to give pure 1-20.

^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (2H, m), 1.45 (9H,s), 1.42 (2H, q), 1.65 (2H, bd), 2.03 (2H, m), 2.66 (5H, m), 3.51 (1H, m), 3.67 (2H, m), 3.80 (2H, m), 4.09 (2H, m), 4.20 (2H, q), 4.40 (2H, s), 4.50 (1H, m), 7.41 (1H, m), 7.50 (1H, d), 8.03 (1H, d), 8.19 (1H, s).



1-21

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[L-Pro-2-(carboxamido)ethyl]-2-[2-(4-piperidinyl)ethyl]-3-oxo(1-21)

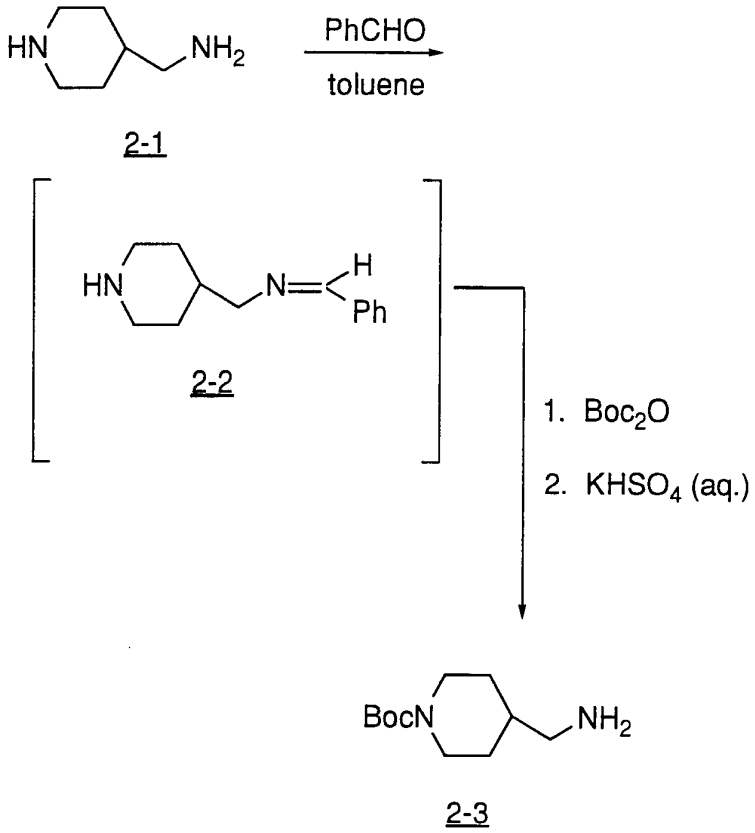
1-20 (0.2 g, 0.34 mmoles) was treated with $LiOH \cdot H_2O$ (0.071 g, 1.7 mmoles) as described for 1-12 to give the desired acid.

^1H NMR (300 MHz, CD_3OD) δ 1.15 (2H, m), 1.44 (9H, s), 1.67 (2H, q), 2.80 (2H, bd), 2.25 (1H, m) 2.73 (2H, m), 3.68 (4H, m), 4.06 (2H, m), 4.55 (2H, s), 7.66 (1H, d), 8.05 (1H, d), 8.17 (1H, s).

This acid (0.15 g) was dissolved is EtOAc (10 ml) and treated with HCl gas as described for 1-13 to give pure 1-21 as a white solid.

^1H NMR (300 MHz, D_2O) δ 1.48 (2H, m), 1.67 (1H, m), 1.76 (2H, m), 2.06 (4H, m), 2.32 (1H, m), 2.62 (1H, m), 2.84 (2H, t), 2.96 (2H, t), 3.43 (2H, d), 3.70 (6H, m), 4.47 (1H, m), 4.66 (2H, s), 7.72 (1H, d), 8.00 (1H, d), 8.09 (1H, s).

SCHEME 2

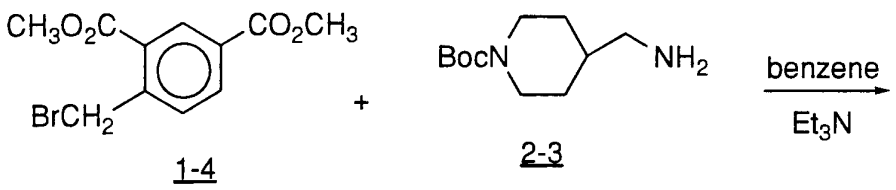


2-1

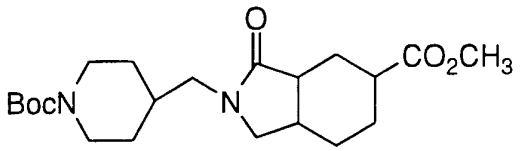
2-2

2-3

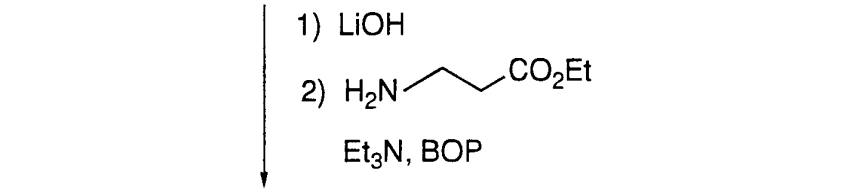
SCHEME 2 CONT'D



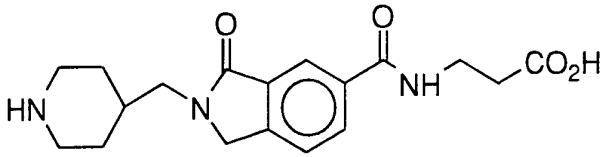
1-4 2-3



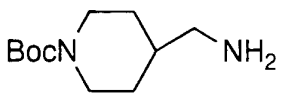
2-4



2-5



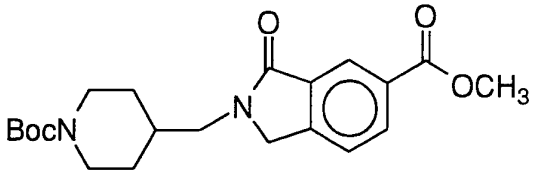
2-6



2-3

4-(N-t-Butyloxycarbonylpiperidinyl)methylamine (2-3)

A solution of 4-(piperidinyl)methylamine (2-1) (22.8 g, 0.2 mmoles) in toluene (250 ml) was treated with benzaldehyde (21.2 g, 0.2 mmoles) at room temperature and the resulting mixture was heated at reflux for 3 hours with the aid of a Dean-Stark trap for water removal. The cooled reaction mixture containing the desired Schiff's base 2-2 was treated portionwise with di-t-butyl dicarbonate (47.96 g, 0.22 moles) and the resulting solution was stirred at room temperature for 16 hours. The solvent was then removed and the residue was cooled to 0-5°C and treated with 1N $KHSO_4$ (220 ml) with stirring for 3 hours. The resulting reaction mixture was extracted with ether (3 x 200 ml) and then made basic with 1N KOH solution and extracted with $CHCl_3$ (4 x 75 ml). The combined organic extract was washed with brine, dried (Na_2SO_4) filtered through celite, and the solvent removed to provide pure 2-3 as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (2H, m), 1.45 (9H, s), 1.60 (1H, m), 1.74 (2H, d), 2.68 (4H, m), 4.15 (2H, bd).

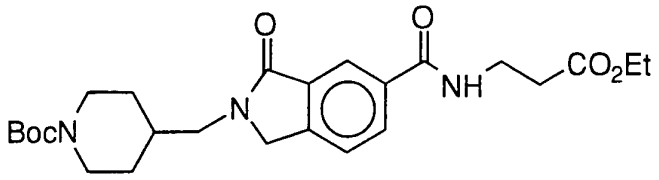


2-4

Methyl-1H-Isoindole-4-carboxylate, 2,3-dihydro-N-[(4-N-t-butyloxy-carbonylpiperidinyl)methyl]-3-oxo (2-4)

A solution of 1-4 (3.01 g, 10.5 mmoles) in benzene (20 ml) was treated at room temperature with 2-3 (2.30 g, 10.7 mmoles) and Et_3N (10.8 mmoles) and the resulting solution was heated at reflux for 2 hours. The solvent was removed and the residue was taken up in EtOAc (200 ml) and extracted with 10% $KHSO_4$ solution (5 x 50 ml), brine and dried ($MgSO_4$). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with hexane (1)/EtOAc (1) to give pure 2-4. R_f 0.25.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (2H, m), 1.45 (9H, s), 1.67 (4H, m), 1.95 (1H, m), 2.70 (2H, t), 3.52 (2H, b), 3.97 (3H, s), 4.13 (2H, b), 4.95 (2H, s), 7.52 (1H, d), 8.23 (1H, d), 8.50 (1H, s).



2-5

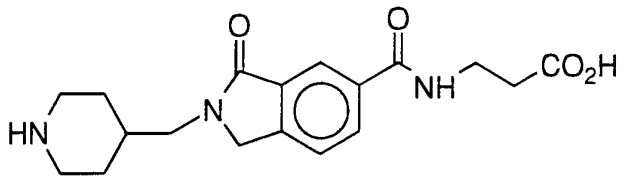
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(carboethoxyethyl]-2-[(4-N-t-butyloxycarbonylpiperidinyl)methyl]-3-oxo (2-5)

A solution of 2-4 (1.92 g, 5.58 mmoles) in 150 ml of THF(1)/MeOH(1)/H_2O(1) was treated with $LiOH \cdot H_2O$ (1.20 g, 28.6 mmoles) at room temperature and the resulting solution was stirred for 1.0 hr. The solvent was then removed and the residue was taken up in H_2O (100 ml) acidified to pH 2 with 10% $KHSO_4$ solution. The desired acid precipitated from solution and was collected.

^{1}H NMR (300 MHz, CD_3OD) δ 1.13 (2H, m), 1.40 (9H, s), 1.50-1.65 (3H, m), 2.70 (2H, b), 3.45 (2H, d), 3.98 (2H, d), 4.45 (2H, s), 7.60 (1H, d), 8.10 (1H, d), 8.21 (1H, s).

This acid (1.62 g, 4.91 mmoles) was dissolved in CH_3CN (25 ml) and treated at 0° successively with Et_3N (34.4 mmoles), β-alanine ethyl ester (5.0 mmoles), and BOP (3.27 g, 7.38 mmoles). The reaction mixture was then stirred at room temperature for 16 hrs. The solvent was removed and the residue purified by flash chromatography in silica gel eluting with EtOAc (7)/hexane (1) to provide 2-5 as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (6H, m), 1.42 (9H, s), 1.67 (5H, m), 1.95 (1H, m), 2.66 (4H, m), 3.50 (2H, b), 3.74 (2H, g), 4.16 (4H, m), 4.45 (2H, s), 7.00 (1H, t), 7.53 (1H, d), 8.11 (2H, m).



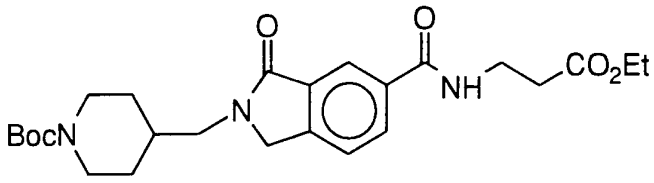
2-6

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[(4-piperidinyl)methyl]-3-oxo (2-6)

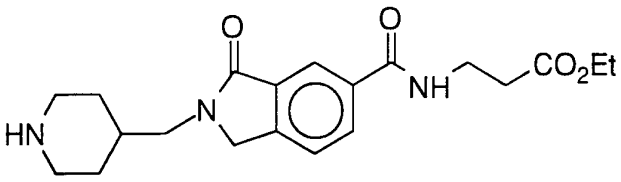
A solution of 2-5 (0.86 g, 2.0 mmoles) in 60 ml of THF(1)/MeOH(1)/H_2O(1) was treated with LiOH•H_2O (0.45 g, 10.7 mmoles) at room temperature and the resulting solution was stirred at room temperature for 1.0 hr. The solvent was removed and the residue was dissolved in H_2O (25 ml), acidified to pH 2-3 with 10% $KHSO_4$ solution and extracted with EtOAc (4 x 25 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed to give the desired acid as a white solid.
^1H NMR (300 MHz, CD_3OD) δ 1.16 (2H, m), 1.39 (9H, s), 1.45 (1H, m), 1.80 (2H, bd), 1.93 (2H, d), 2.58 (2H, t), 2.70 (2H, b), 3.45 (2H, d), 3.57 (2H, t), 4.00 (2H, m), 7.59 (1H, d), 8.00 (1H, d), 8.09 (1H, s).

This acid (0.80 g, 1.89 mmoles) was treated with HCl gas in EtOAc solution as described for 2-3 to provide pure 2-6 as a white solid.
^1H NMR (300 MHz, CD_3OD) δ 1.43 (2H, m), 1.85 (2H, m), 2.10 (1H,m), 2.56 (2H, t), 2.90 (2H, t), 3.34 (2H, bd), 3.54 (4H, m), 4.52 (2H, s), 7.61 (1H, d), 8.00 (1H, d), 8.10 (1H, s).

2-5 can also be converted to 2-7 as shown below:



2-5

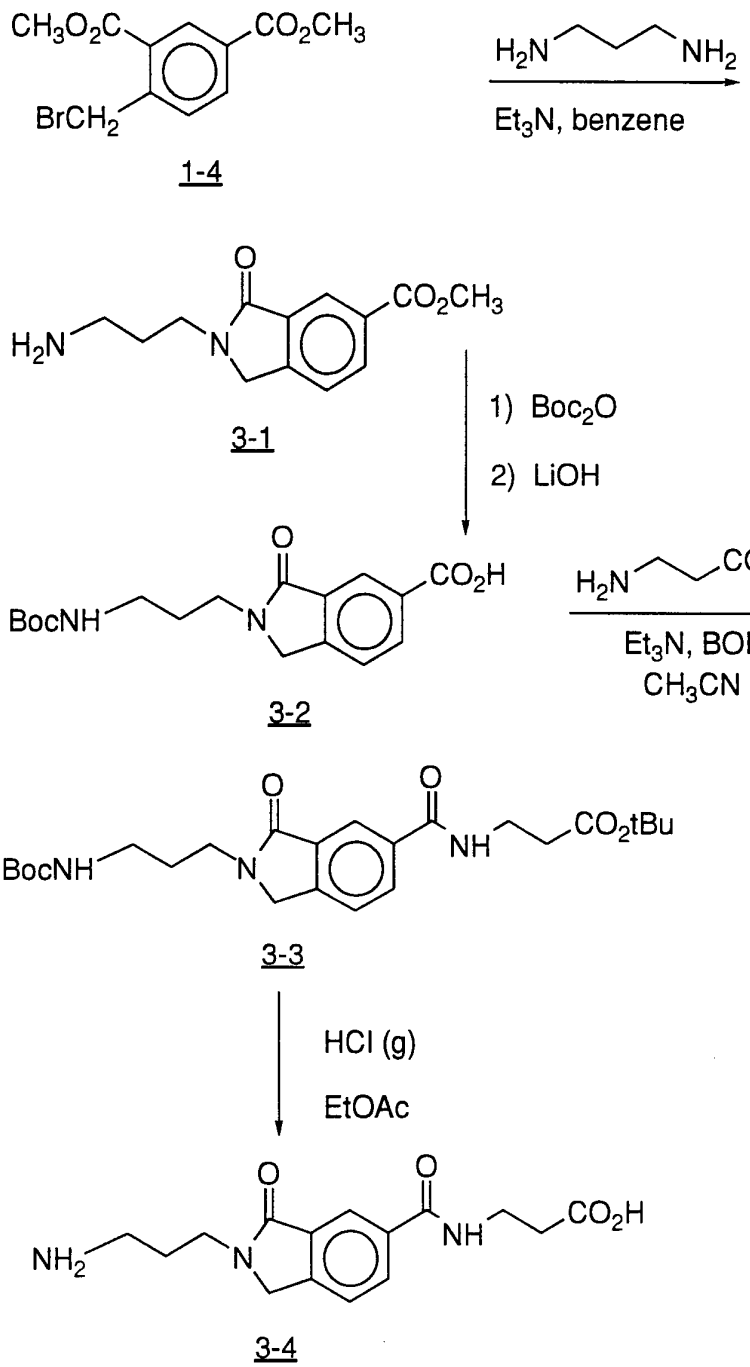


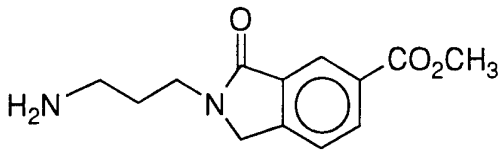
2-7

1-H-Isoindole-5-carboxamide,2,3-dihydro-N-[(2-carboethoxy)ethyl]-2-[2-(4-piperidinyl)methyl]-3-oxo(2-7)

Treatment of 2-5 (0.90g, 2.09 mmoles) in EtOAc with HCl gas as described for 1-12 gave 2-7 as an white, solid.
^{1}H NMR (300 MHz, CD_3OD) δ 1.09 (3H, t), 1.45 (2H, m), 1.86 (2H, bd), 2.13 (2H, m), 2.60 (2H, t), 2.90 (2H, t), 3.32 (2H, bd), 3.56 (4H, m), 4.08 (2H, q), 4.56 (2H, s), 7.62 (1H, d), 8.00 (1H, d), 8.09 (1H, s).

SCHEME 3


CH3O2C
CO2CH3
BrCH2
1-4
H2N
NH2
Et3N, benzene
O
CO2CH3
H2N
N
3-1
1) Boc2O
2) LiOH
O
CO2H
BocNH
N
3-2
H2N
CO2tBu
Et3N, BOP
CH3CN
O
O
NH
CO2tBu
BocNH
N
3-3
HCl (g)
EtOAc
O
O
NH
CO2H
NH2
N
3-4

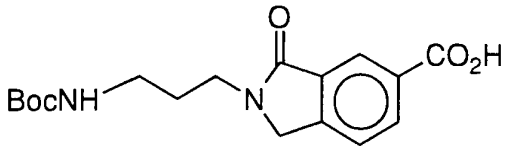


3-1

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[3-aminopropyl]-3-oxo (3-1)

A solution of 1-4 (2.58 g, 8.99 mmoles in benzene (10 ml) was treated with Et3N (12.9 mmoles) and 1,3-diaminopropane (13.0 mmoles) at room temperature and the resulting mixture was heated at reflux for 2 hrs. The reaction mixture was cooled and the solvent removed to give 3-1.

^{1}H NMR (300 MHz, CD_3OD) δ 1.53 (9H, s), 1.79 (2H, m), 3.02 (2H, m), 3.58 (2H, m), 3.84 (3H, s), 4.48 (2H, s), 7.58 (1H, d), 8.10 (1H, d), 8.20 (1H, s).



3-2

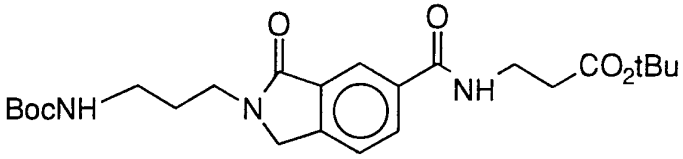
1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[3-(N-t-butyloxy-carbonylamino)propyl]-3-oxo (3-2)

3-1 (2.22 g, 8.99 mmoles) was suspended in 100 ml of THF(1)/H_2O(1) and treated with Et3N (9.3 mmoles) and di-t-butyl dicarbonate (4.0 g, 18.3 mmoles) and the resulting mixture was stirred vigorously for 5 hrs. The solvent was removed and the residue was purified by flash chromatography to give the desired protected ester.

^{1}H NMR (300 MHz, CD_3OD) δ 1.53 (9H, s), 1.80 (2H, m), 3.03 (2H, m), 3.58 (2H, m), 3.86 (3H, s), 4.48 (2H, s), 7.55 (1H, d), 8.10 (1H, d), 8.20 (1H, s).

This ester (0.67 g, 1.93 mmoles) was treated with $LiOH \cdot H_2O$ (0.41 g, 9.76 mmoles) in 60 ml of THF(1)/MeOH(1)/H_2O(1) at room temperature for 1 hr. Solvent removal gave a residue that was dissolved in 25 ml H_2O, acidified to pH 2-3 with 10% $KHSO_4$ solution and extracted with EtOAc (4x25 ml). The organic extract was washed with brine, dried ($MgSO_4$) and the solvent removed to give 3-2 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 1.35 (9H, s), 1.80 (2H, m), 3.04 (2H, t), 3.62 (2H, t), 4.55 (2H, s), 7.62 (1H, d), 8.20 (1H, d), 8.32 (1H, s).

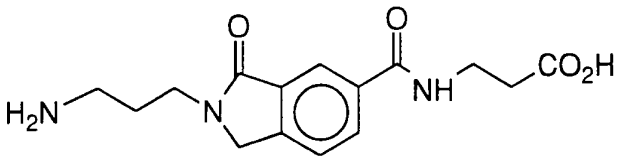


3-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxycarbonyl)-ethyl]-2-[3-(N-t-butyloxycarbonylamino)propyl]-3-oxo (3-3)

A solution of 3-2 (0.65 g, 1.94 mmoles) in 10 ml CH_3CN was cooled to 0-10° and treated with Et_3N (13.6 mmoles) and BOP (1.30 g, 2.93 mmoles) and the resulting solution was stirred at room temperature for 16 hrs. The solvent was then removed and the residue was taken up in EtOAc (100 ml) extracted with H_2O (4x25 ml), 10% $KHSO_4$ solution and dried ($MgSO_4$). Solvent removal give a residue that was purified by flash chromatography on silica gel eluting with $CHCl_3$(95)/MeOH(5) to give pure 3-3 as a white solid. R_f 0.3 (silica gel, $CHCl_3$(95)/MeOH(5)).

^1H NMR (300 MHz, $CDCl_3$), δ 1.46 (9H, s), 1.53 (9H, s), 1.90 (2H, m), 2.62 (2H, t), 3.60 (2H, m), 3.76 (4H, m), 4.50 (2H, s), 7.00 (1H, 6t), 7.62 (1h, d). 8.17 (1H, d), 8.20 (1H, s).



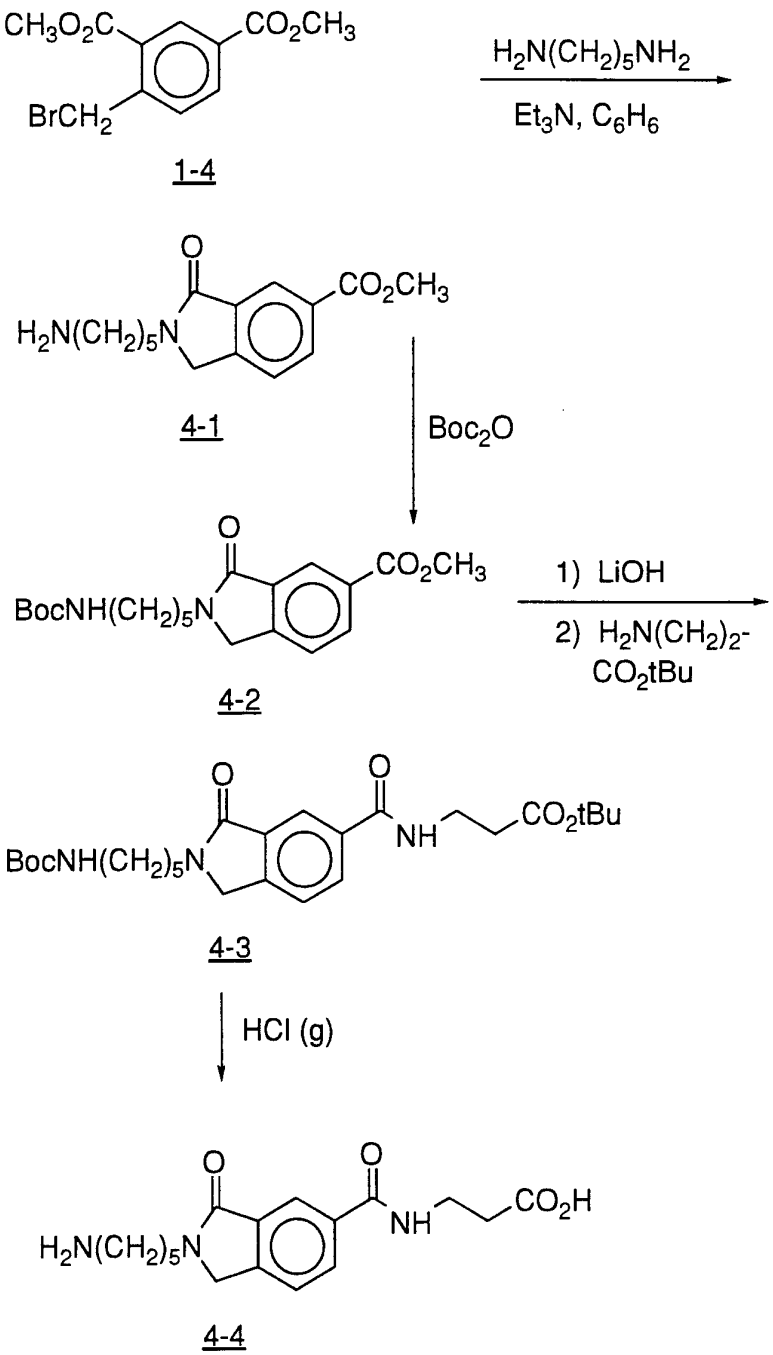
3-4

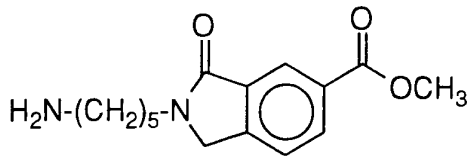
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[3-aminopropyl]-3-oxo (3-4)

3-3 (0.77g, 1.67 mmoles) was suspended in EtOAc (25 ml) and after cooling to -70°, HCl gas was bubbled into the mixture for 5 minutes at which time the reaction mixture was homogeneous. The reaction mixture was then stirred at 0-5° for 30 minutes. The solvent was removed and the residue was dried at high vacuum to provide pure 3-4 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 2.00 (2H, m), 2.60 (2H, t) 2.92 (2H, t), 3.59 (2H, m), 3.70 (2H, t), 4.28 (2H, s), 7.63 (1H, d), 8.02 (1H, d), 8.12 (1H, s).

SCHEME 4


CH3O2C
CO2CH3
BrCH2
1-4
H2N(CH2)5NH2
Et3N, C6H6
O
CO2CH3
H2N(CH2)5N
4-1
Boc2O
BocNH(CH2)5N
4-2
1) LiOH
2) H2N(CH2)2-CO2tBu
NH
CO2tBu
4-3
HCl (g)
CO2H
4-4

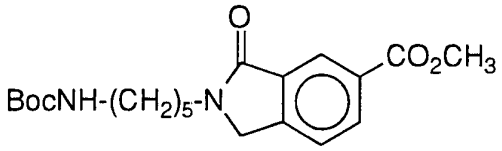


4-1

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[5-aminopentyl]-3-oxo (4-1)

A solution of 1-4 (2.56 g, 8.92 mmoles) in benzene (15 ml) was treated with Et_3N (11.5 mmoles) and 1,5-diaminopentane (11.9 mmoles) and the resulting reaction mixture was heated at reflux for 3 hrs. The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with 25% MeOH in $CHCl_3$ (MHz) to provide pure 4-1.

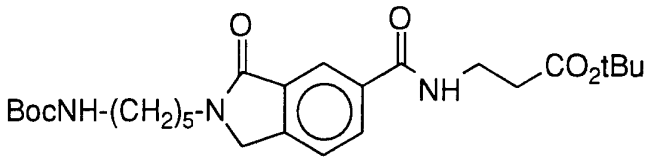
^1H NMR (300 MHz, $CDCl_3$) δ 1.77 (6H, m), 2.45 (2H, bs), 2.71 (2H, t), 3.63 (2H, t), 4.44 (2H, s), 7.52 (1H, d), 8.22 (1H, d), 8.49 (1H, s).



4-2

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[5-(N-t-butyloxy-carbonylamino)pentyl]-3-oxo (4-2)

A solution of 4-1 (0.64 g, 2.32 mmoles) in CH_2Cl_2 (10 ml) was treated at room temperature with Et_3N (2.29 mmoles) and Boc_2O (0.74 g, 3.39 mmoles) for 48 hrs. The solvent was then removed and the residue was purified by flash chromatography on silica gel eluting with hexane(7)/acetone(3) to give pure 4-2.



4-3

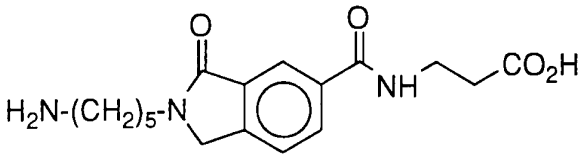
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(2-t-butyloxy-carbonyl)ethyl]-2-[5-N-t-butyloxycarbonylamino)pentyl]-3-oxo (4-3)

A solution of 4-2 (0.71 g, 1.89 mmoles) in THF(1)/MeOH(1)/H_2O(1) (60 ml) was treated with $LiOH \cdot H_2O$ (0.42 g, 10.0 mmoles) at room temperature for 0.5 hr. The solvent was then removed and the residue was dissolved in H_2O (50 ml), acidified to pH 2-3 with 10% $KHSO_4$ solution and extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and the solvent removed to give the desired acid.

^1H NMR (300 MHz, CD_3OD) δ 1.30 (9H, s), 1.45 (3H, m), 1.63 (3H, m), 2.92 (2H, t), 3.55 (2H, t), 4.47 (2H, s), 7.58 (1H, d), 8.16 (1H, d), 8.03 (1H, s).

This acid (0.75 g, 2.07 mmoles) was dissolved in CH_3CN (15 ml) and was treated at room temperature with β-alanine t-butyl ester (0.39 g, 2.54 mmoles), BOP (1.4 g, 3.16 mmoles), Et_3N (6.1 mmoles) and the resulting solution was stirred at room temperature for 20 hrs. The solvent was then removed and the residue was dissolved in EtOAc and extracted with H_2O, 10% $KHSO_4$ solution and brine. The organic phase was dried ($MgSO_4$) and was solvent was removed to give a residue that was purified by flash chromatography on silica gel eluting with EtOAc(7)/hexane(3) to give pure 4-3.

^1H NMR (300 MHz, CD_3OD) δ 1.39 (9H, s), 1.45 (2H, m), 1.65 (2H, m), 2.50 (2H, t), 2.96 (2H, q), 3.53 (4H, q), 4.47 (2H, s), 7.58 (1H, d), 7.96 (1H, d), 8.08 (1H, s).



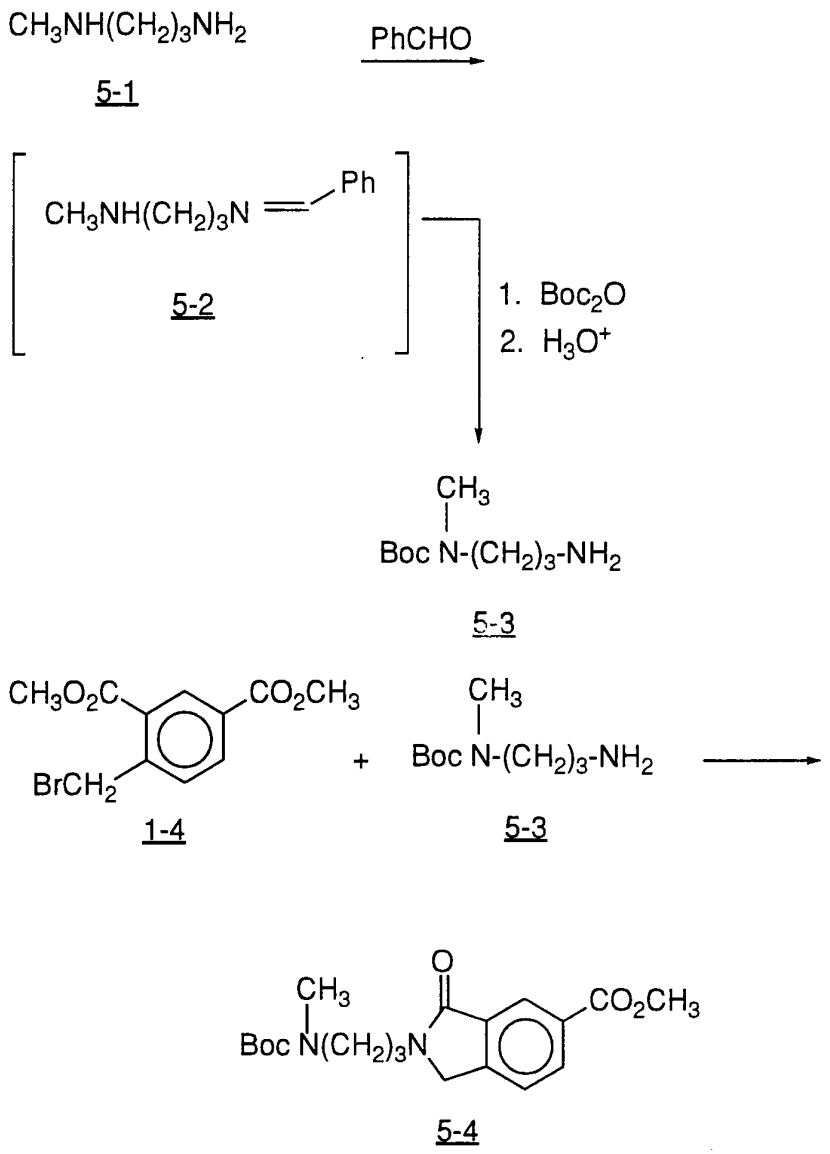
4-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[5-aminopentyl]-3-oxo (4-4)

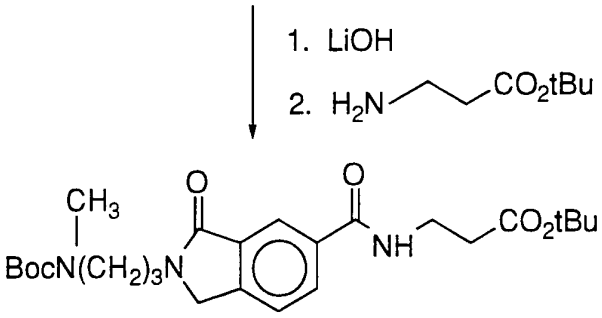
A solution of 4-3 (0.71 g, 1.45 mmoles) in EtOAc (20 ml) was cooled to -78° and treated with HCl gas for 10 minutes. The resulting solution was stirred in at 0° for 0.5 hr. The solvent was removed to provide 4-4 as white solid.

^{1}H NMR (300 MHz, D_2O) δ 1.29 (2H, m), 1.63 (4H,m), 2.62 (2H,t, 2.87 (2H, t), 3.52 (4H, m), 4.40 (2H, s), 7.51 (1H, d), 7.80 (2H, m).

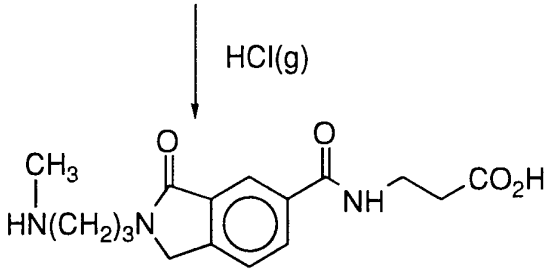
SCHEME 5


CH3NH(CH2)3NH2
PhCHO
5-1
CH3NH(CH2)3N
Ph
5-2
1. Boc2O
2. H3O+
CH3
Boc N-(CH2)3-NH2
5-3
CH3O2C
CO2CH3
BrCH2
1-4
+
CH3
Boc N-(CH2)3-NH2
5-3
O
CH3
Boc N(CH2)3N
CO2CH3
5-4

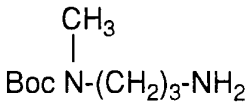
SCHEME 5 CONT'D



5-5



5-6



5-3

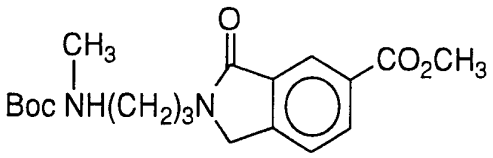
N-t-Butyloxycarbonyl-N-methyl-1,3-diaminopropane (5-3)

A solution of N-methyl-1,3-diaminopropane (2.05 g, 23.2 mmoles) in toluene (30 ml) was treated with benzaldehyde (2.41 g, 22.7 mmoles) and the resulting mixture was heated at reflux with use of a Dean-Stark trap. After 2 hrs. the reaction mixture was cooled and treated with Boc_2O (5.57 g, 25.5 mmoles) portionwise and the resulting solution was stirred for 48 hrs.

The solvent was then removed and the residue was cooled to 0-5° and acidified to pH 2-3 with 10% $KHSO_4$ solution (25 ml) and the

resulting slurry was stirred for 3 hrs. This mixture was then extracted with EtOAc and the aqueous phase was adjusted to pH 9 with 1N NaOH and extracted with $CHCl_3$ (5x25 ml). The dried organic phase was concentrated to give 5-3 as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.72 (2H, bt), 2.16 (2H, bs), 2.75 (2H, t), 2.87 (3H, s), 3.34 (2H, bs).

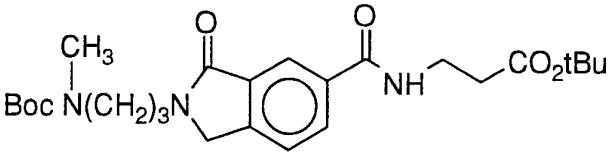


5-4

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[2-(3-N-t-butyloxycarbonyl-N-methylamino)propyl]-3-oxo (5-4)

A solution of 1-4 (2.0 g, 6.97 mmoles) in benzene (10 ml) was treated with 5-3 (1.19 g, 6.32 mmoles) and Et_3N (7.17 mmoles) and the resulting solution was heated at reflux for 24 hrs. The cooled reaction mixture was then dissolved in EtOAc (150 ml), washed with 10% $KHSO_4$ solution (4x50 ml), brine (50 ml) and dried ($MgSO_4$). The solvent was removed to give an oil that was purified by flash chromatography on silica gel eluting with EtOAc(7)/hexane(1) to give pure 5-4 as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.92 (2H, m), 2.90 (3H, s), 3.30 (2H, t), 3.68 (2H, t), 3.97 (3H, s), 4.50 (2H, s), 7.55 (1H, d), 8.26 (1H, d), 8.52 (1H, s).



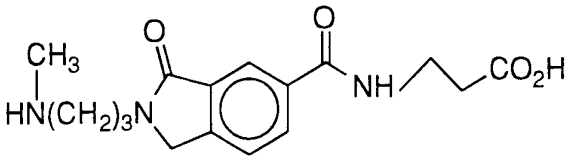
5-5

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxy-carbonyl)ethyl]-2-[3-(N-t-butyloxycarbonyl-N-methylamino)propyl]-3-oxo (5-5)

A solution of 5-4 (1.28 g, 3.53 mmoles) in THF(1)/MeOH-(1)/H_2O(1) (105 ml) was treated with LiOH•H_2O (0.76 g, 18.1 mmoles) and the resulting solution was stirred at room temperature for 30 minutes. The solvent was then removed and the residue was taken up in H_2O (30 ml), acidified to pH 2-3 with 10% $KHSO_4$ solution, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed to provide the desired acid.
^1H NMR (300 MHz, CD_3OD) δ 1.34 (9H,s), 1.86 (2H, m), 2.78 (3H, s), 3.22 (2H, m), 3.55 (2H, t), 4.50 (2H, s), 7.60 (1H, d), 8.17 (1H, d), 8.30 (1H, s).

This acid (1.28 g, 3.59 mmoles) was dissolved in CH_3CN (20 ml) and treated successively with β-alanine t-butyl ester hydrochloride (0.65 g, 3.59 mmoles), Et_3N (2.51 mmoles), and BOP (2.39 g, 5.40 mmoles) and the resulting cloudy suspension was stirred at room temperature for 20 hrs. The reaction mixture was then concentrated and the residue was taken up in EtOAc (100 ml), extracted with H_2O (2x25 ml), 10% $KHSO_4$ solution (4x25 ml), brine and dried ($MgSO_4$). Solvent removal gave a residue that was purified by flash chromatography on silica gel eluting with acetone(3)/hexane(7) to give pure 5-5 as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H,s), 1.44 (9H, s), 1.93 (2H, m), 2.37 (2H, t), 2.88 (3H, s), 3.30 (2H, t), 3.68 (4H, m), 4.47 (2H, s), 6.98 (1H, bt), 7.55 (1H, d), 8.09 (1H, d), 8.12 (1H, s).



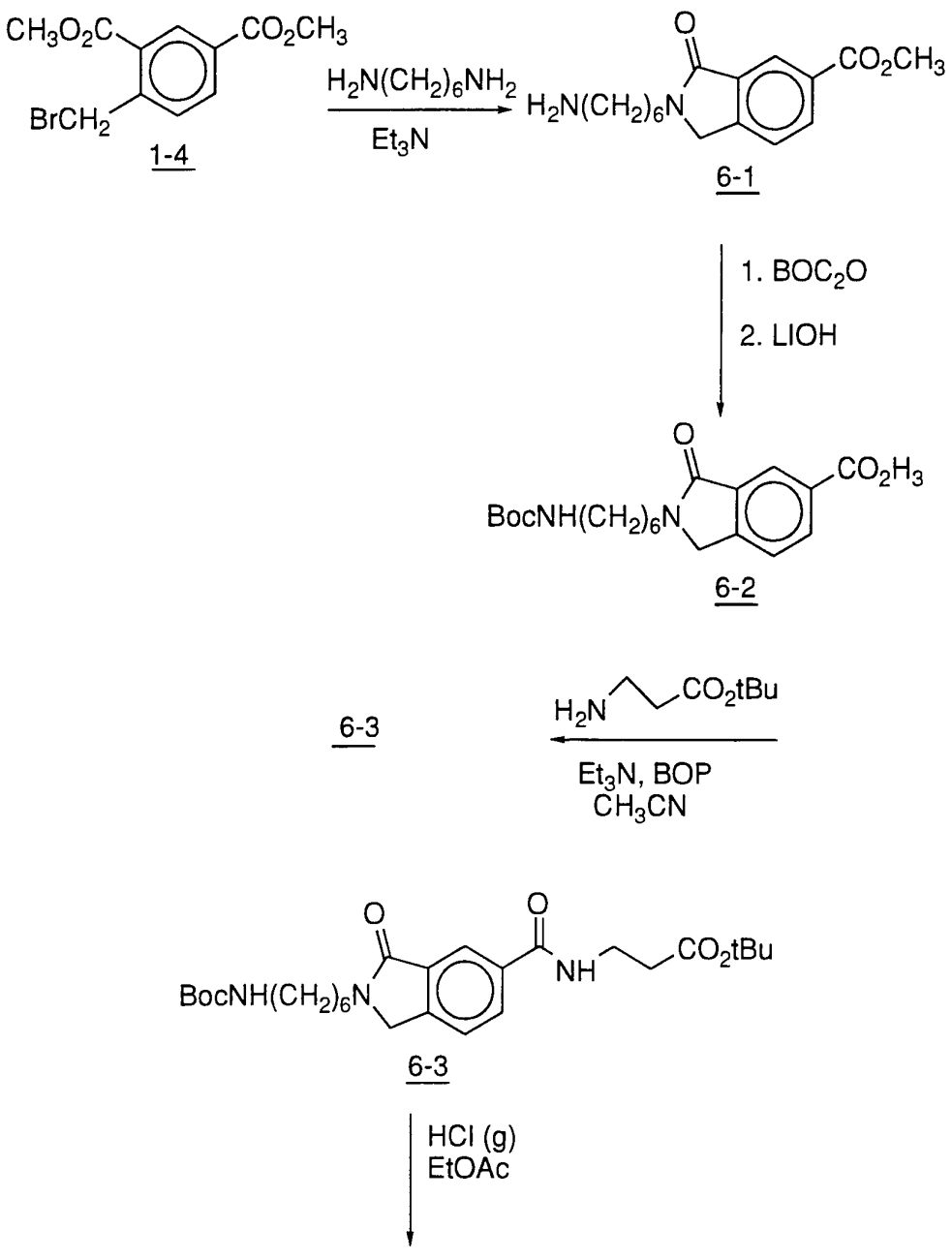
5-6

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[3-(N-methylamino)propyl]-3-oxo (5-6)

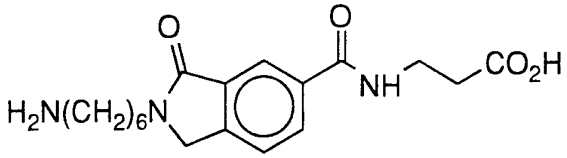
A solution of 5-5 (1.42 g, 2.09 mmoles) in EtOAc (40 ml) was cooled to -78° and treated with HCl gas for 3-5 minutes. The resulting solution was stirred at 0° for 0.5 hr. The solvent was then removed to provide 5-6 as a white solid.

^{1}H NMR (300 MHz, D_2O) δ 2.00 (2H, m), 2.62 (5H, m), 3.00 (2H, t), 3.60 (4H, m), 4.29 (2H, s), 7.75 (1H, d), 7.83 (1H, d), 7.88 (1H, s).

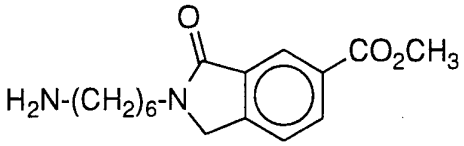
SCHEME 6


CH3O2C
CO2CH3
BrCH2
1-4
H2N(CH2)6NH2
Et3N
O
H2N(CH2)6N
CO2CH3
6-1
1. BOC2O
2. LIOH
O
BocNH(CH2)6N
CO2H3
6-2
6-3
H2N
CO2tBu
Et3N, BOP
CH3CN
O
O
BocNH(CH2)6N
NH
CO2tBu
6-3
HCl (g)
EtOAc

SCHEME 6 CONT'D



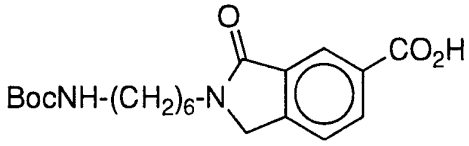
6-4



6-1

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[6-aminohexyl]-3-oxo (6-1)

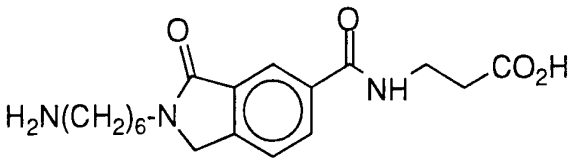
Treatment of 1-4 with 1,6-diaminohexane as described for 1-9 provided 6-1 as a white solid. R_f 0.5 (silica gel, hexane (9)/EtOAc (1).



6-2

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[6-N(t-butyloxy-carbonylamino)hexyl]-3-oxo (6-2)

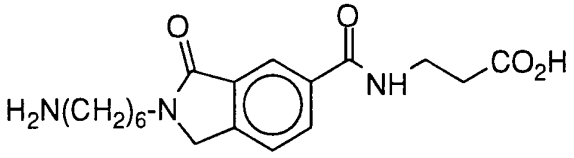
Treatment of 6-1 with Boc_2O (1 equiv) and triethylamine (2 equivalents) in H_2O(1)/THF(1) (100 ml) at room temperature for 48 hours followed by solvent removal gave crude BOC-protected derivative. Hydrolysis of this with $LiOH \cdot H_2O$ (4 equiv.) as described for 1-10 gave 6-2 as an oil. ^1H NMR/(300 MHz, CD_3OD) δ 1.32 (17H, m), 1.68 (2H, m) 2.95 (2H, t), 4.50 (2H, s), 7.62 (1H, d), 8.19 (1H, d), 8.31 (1H, s).



6-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxy-carbonyl)ethyl]-2-[6-N-(t-butyloxycarbonylamino)hexyl]-3-oxo (6-3)

Treatment of 6-2 (1.18 g, 3.12 mmoles) with t-butyl β-alanine (0.54 g, 3.51 mmoles) as described for 1-11 gave crude 6-3. This was purified by flash chromatography on silica gel eluting with pet ether (6)/EtOAc (4) to provide 6-3 as an oil. Rf 0.25 (silica gel, pet ether (7)/acetone (3)).

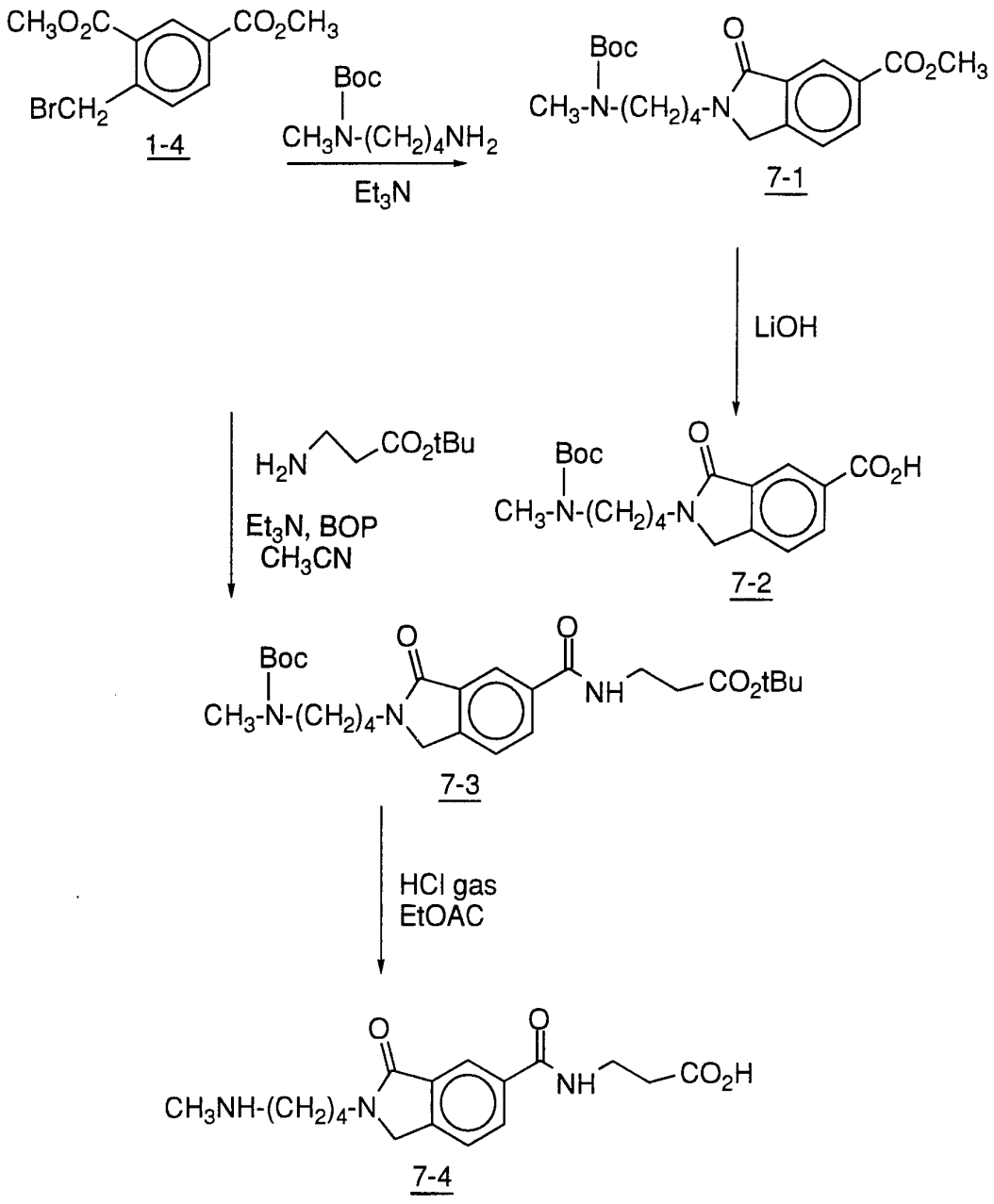


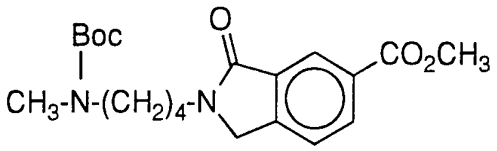
6-4

1-H-Isoindole-5-carboxamide,2,3-dihydro-N-(2-carboxyethyl)-2-[6-aminohexyl]-3-oxo (6-4)

6-3 (0.44 g) was dissolved in EtOAc (25 ml) cooled to -78° and treated with HCl gas for 5 minutes. The reaction mixture was then stirred at 0° for 30 minutes and the solvent was removed. The residue was purified by flash chromatography on silica gel eluting with EtOH(9)/H_2O(1)/NH_4OH(1) to provide 6-4 as a white solid.
^1H NMR (300 MHz, CD_3OD) δ 1.42 (4H, m), 1.68 (4H, m), 2.63 (2H, t), 2.88 (2H, t), 3.60 (4H, m), 4.52 (2H, s), 7.60 (1H, d), 7.97 (1H, d), 8.10 (1H, s).

SCHEME 7

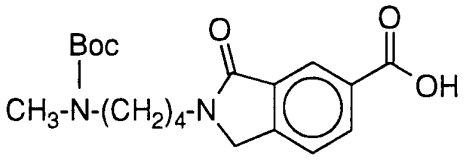

CH3O2C
CO2CH3
BrCH2
1-4
Boc
CH3N-(CH2)4NH2
Et3N
Boc
CH3-N-(CH2)4-N
O
CO2CH3
7-1
LiOH
H2N
CO2tBu
Et3N, BOP
CH3CN
Boc
CH3-N-(CH2)4-N
O
CO2H
7-2
Boc
CH3-N-(CH2)4-N
O
O
NH
CO2tBu
7-3
HCl gas
EtOAC
CH3NH-(CH2)4-N
O
O
NH
CO2H
7-4



7-1

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[4-(N-methyl-N-t-butyloxycarbonylamino)butyl]-3-oxo (7-1)

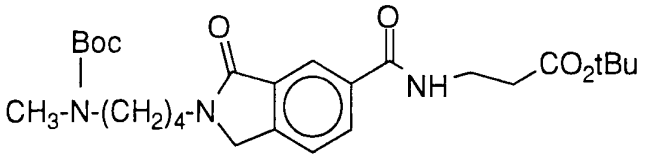
Treatment of 1-4 with 4-(N-methyl-N-t-butyl-oxycarbonylamino)butylamine (prepared as described for 5-3) as described for 1-9 provided crude 7-1. This was purified by flash chromatography on silica gel eluting with EtOAc(7)/hexane(3) to give pure 7-1. R_f 0.3 (silica gel, EtOAc(7)/hexane(3). ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.60 (4H, m), 7.52 (1H, d), 8.23 (1H, d), 8.23 (1H, d), 8.50 (1H, s).



7-2

1H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[4-(N-methyl-N-t-butyloxycarbonylamino)butyl]-3-oxo (7-2)

Treatment of 7-1 (1.16 g, 2.08 mmoles) with $LiOH \cdot H_2O$ (0.65 g, 15.5 mmoles) in $THF(1)/CH_3OH(1)/H_2O(1)$ (75 ml) as described for 1-10 gave 7-2 as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 1.67 (10H, m), 1.80 (2H, m), 1.89 (2H, m), 3.05 (3H, s), 3.50 (2H, t), 3.88 (2H, t), 4.78 (2H, s), 7.90 (1H, d), 8.45 (1H, d), 8.60 (1H, s).

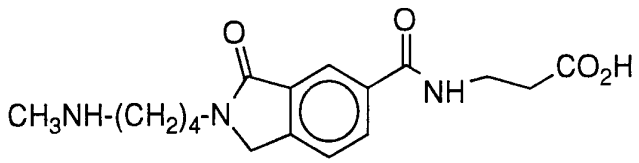


7-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxy-carbonyl)-ethyl]-2-[4-(N-t-butyloxycarbonylN-methylamino)butyl]-3-oxo (7-3)

Treatment of 7-2 (1.04 g, 2.86 mmoles) with β-alanine t-butyl ester (0.54 g, 2.97 mmoles) as described for 1-11 gave crude 7-3. This was purified by flash chromatography on silica gel eluting with hexane(6)/acetone(4) to give 7-3 as an oil. R_f 0.4 (silica gel, EtOAc(7)/hexane(3).

^{1}H NMR (300 MHz, $CHCl_3$) δ 1.46 (18H, m), 1.60 (4H, m), 2.58 (2H, t), 2.83 (3H, s), 3.28 (2H, t), 3.70 (4H, m), 4.45 (2H, s), 7.52 (1H, d), 8.09 (1H, d), 8.11 (1H, s).



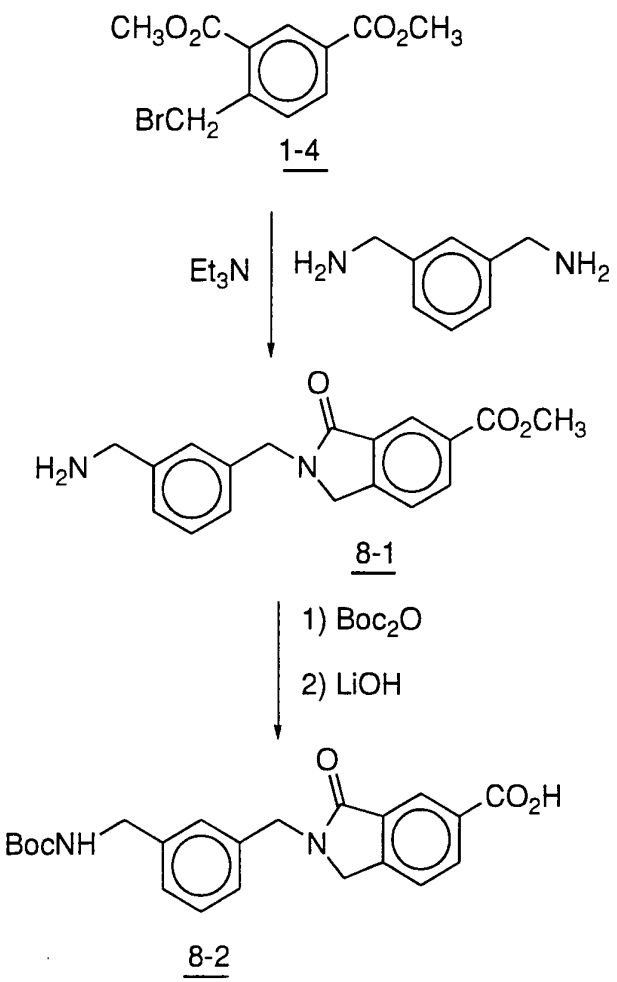
7-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[4-(N-methylamino)butyl]-3-oxo (7-4)

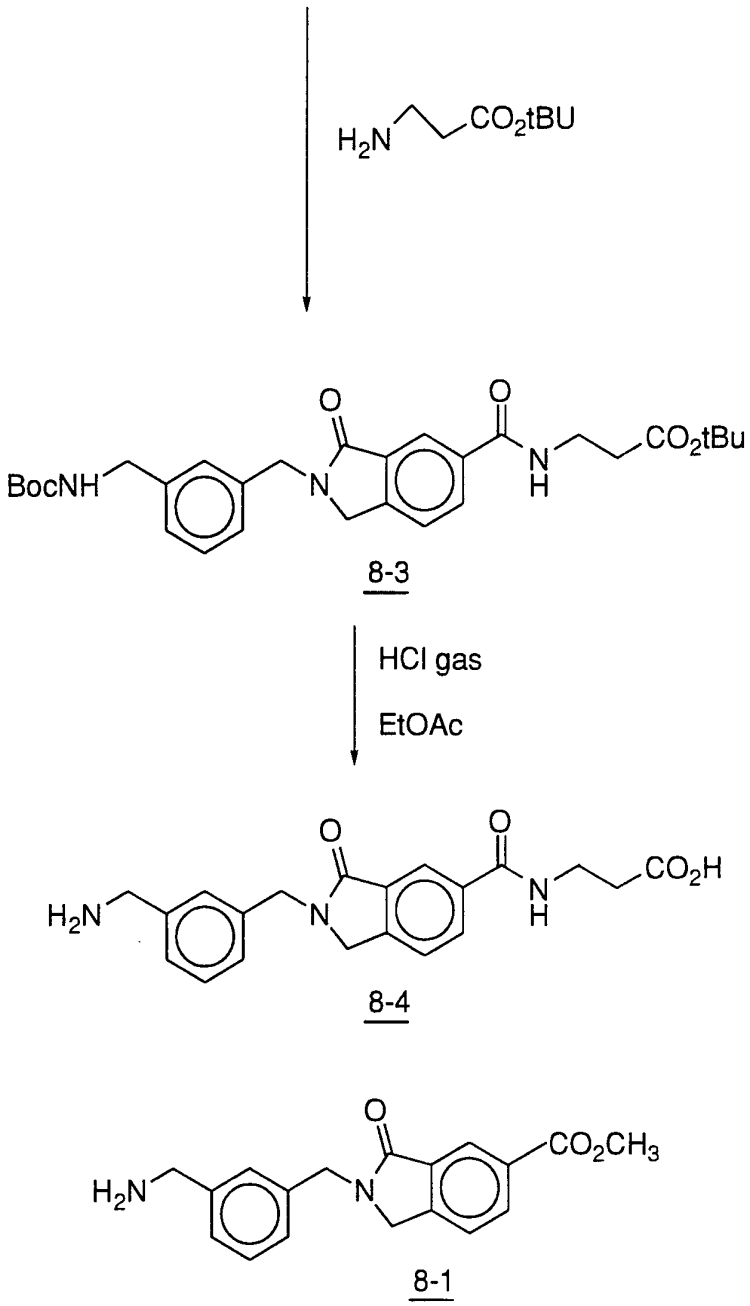
Treatment of 7-3 with HCl gas in EtOAc solution as described for 6-4 gave 7-4 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.67 (4H, m), 2.58 (5H, m), 2.95 (2H, t), 3.50 (4H, m), 4.50 (2H, s), 7.56 (1H, d), 7.97 (1H, d), 8.08 (1H, s).

SCHEME 8

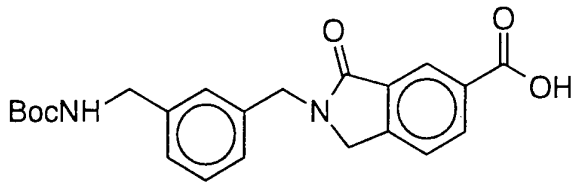

CH3O2C
CO2CH3
BrCH2
1-4
Et3N
H2N
NH2
O
CO2CH3
H2N
N
8-1
1) Boc2O
2) LiOH
O
CO2H
BocNH
N
8-2

SCHEME 8 CONT'D



Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[(3-aminomethyl-phenyl)methyl]-3-oxo (8-1)

Treatment of 1-4 (2.15 g, 7.49 mmoles) with m-xylenediamine (9.85 mmoles) as described for 1-9 gave crude 8-1. This was purified by flash chromatography on silica gel eluting with CH_3OH (10/$CHCl_3$ (NH_4OH) (90) to give pure 8-1 as a white solid. Rf 0.7 silica gel, CH_3OH (10)/$CHCl_3$ (NH_4OH) (90).



8-2

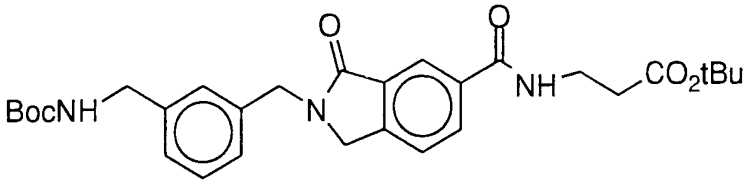
1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[(3-N-t-butyloxy-carbonylaminomethylphenyl)methyl]-3-oxo (8-2)

8-1 (1.76 g, 5.67 mmoles) was dissolved in CH_2Cl_2 (25 ml) and treated with Boc_2O (1.50 g, 6.87 mmoles) and Et_3N (6.45 mmoles) as described for 6-2 to give the desired N-protected ester. Rf 0.25 (silica gel, EtOAc (1)/hexane (1)).

^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.65 (1H, m), 2.06 (2H, s), 4.30 (4H, m), 4.81 (2H, s), 7.27 (6H, m), 7.47 (1H, d), 8.22 (1H, d), 8.55 (1H, s).

This acid was treated with $LiOH \cdot H_2O$ as described for 6-2 to provide 8-2 as a white solid. Rf 0.1 (silica gel, $CHCl_3$ (97)/CH_3OH (1)/HOAc (1)).

^1H NMR (300 MHz, CD_3OD) δ 1.32 (9H, s), 4.12 (2H, s), 4.38 (2H, s), 4.73 (2H, s), 7.12 (4H, m), 7.25 (1H, m), 7.52 (1H, d).

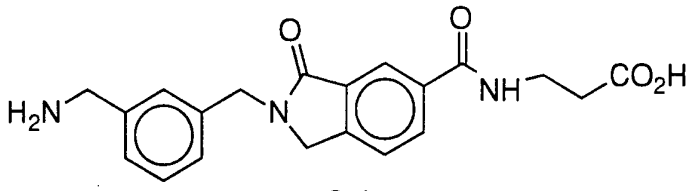


8-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxy-carbonyl)ethyl]-2-[(3-N-t-butyloxycarbonylaminomethylphenyl)-methyl]-3-oxo (8-3)

Treatment of 8-2 (0.80 g, 2.02 mmoles) with β-alanine t-butyl ester (0.35 g, 2.28 mmoles), BOP (1.35 g, 3.04 mmoles) and Et_3N (14.3 mmoles) as described for 1-11 gave crude 8-3. This was purified by flash chromatography on silica gel eluting with hexane (6)/acetone (4) to give pure 8-3.

^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.47 (9H, s), 2.59 (2H, t), 3.72 (2H, m), 4.30 (4H, s), 4.82 (2H, s), 4.88 (1H, m), 7.28 (5H, m), 7.48 (1H, d), 8.08 (1H, d), 8.19 (1H, s).



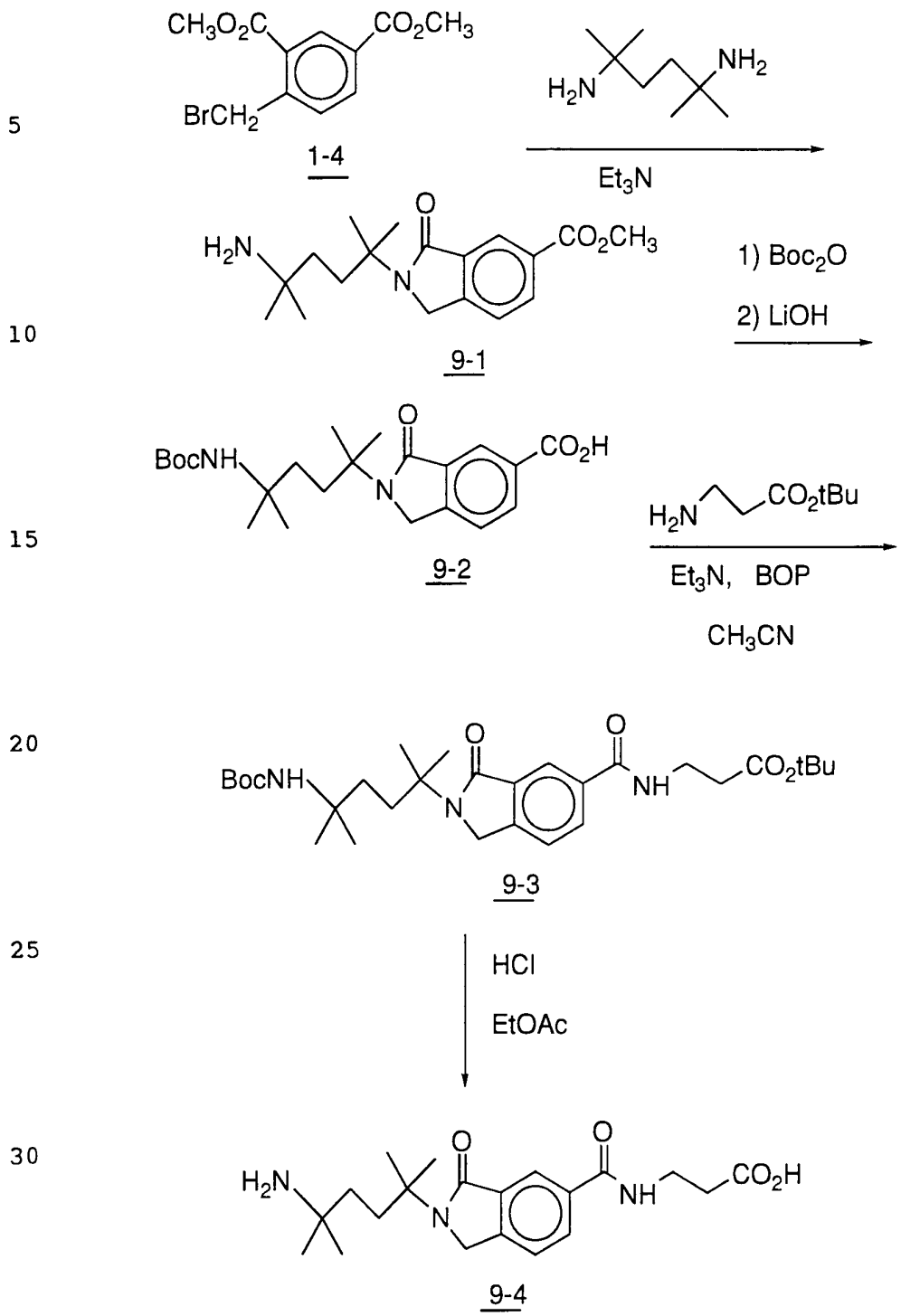
8-4

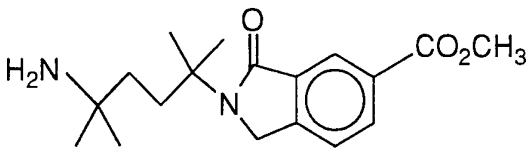
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[(3-aminomethylphenyl)methyl]-3-oxo (8-4)

8-3 (0.872 g, 1.67 mmoles) was dissolved in EtOAc (25 ml) and treated with HCl as described for 6-4 to give pure 8-4.

^1H NMR (300 MH_3, CD_3OD) δ 2.58 (2H, t), 3.56 (2H, t), 4.00 (4H, s), 4.42 (2H, s), 7.32 (4H, m), 7.52 (1H, d), 7.95 (1H, d), 8.11 (1H, s).

SCHEME 9

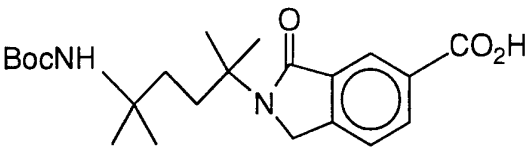

CH3O2C
CO2CH3
BrCH2
1-4
H2N
NH2
Et3N
H2N
O
N
CO2CH3
9-1
1) Boc2O
2) LiOH
BocNH
CO2H
9-2
H2N
CO2tBu
Et3N, BOP
CH3CN
BocNH
NH
CO2tBu
9-3
HCl
EtOAc
H2N
NH
CO2H
9-4



9-1

Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[(4-amino-1,1,4,4-tetramethyl)butyl]-3-oxo (9-1)

Treatment of 1-4 (2.51 g, 8.74 mmoles) with 1,1,4,4,-tetramethyl-1,4-diaminobutane (1.50 g, 10.40 mmoles) as described for 1-9 provided 9-1. R_f 0.25 silica gel, 10% CH_3OH in $CHCl_3/NH_4OH$.

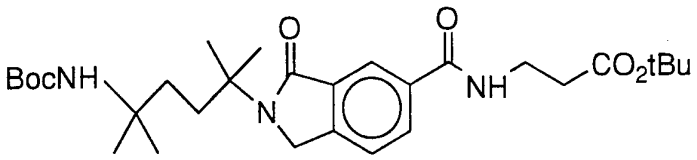


9-2

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[(4-N-t-butyloxy-carbonylamino)-1,1,4,4-tetramethyl)butyl]-3-oxo (9-2)

9-1 was treated with Boc_2O and Et_3N as described for 6-2 to give the desired Boc-protected ester. R_f 0.3 (silica gel, hexane (7)/acetone/3).

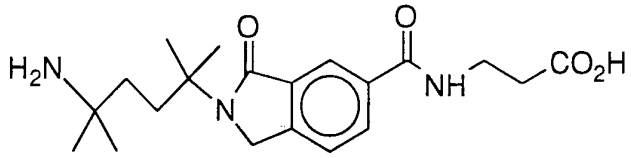
This ester (1.03 g, 2.46 mmoles) was treated with $LiOH \cdot H_2O$ (0.54 g, 12.9 mmoles) in THF (1)/CH_3OH (1)/H_2O (1) (60 ml) as described for 6-2 to give pure 9-2. R_f 0.35 (silica gel, EtOAc).
^1H NMR (300 MHz, CD_3OD) δ 1.10 (6H, s), 1.28 (9H, s), 1.48 (6H, s), 4.60 (2H, s), 7.55 (1H, d), 8.16 (1H, d), 8.26 (1H, s).



9-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-t-butyloxy-carbonyl)-ethyl]-2-[4-(N-t-butyloxycarbonyl-amino)-(1,1,4,4-tetramethyl)butyl]-3-oxo (9-3)

9-2 (1.05 g, 2.83 mmoles) was treated with β-alanine t-butyl ester (0.48 g, 3.12 mmoles), Et_3N (20.0 mmoles) and BOP (1.91 g, 4.31 mmoles) in CH_3CN (15 ml) as described for 1-11 to provide crude 9-3. This was purified by flash chromatography on silica gel eluting with pet ether (7)/acetone (3) to give pure 9-3. R_f 0.3 silica gel, pet ether (7)/acetone (3).

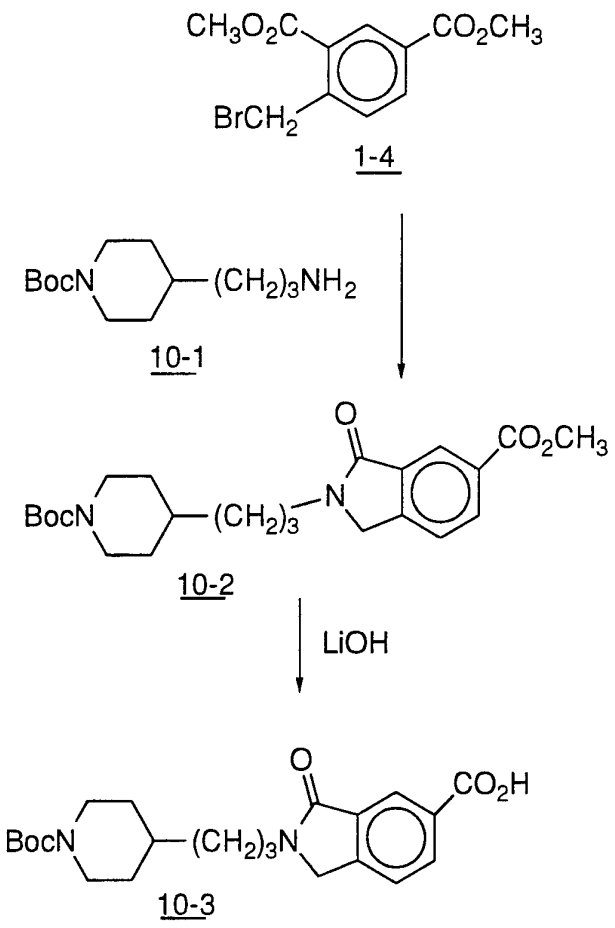


9-4

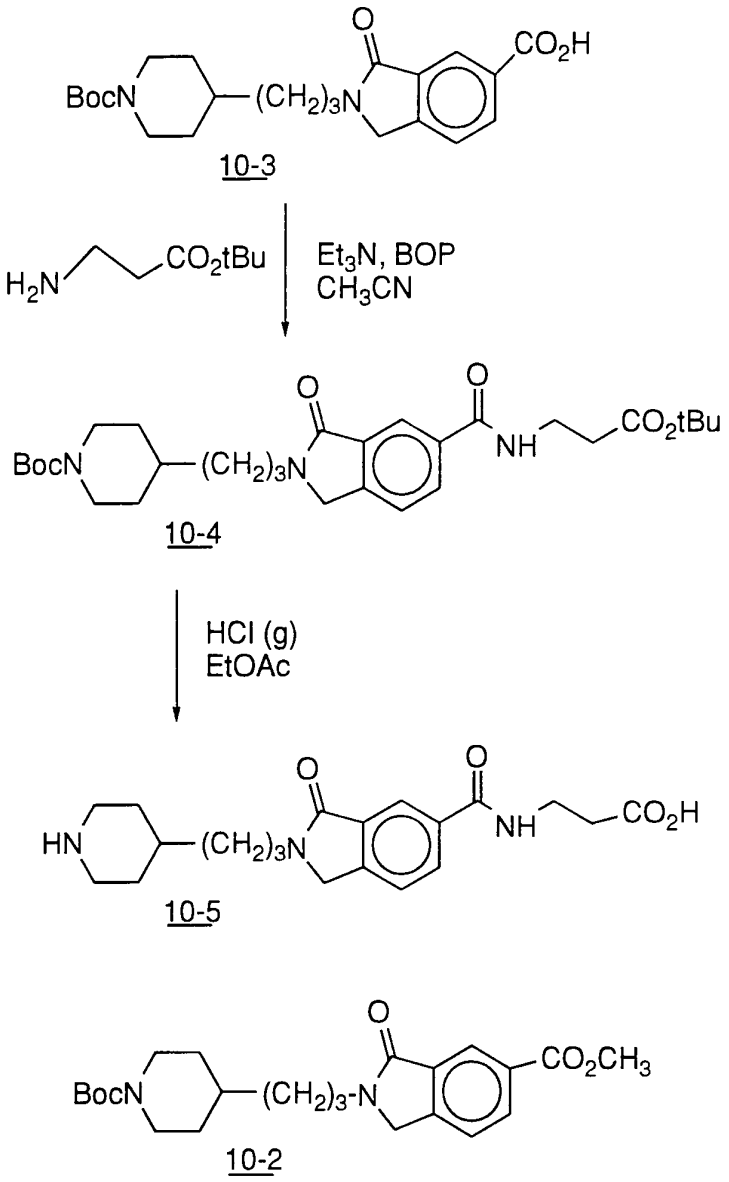
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[(4-amino-1,1,4,4-tetramethyl)butyl]-3-oxo (9-4)

9-3 (1.23 g) was dissolved in EtOAc (25 ml), cooled to -78° and treated with HCl gas as described for 6-4 to give pure 9-4. ^1H NMR (300 MHz, CD_3OD) δ 1.26 (6H, s), 1.53 (8H, m), 2.59 (2H, t), 3.57 (2H, m), 4.63 (2H, s), 7.57 (1H, d), 7.98 (1H, d), 8.06 (1H, s).

SCHEME 10


CH3O2C
CO2CH3
BrCH2
1-4
BocN
(CH2)3NH2
10-1
O
CO2CH3
BocN
(CH2)3
N
10-2
LiOH
O
CO2H
BocN
(CH2)3N
10-3

SCHEME 10 CONT'D

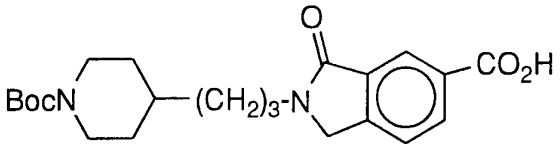


Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[3-(4-N-t-butyloxy-carbonylpiperidinyl)propyl]-3-oxo (10-2)

Treatment of 1-4 (4.59 g, 16.0 mmoles) with 3-(4-N-t-butyloxycarbonylpiperidinyl)propylamine (prepared from 1-6 by nitrile formation followed by catalytic hydrogenation) (4.36 g, 15.6 mmoles) as described for 1-9 gave crude 10-2. This was purified by flash

chromatography on silia gel eluting with hexane (3)/ethyl acetate (1) to give pure 10-2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (2H, m), 1.30 (2H, m), 1.45 (9H, s), 1.68 (4H, m), 2.66 (2H, m), 3.62 (2H, t), 3.95 (3H, s), 4.10 (2H, m), 4.44 (2H, s), 7.52 (1H, d), 8.23 (1H, d), 8.50 (1H, s).

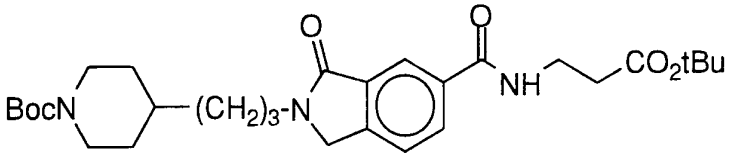


10-3

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-N-[3-(4-N-t-butyloxy-carbonylpiperidinyl)propyl]-3-oxo (10-3)

Treatment of 10-2 (2.79 g, 6.91 mmoles) with $LiOH \cdot H_2O$ (1.48 g, 35.2 mmoles) in THF (1)/MeOH (1)/H_2O (1) as described for 1-10 provided 10-3 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 0.95 (2H, m), 1.23 (3H, m), 1.35 (9H, s), 1.66 (3H, m), 2.65 (2H, m), 3.56 (2H, t), 3.96 (2H, bd), 4.50 (2H, s), 7.60 (1H, d), 8.17 (1H, d), 8.30 (1H, s).

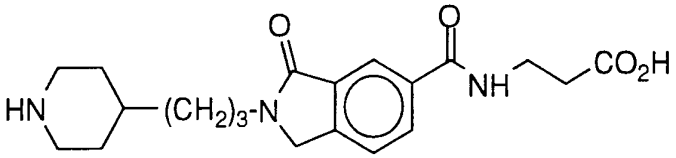


10-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(t-butyloxy-carbonyl)ethyl]-2-[3-(4-N-t-butyloxycarbonyl-piperdinyl)propyl]-3-oxo (10-4)

Treatment of 10-3 (1.28 g, 3.28 mmoles) with β-alanine t-butyl ester (0.64 g, 3.52 mmoles), Et_3N (3.3 mmoles), BOP (2.16 g) in CH_3CN as described for 1-11 gave crude 10-4. This was purified by flash chromatography on silica gel eluting with hexane (7)/acetone (3) to give pure 10-4.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (2H, m), 1.30 (3H, m), 1.45 (9H, s), 1.68 (4H, m), 2.62 (4H, m), 3.62 (2H, t), 3.70 (2H, t), 4.08 (2H, bd), 4.23 (2H, s), 7.52 (1H, d), 8.10 (1H, d), 8.13 (1H, s).



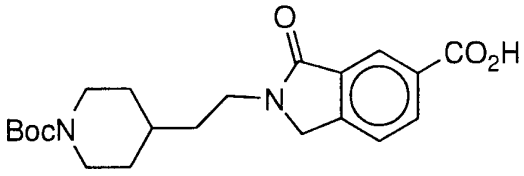
10-5

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxyethyl)-2-[3-(4-piperidinyl)propyl]-3-oxo (10-5)

Treatment of 10-4 (1.18 g) in EtOAc (30 ml) -78° with HCl gas as described for 6-4 gave pure 10-5 as a white solid. R_f 0.4 (silica gel, EtOAc).

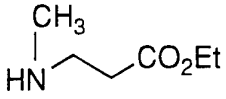
^{1}H NMR (300 MHz, CD_3OD) δ 1.30 (4H, m), 1.67 (4H, m), 1.89 (2H, bd), 2.60 (2H, t), 2.40 (2H, t), 3.19 (2H, bd), 3.58 (4H, m), 4.50 (2H, s), 7.60 (1H, d), 7.99 (1H, d), 8.08 (1H, s).

SCHEME 11



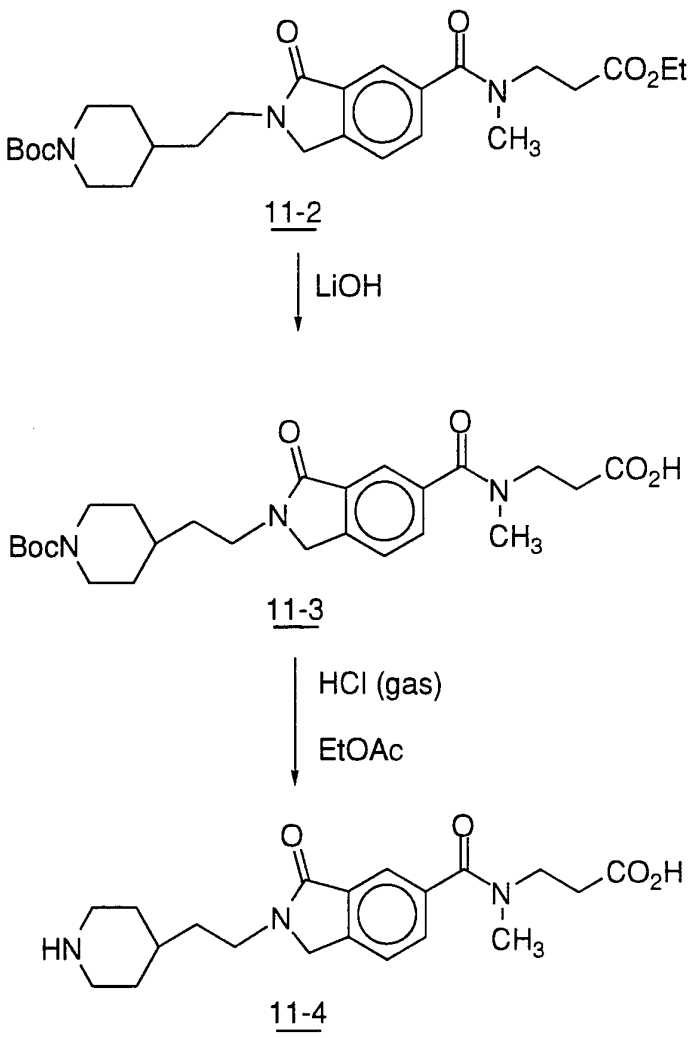
1-10

+



11-1

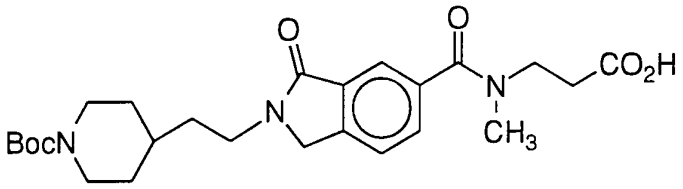
SCHEME 11 CONT'D



1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-methyl-N-2-(carboethoxy)ethyl]-2-[2-(4-N-t-butyloxycarbonyl-piperidinyl)-ethyl]-3-oxo (11-2)

Treatment of 1-10 (0.2 g, 0.54 mmoles) with ethyl 3-(N-methyl)aminopropionate (0.14 g, 1.08 mmoles) (Appl. Polymer Sci., 1969, 13, 227), N-methylmorpholine (1.08 mmoles), and BOP (0.35 g, 0.8 mmoles) in CH_3CN (3 ml) as described for 1-11 gave crude 11-2. This was purified by flash chromatography on silica gel eluting with EtOAc to give pure 11-2 as a white solid.

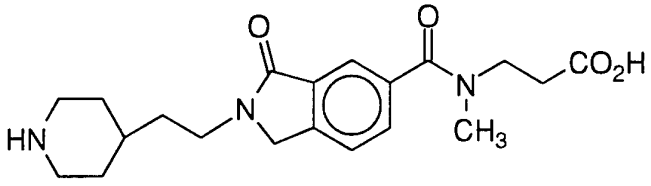
^{1}H NMR (300 MHz, CD_3OD) δ 1.20 (6H, m), 1.45 (9H, s), 1.67 (2H, q), 1.80 (2H, bd), 2.73 (2H, m), 3.00 (3H, s), 3.08 (1H, bs), 3.71 (2H, t), 3.84 (1H, m), 4.05 (4H, m), 4.17 (1H, m), 4.56 (2H, s), 7.66 (2H, m), 7.77 (1H, s).



11-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-methylN-(2-carboxyethyl)]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)ethyl]-3-oxo (11-3)

11-2 (0.23 g, 0.49 mmoles) was treated with $LiOH•H_20$ (0.096 g, 2.3 mmoles) as described for 8-2 to give 11-3 as a white solid.



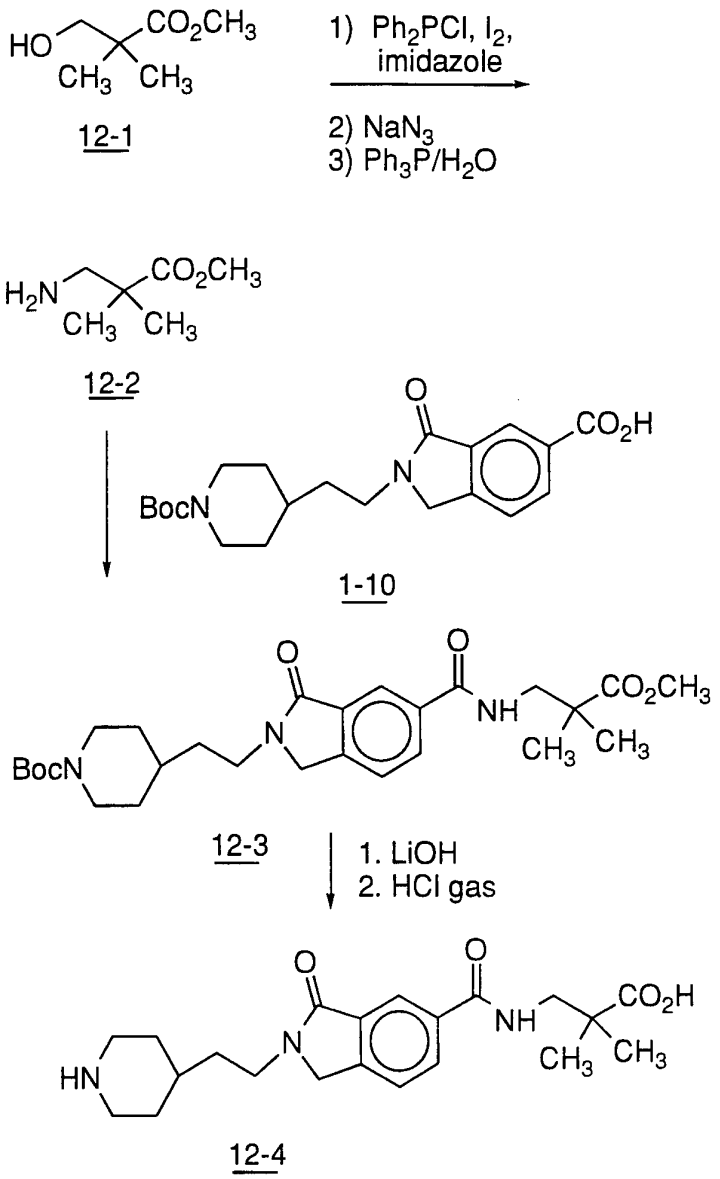
11-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-methyl-N-(2-carboxyethyl)]-2-[(4-piperidinyl)ethyl]-3-oxo (11-4)

11-3 (0.2 g, 0.45 mmoles) in EtOAc was treated with HCl gas as described for 8-4 to give pure 11-4 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.14 (1H, t), 1.37 (2H, m), 1.50 (1H, m), 1.63 (2H, q), 1.92 (2H, bd), 2.51 (1H, t), 2.67 (1H, t), 2.83 (2H, m), 3.31 (2H, bd), 3.54 (1H, t), 3.60 (2H, t), 3.73 (1H, t), 4.49 (2H, s), 7.57 (2H, q), 7.65 (1H, s).

SCHEME 12



Methyl 3-amino-2,2-dimethylpropionate (12-2)

12-1 (Aldrich, 5.0 g, 38 mmoles) in toluene (150 ml) at room temperature was treated with chlorodiphenyl phosphine (49.4 mmoles) followed by imidazole (5.7 g, 83.6 mmoles) and I2 (12.5 g, 49.4 mmoles) and the resulting brown solution was stirred for 0.5 hours. This mixture was poured into 150 ml saturated Na2CO3 solution and the

organic layer was separated and washed with saturated Na_2CO_3 solvent, 5% Na_2SO_4 solution, H_2O, and 10% $KHSO_4$ solution. The nearly colorless organic layer was then washed with brine, dried (Na_2SO_4) and the solvent was removed to produce a yellow residue. This was purified by flash chromatography on silica gel eluting with hexane (6)/EtOAc (4) to give the desired iodo intermediate as an oil.

R_f 0.9 (silica gel, hexane (6)/EtOAc (4)).

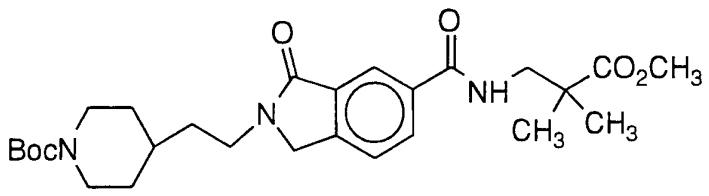
^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (6H, s), 3.40 (2H, s), 3.75 (3H, s).

This iodo compound (3.9 g, 16 mmoles) was dissolved in DMSO (80 ml) and treated with NaN_3 (2.1 g, 32 mmoles) at 70° for 2 hours. The cooled reaction next was diluted with EtOAc and extracted with H_2O and brine. The organic phase was washed with brine, dried (Na_2SO_4) and the solvent was removed to give the desired azide as a foam.

^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (6H, s), 3.45 (2H, s), 3.75 (3H, s).

This azide (2.0 g, 12.7 mmoles) was dissolved in THF (50 ml) and treated with H_2O (25 ml) and triphenyl phosphine (13.3 g, 50.8 mmoles) at room temperature for 2 hours. The THF was removed under vacuum and the resulting residue was acidified to pH 2-3 with 10% $KHSO_4$ solution. This was filtered to remove triphenyl phosphine and the filtrate was extracted with EtOAc. The acidic aqueous phase was then basified with 10% NaOH and extracted with Et_2O. The combined ether extracts were washed with brine, dried (Na_2SO_4) and the solvent removed to give 12-2 as a clear oil. R_f 0.35 (silica gel, CH_2Cl_2 (9)/CH_3OH (1)/H_2O (1).

^1H NMR (300 MHz, CD_3OD) δ 1.22 (6H, s), 2.75 (2H, s), 3.75 (3H, s).

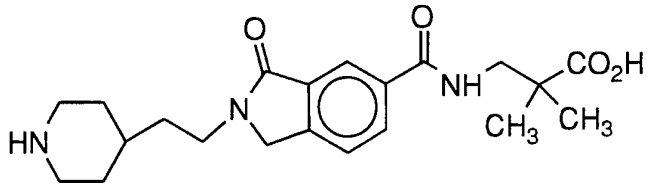


12-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[(2-carbomethoxy-2-methyl)propyl]-2-[2-(4-N-t-butyloxycarbonyl-piperidinyl)ethyl]-3-oxo (12-3)

Treatment of 1-10 (1.0 g, 2.7 mmoles) with 12-2 (0.524 g, 4.0 mmoles), N-methylmorpholine (4.0 mmoles) and BOP (1.78 g, 4.0 mmoles) in CH_3CN (15 ml) as described for 6-3 provided crude 12-3. This was purified by flash chromatography on silica gel eluting with EtOAc (9)/Hexane (1) to give pure 12-3 as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (2H, m), 1.33 (6H, s), 1.48 (9H, s), 1.80 (2H, bd), 2.71 (2H, bt), 3.64 (2H, d), 3.73 (2H, t), 3.77 (3H, s), 4.13 (2H, m), 4.44 (2H, s), 6.94 (1H, t), 7.57 (1H, d), 8.11 (1H, d), 8.13 (1H, s).



12-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[(2-carboxy-2-methyl)-propyl]-2-[2-(4-piperidinyl)ethyl]-3-oxo (12-4)

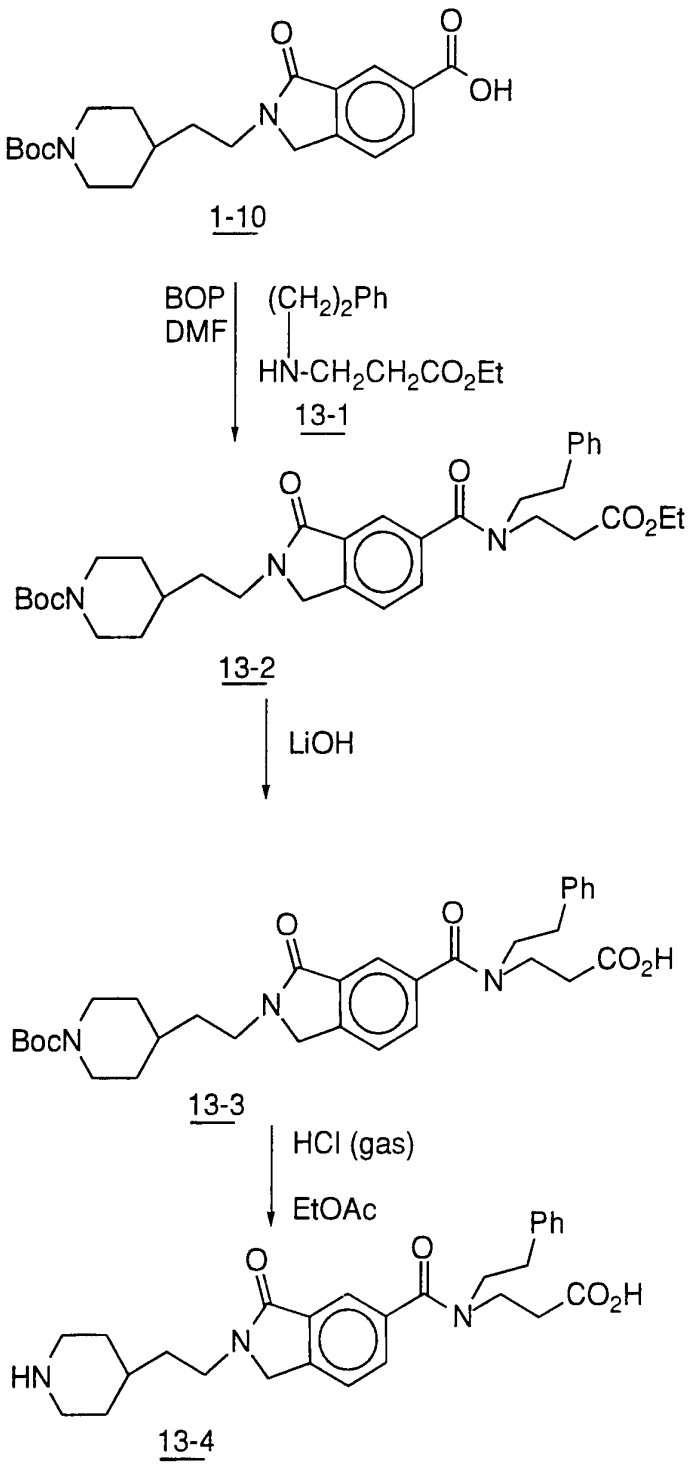
12-3 (0.5 g, 1.0 mmoles) was treated with $LiOH \cdot H_2O$ (0.216 g, 5.0 mmoles) as described for 6-2 to give the desired acid as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 1.13 (2H, m), 1.25 (6H, s), 1.45 (9H, s), 1.65 (2H, m), 1.80 (2H, bd), 2.72 (2H, m), 3.68 (2H, m0, 3.70 (2H, t), 4.05 (2H, bd), 4.56 (2H, s), 7.67 (1H, d), 8.04 (1H, dd), 8.15 (s).

This acid (0.40 g) was dissolved in EtOAc and was treated with HCl gas as described for 6-4 to give pure 12-4 as a white solid.

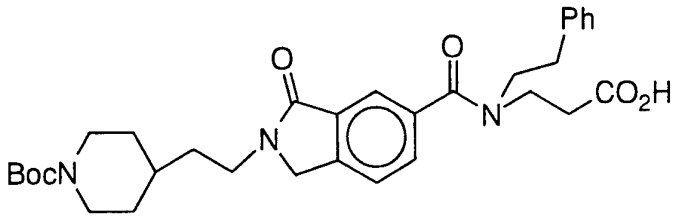
^1H NMR (300 MHz, D_2O) δ 1.14 (6H, s), 1.35 (2H, m), 1.49 (1H, m), 1.60 (2H, q), 1.90 (2H, bd), 2.81 (2H, t), 3.30 (2H, bd), 3.47 (2H, s), 3.57 (2H, t), 4.48 (2H, s), 7.55 (1H, d), 7.82 (1H, d), 7.90 (1H, s).

SCHEME 13


BocN
O
O
OH
N
1-10
BOP
DMF
(CH2)2Ph
HN-CH2CH2CO2Et
13-1
Ph
CO2Et
13-2
LiOH
CO2H
13-3
HCl (gas)
EtOAc
HN
13-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-phenethyl-N-2-carboethoxyethyl]-2-[2-(4-N-t-butyloxy-carbonylpiperidinyl)ethyl]-3-oxo (13-2)

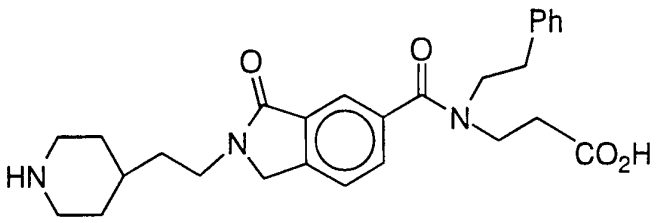
1-10 (0.388 g, 1.0 mmoles) was treated with ethyl 3-(N-phenethyl)aminopropionate (0.22 g, 1.0 mmoles) (prepared by treatment of phenethylamine with ethyl acrylate), triethylamine (0.243 g, 2.4 mmoles) and BOP (0.53 g, 1.2 mmoles) in DMF (15 ml) and the resulting solution was stirred at room temperature for 18 hours. The solvent was then removed and the residue was diluted with H_2O (100 ml) and extracted with EtOAc (3 x 100 ml portions). The organic phase was washed with 10% $KHSO_4$ solution, brine, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Solvent removal gave 13-2 as an oil.
^1H NMR (300 MHz, $CDCl_3$) δ 1.07-1.35 (6H, m), 1.48 (9H, s), 1.62 (3H, m), 1.75 (2H, bd), 2.72 (4H, m), 3.00 (1H, m), 3.50 (2H, m), 3.67 (2H, t), 3.83 (2H, m), 4.10 (5H, m), 4.38 (2H, s), 6.94 (1H, bs), 7.30 (6H, m), 7.50 (1H, m), 7.67 (1H, m).



13-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-phenethyl-N-(2-carboxyethyl)]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl)-ethyl]-3-oxo (13-3)

13-2 (0.60 g, 1.0 mmoles) was treated with $LiOH \cdot H_2O$ (0.127 g, 3.0 mmoles) as described for 6-2 to give 13-3 as a white solid.
R_f 0.45 (silica gel, $CHCl_3$ (9)/MeOH (5)/HOAc (1).
^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (2H, m), 1.47 (9H, s), 1.63 (3H, m), 1.75 (2H, bd), 2.67 (2H, t), 2.80 (3H, m), 3.42 (1H, m), 3.57 (1H, m), 3.67 (2H, t), 3.80 (2H, m), 4.08 (3H, m), 4.37 (2H, s), 6.93 (1H, m), 7.25 (6H, m), 7.48 (1H, m), 7.70 (1H, m).



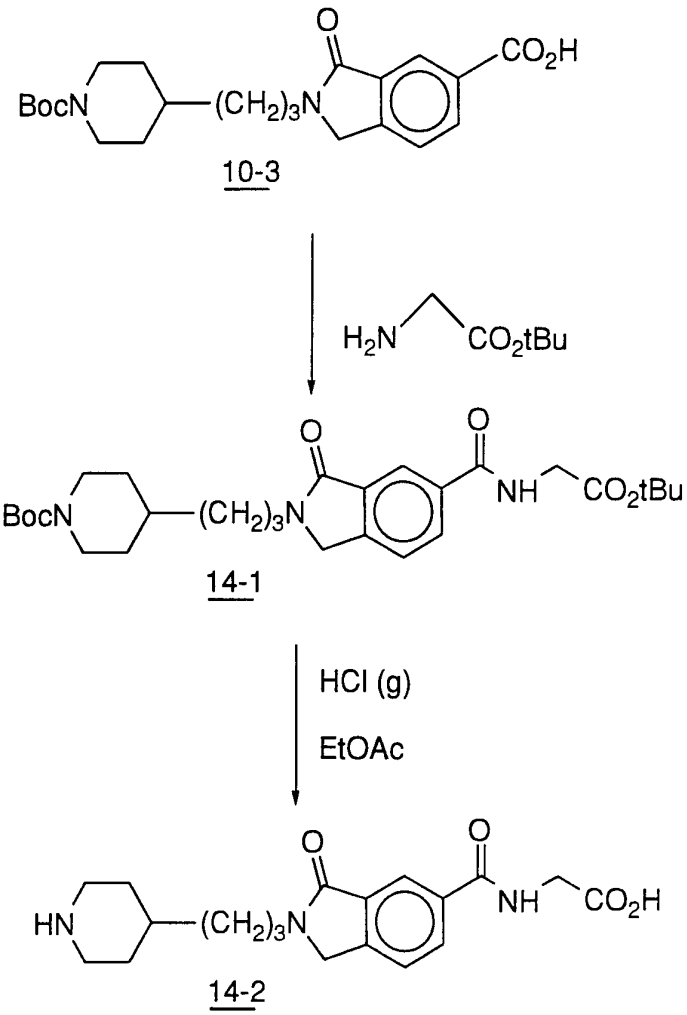
13-4

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[N-phenethyl-N-(2-carboxyethyl)]-2-[2-(4-piperidinyl)ethyl]-3-oxo (13-4)

13-3 was treated with HCl (gas) in EtOAc as described for 6-4 to give pure 13-4 as a white solid. R_f 0.25 (silica gel, EtOH (10)/H_2O (1)/NH_4OH (1)).

^1H NMR (300 MHz, CD_3OD) δ 1.45 (2H, m), 1.62 (2H, m), 1.71 (2H, m), 2.07 (2H, bd), 2.45 (1H, m), 2.78 (2H, m), 2.95 (3H, m), 3.37 (3H, bd), 3.57 (1H, bt), 3.72 (2H, t), 3.83 (2H, m), 3.55 (2H, s), 6.95 (1H, m), 7.20 (4H, bs), 7.33 (1H, bs), 7.45 (1H, bs), 7.55 (1H, m), 7.66 (1H, m).

SCHEME 14



1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[t-butyloxycarbonyl-methyl]-2-[3-(4-N-t-butyloxycarbonylpiperidinyl)propyl]-3-oxo (14-1)

Treatment of 10-3 with glycine t-butyl ester as described for 6-3 gave 14-1.

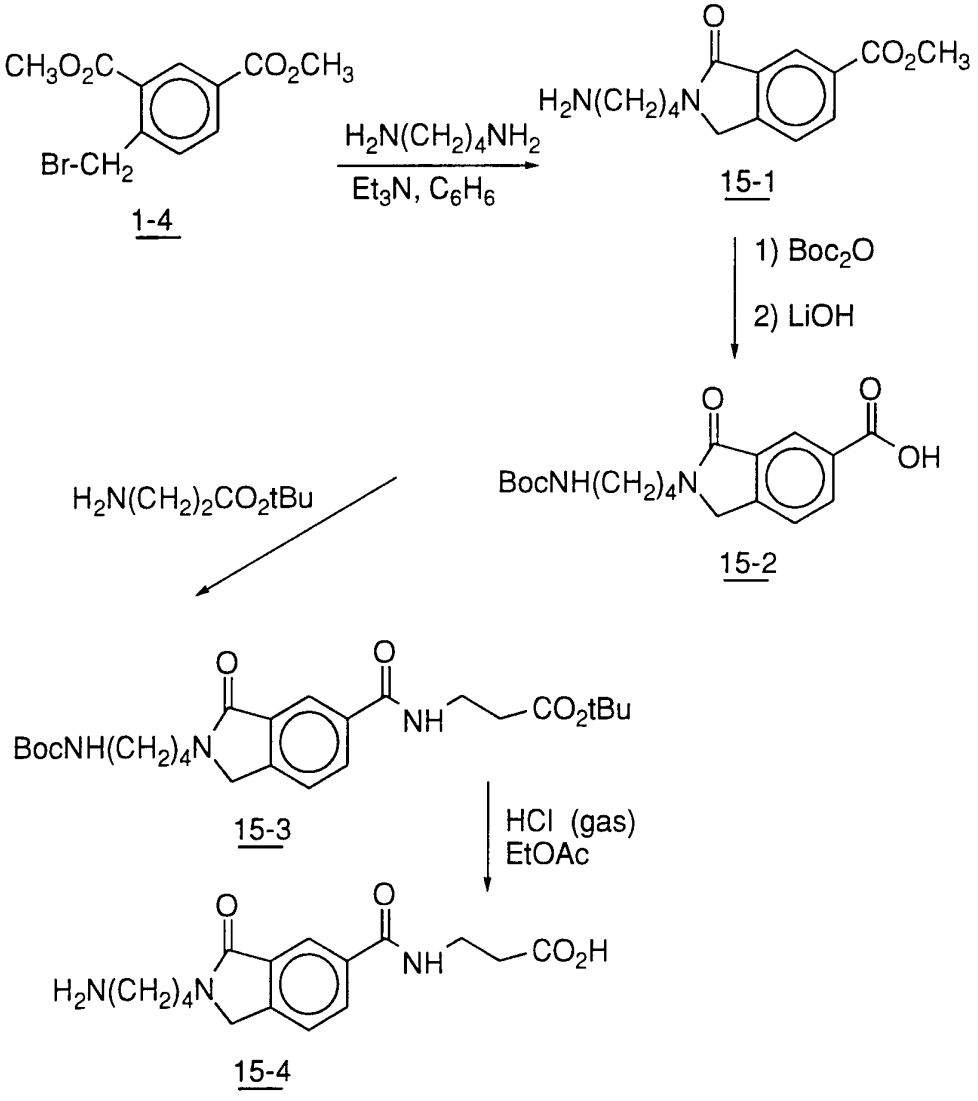
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (2H, m), 1.30 (2H, m), 1.41 (9H, s), 1.52 (9H, s), 1.73 (4H, m), 2.69 (2H, t), 3.65 (2H, t), 4.10 (2H, bd), 4.16 (2H, d), 4.45 (2H, s), 7.53 (1H, d), 8.10 (1H, d), 8.22 (1H, s).

1-H-Isoindole-5-carboxamide, 2,3,-dihydro-N-[carboxymethyl]-2-[3-(4-piperidinyl)propyl]-3-oxo (14-2)

Treatment of 14-1 with HCl gas in EtOAc as described for 6-4 gave 14-2 as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.30 (4H, m), 1.65 (4H, m), 1.90 (2H, bd), 2.59 (2H, t), 2.90 (2H, t), 3.30 (2H, bd), 3.58 (4H, m), 4.50 (2H, s), 7.58 (1H, d), 7.98 (1H, d), 8.07 (1H, s).

SCHEME 15



Methyl-1H-Isoindole-5-carboxylate, 2,3-dihydro-N-[2-(4-aminobutyl)]-3-oxo(15-1)

1-4 (2.56g, 8.92mmoles)was treated with 1,4-diaminobutane (10.9 mmoles) as described for 1-9 to give crude 15-1. This was purified by flash chromatography on silica gel eluting with 25% $CH_3OH/CHCl_3$-(NH_3) to give pure 15-1 as a solid.

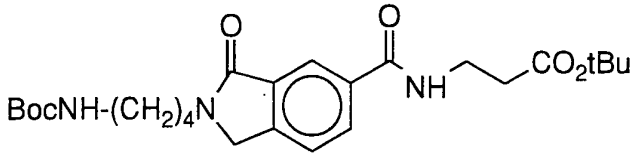
^1H NMR (300 MHz, CD_3OD) δ 1.61 (2H, m), 1.75 (2H, m), 2.90 (2H, t), 3.24 (1H, m), 3.63 (2H, t), 3.85 (3H, s), 4.53 (2H, s), 7.62 (1H, d), 8.18 (1H, d) 8.28 (1H, s).

1-H-Isoindole-5-carboxylic acid-2,3-dihydro-N-[2-(4-N-t-butyloxy-carbonyamino)butyl]-3-oxo(15-2)

15-1 (1.11g, 4.24mmoles) was treated with Boc_2O (1.17g, 5.36 mmoles) as described for 3-1. Crude residue was purified by flash chromatography on silica gel eluting with 30% acetone/hexane to give the desired protected ester as an oil. R_f 0.7 silica gel, 30% acetone/hexane.

This ester (0.85g, 2.34mmoles) was dissolved in THF(1)/CH_3OH(1)/H_2O(1) (30ml) and treated with $LiOH \cdot H_2O$ (0.52g, 12.4mmoles) as described for 3-2 to give 15-2 as a white solid.

^1H NMR (300 MHz, CD_3OD) δ 1.36 (9H, s), 1.44 (2H, m), 1.66 (4H, m), 3.01 (2H, t), 3.60 (2H, t), 4.54 (2H, s), 7.62 (1H, d), 8.20 (1H, d), 8.35 (1H, s).

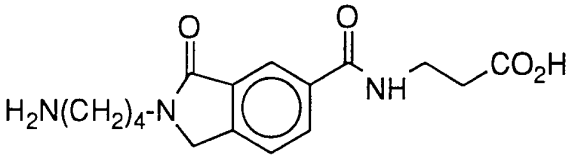


15-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-(t-butyloxy-carbonyl)-ethyl]-2-[4-(N-t-butyloxycarbonyl)butyl]-3-oxo(15-3)

Treatment of 15-2 (0.75g, 2.07mmoles) in CH_3CN (12ml) with β-alanine t-butyl ester (0.39g, 2.54mmoles), Et_3N (14.3 mmoles) and BOP (1.40g, 3.16 mmoles) as described for 3-3 gave crude 15-3.

This was purified by flash chromatography on silica gel eluting with 75% EtOAc/hexane to give pure 15-3 as a white solid. Rf 0.25 (silica gel, 75% EtOAc/hexanes).
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.44 (9H, s), 1.52 (2H, m), 1.77 (2H, m), 2.55 (2H, t), 3.19 (2H, m), 3.67 (4H, m), 4.43 (2H, s), 7.00 (1H, bt), 7.52 (1H, d), 8.09 (1H, d), 8.10 (1H, s).

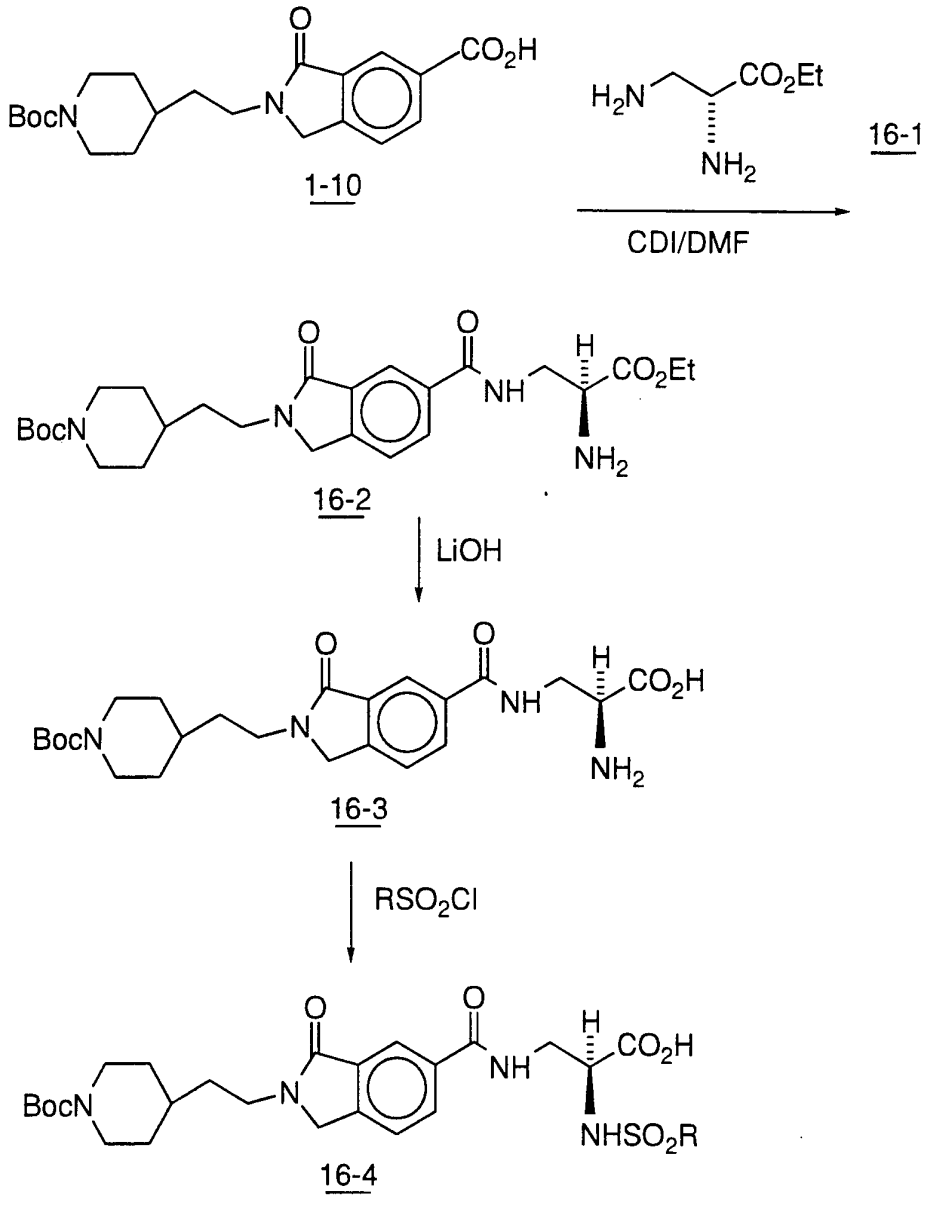


15-4

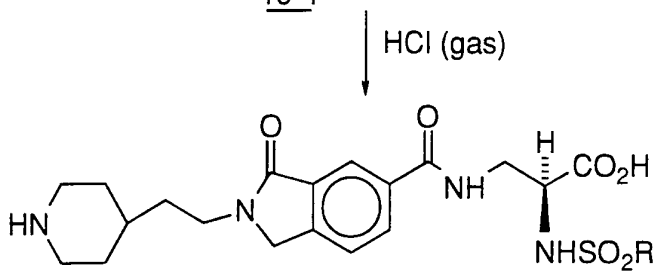
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[2-carboxyethyl]-2-[4-aminobutyl]-3-oxo(15-4)

Treatment of 15-3 (0.51g, 1.07mmoles) in EtOAc with HCl gas as described for 3-4 provided pure 15-4 as a white solid.
^{1}H NMR (300 MHz, D_2O), δ 1.63 (4H, m), 2.64 (2H, t), 2.92 (2H, t), 3.52 (4H, m), 4.46 (2H, s), 7.55 (1H, d), 7.81 (1H, d), 7.85 (1H, s).

SCHEME 16


BocN
N
O
CO2H
1-10
H2N
CO2Et
NH2
16-1
CDI/DMF
NH
H
16-2
LiOH
16-3
RSO2Cl
NHSO2R
16-4

16-4



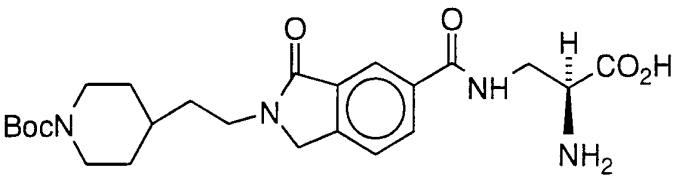
16-5

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[ethyl-3-(2(S)-aminopropionate)]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl]-3-oxo (16-2)

A solution of 1-10 (1.5g, 3.87 mmoles) in DMF (15ml) at room temperature was treated with carbonyl diimidazole (0.627g, 3.87 mmoles) (CDI) and after 2 hours this solution was added dropwise to a DMF solution of ethyl 2(S),3-diaminopropionate (1.5g, 7.74 mmoles) and N-methylmorpholine (23.2 mmoles). The reaction mixture was then stirred at room temperature for 16 hrs.

The solvent was then removed and the residue was dissolved in EtOAc and 10% aqueous $KHSO_4$ solution. The aqueous phase was separated, washed with EtOAc and made basic to pH 12. This was extracted with EtOAc, and the extracts were combined, washed with brine, and dried (Na_2SO_4). Solvent removal provided 16-2.

^1H NMR (300 MHz, CD_3OD) δ 1.24 (2H, m), 1.46 (3H, t), 1.43 (9H, s), 1.66 (2H, q), 1.80 (2H, bd), 3.67 (4H, m), 4.10 (2H, bd), 4.17 (2H, q), 4.57 (2H, s), 7.04 (1H, d), 7.67 (1H, m), 8.06 (1H, m), 8.17 (1H, d).

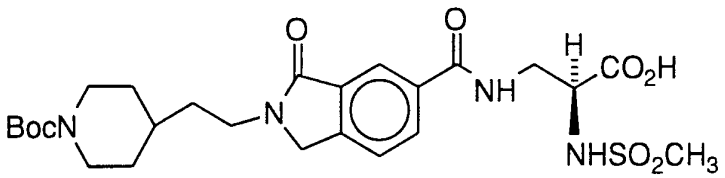


16-3

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-[2(S)-amino-propanoic acid]-2-[2-(4-N-t-butyloxycarbonylpiperidinyl]-3-oxo (16-3)

Treatment of 16-2 (0.6 g, 1.2 mmoles) with $LiOH \cdot H_2O$ (0.25 g, 6.0 mmoles) as described for 1-10 gave 16-3.

^1H NMR (300 MHz, D_2O) δ 0.92 (2H, m), 1.27 (9H, s), 1.46 (4H, m), 2.58 (2H, t), 3.48 (4H, m), 3.83 (2H, bd), 4.38 (2H, s), 6.96 (1H, s), 7.50 (1H, d), 7.82 (1H, d), 7.87 (1H, s).

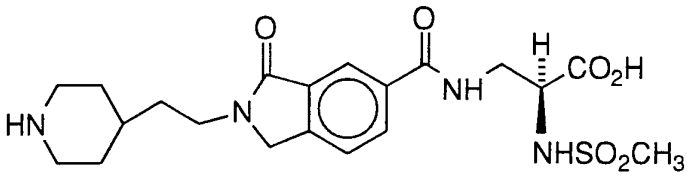


16-6

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-[2(S)-methyl-sulfonylamino)propanoic acid)]-2-[2-(4-N-t-butyloxycarbonyl-piperidinyl]-3-oxo (16-6)

A solution of 16-6 (0.55 g, 1.2 mmoles) in H_2O (15ml)/dioxane (3ml) was cooled to 0-10° and treated with 1N NaOH soln. (1.5ml) and methane sulfonyl chloride (2.4 mmoles) in 3 ml dioxane was added dropwise while also adding 1N NaOH solution to keep the pH at 10-12. This cycle of CH_3SO_2Cl addition at basic pH was carried out 5 times at which point all 16-6 was consumed. The acidity was carefully adjusted to pH 2-3 with 10% $KHSO_4$ solution and this was extracted with EtOAc (4 portions). The combined organics were washed with brine, dried (Na_2SO_4) and the solvent removed. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2 (9)/MeOH (0.8)/HOAc (0.8) to give 16-6 as a white solid. R_f 0.31.

^1H NMR (300 MHz, CD_3OD) δ 1.25 (2H, m), 1.45 (9H, s), 1.65 (2H, q), 1.80 (2H, bd), 2.72 (2H, m), 2.97 (3H, s), 3.70 (3H, m), 3.86 (1H, m), 4.05 (2H, bd), 4.34 (1H, m), 4.56 (2H, s), 7.66 (1H, d), 8.08 (1H, d), 8.19 (1H, s).

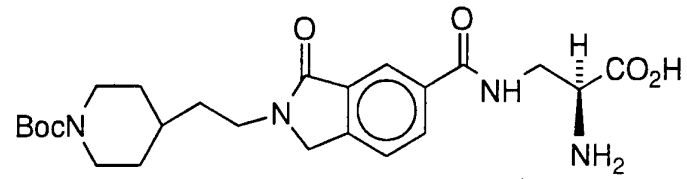


16-7

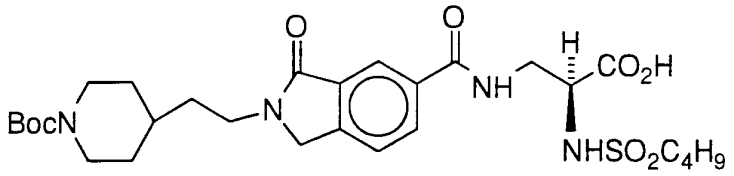
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(2(S)-methyl-sulfonylamino)propionic acid]-2-[2-(4-piperidinyl)ethyl]-3-oxo (16-7)

Treatment of 16-6 (0.22 g, 0.39 mmoles) with HCl gas in EtOAc as described for 1-12 gave 16-7 as a white solid.

^{1}H NMR (300 MHz, D_2O) δ 1.35 (2H, m), 1.59 (2H, m), 1.87 (2H, bd), 2.78 (2H, bt), 2.95 (3H, m), 3.27 (2H, bd), 3.55 (3H, m), 3.78 (1H, m), 4.20 (1H, m), 4.48 (2H, s), 7.56 (1H, m), 7.87 (1H, m), 7.95 (1H, bs).

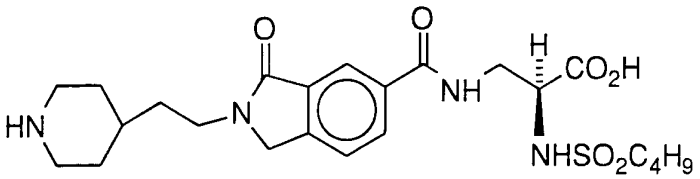


16-3



16-8

HCl gas
EtOAc



16-9

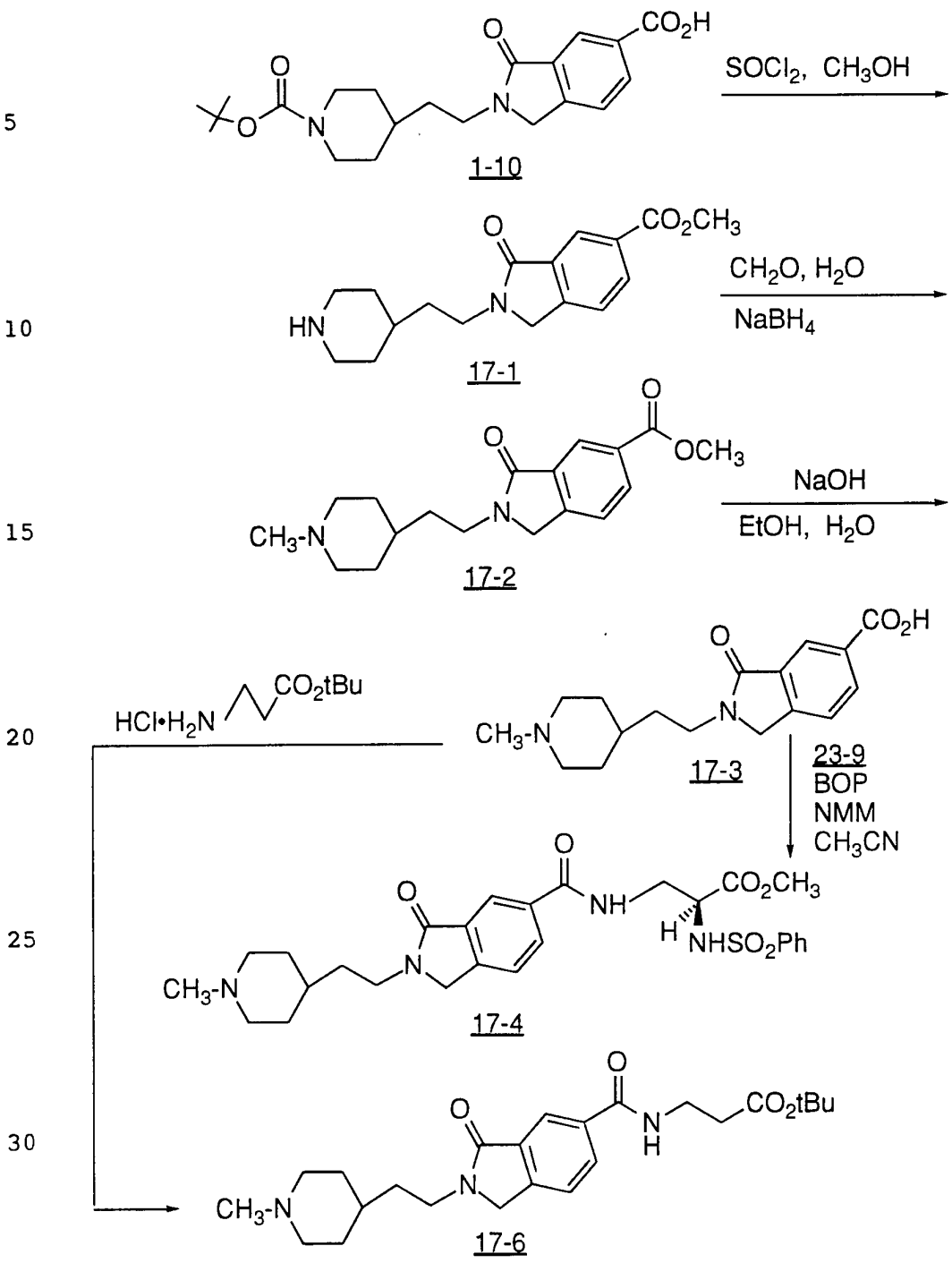
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(2(S)-n-butylsulfonyl-amino)propanoic acid]-2-[2-(4-N-t-butyloxy-carbonylpiperidinyl)]-3-oxo (16-8)

Treatment of 16-3 (0.836 mmoles) with n-butylsulfonyl chloride (1.67 mmoles) as described for 16-6 gave 16-8 as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (6H, m), 1.13 (2H, m), 1.35 (4H, m), 1.45 (9H, s), 1.65 (2H, m), 1.75 (2H, m), 2.70 (2H, m), 3.04 (2H, t), 3.68 (2H, m), 3.83 (1H, m), 4.04 (2H, bd), 4.53 (2H, s), 7.62 (1H, d), 8.05 (1H, d), 8.18 (1H, s).

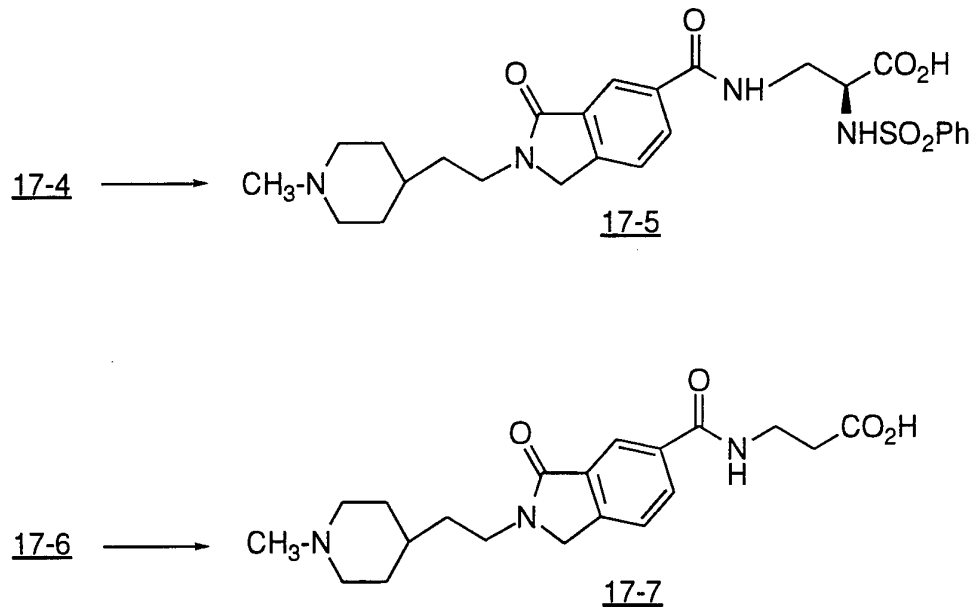
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(2(S)-n-butylsulfonyl-amino)propionic acid]-2-[2-(4-piperidinyl)ethyl]-3-oxo (16-9)

Treatment of 7-8 in EtOAc with HCl gas as described for 1-12 gave pure 16-9 as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 0.59 (2H, t), 1.12 (2H, m), 1.35 (2H, m), 1.50 (2H, m), 1.59 (2H, m), 1.90 (2H, bd), 2.80 (2H, t), 2.98 (2H, t), 3.29 (2H, bd), 3.42 (1H, m), 3.60 (2H, t), 3.70 (1H, m), 4.50 (2H, s), 7.59 (1H, d), 7.91 (1H, d), 7.98 (1H, s).

SCHEME 17


CO2H
O
O
N
SOCl2, CH3OH
1-10
CO2CH3
HN
CH2O, H2O
NaBH4
17-1
OCH3
CH3-N
NaOH
EtOH, H2O
17-2
HCl•H2N
CO2tBu
17-3
23-9
BOP
NMM
CH3CN
NH
H
NHSO2Ph
17-4
17-6

SCHEME 17 CONT'D



Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2-[2-(piperidin-4-yl)ethyl]3-oxo (17-1)

A solution of 1-10 (1.7 g, 4.4 mmol) in CH_3OH (30 mL) was cooled to 0°C and treated with thionyl chloride (1.6 mL, 22 mmol) dropwise over five minutes. The solution was warmed to room temperature and stirred for 20 h, then concentrated to give 17-1 as a white solid.

R_f (10:1:1 EtOH/H_2O/NH_4OH) 0.29

^1H NMR (300 MHz, CD_3OD) δ 8.25 (s, 1H), 8.15 (d, 1H), 7.6 (d, 1H), 4.5 (s, 2H), 3.82 (s, 3H), 3.7 (t, 2H), 3.2 (m, 2H), 2.82 (t, 2H), 1.95 (bd, 2H), 1.6 (m, 2H), 1.5 (m, 1H), 1.32 (m, 2H).

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2-[2-(N-methyl piperidin-4-yl)ethyl]-3-oxo (17-2)

A solution of 17-1 (1.32 g, 4.4 mmol) in boiling EtOH and treated with aqueous formaldehyde (11.5 mL, 37% by weight in H_2O, 0.14 mole) and acetic acid (3.45 mL). After refluxing for 2h, the reaction

was cooled to room temperature and treated with $NaBH_4$ (1.17 g, 30.8 mmol). After 5 h the reaction was quenched with 1N HCl, then basified with saturated $NaHCO_3$ and 1N NaOH to pH 10, diluted with H_2O (200 mL) and extracted with 4 x 300 mL $CHCl_3$. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to give 17-2 as an off-white solid.
Rf (10:1:1 EtOH/NH_4OH/H_2O) 0.2
^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.25 (d, 1H), 7.55 (d, 1H), 4.45 (s, 2H), 3.97 (s, 3H), 3.7 (m, 2H), 3.0 (m, 2H), 2.4 (m, 3H), 2.1 (m, 2H), 1.88 (bd, 2H), 1.68 (m, 2H), 1.5 (m, 1H), 1.25 (m, 2H).

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-2-[2-(N-methylpiperidin-4-yl)ethyl]-3-oxo (17-3)

A solution of 17-2 (1.23 g, 3.9 mmol) in EtOH (20 mL) was treated with 1N NaOH (5.9 mL, 3.9 mmol) at room temperature for 16h, then concentrated to give 17-3 as a yellow solid.
^1H NMR (400 MHz, CD_3OD) δ 8.4 (s, 1H), 8.21 (d, 1H), 7.6 (d, 1H), 4.55 (s, 2H), 3.7 (m, 2H), 2.85 (d, 2H), 2.23 (s, 3H), 2.0 (m, 2H), 1.85 (m, 2H), 1.7 (m, 2H), 1.35 (m, 3H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[methyl 3-(2(S)-phenyl-sulfonylamino)propionate]-2-[2-(N-methylpiperidin-4-yl)ethyl]-3-oxo (17-4)

A solution of 17-3 (0.32 g, 1.02 mmol) and 22-3 (0.3 g, 1.02 mmol) in CH_3CN (5 mL) was treated with N-methylmorpholine (0.22 mL, 2.04 mmol) and BOP reagent (0.45 g, 1.02 mmol). After 72 h the solution was concentrated and the residue chromatographed (5.02, 10% $CH_3OH/CHCl_3$ saturated with NH_3) to give 17-4 as a yellow solid.
Rf (10% $CH_3OH/CHCl_3$ saturated with NH_3) 0.26
^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.06 (d, 1H), 7.85 (d, 2H), 7.5 (m, 4H), 7.1 (m, 1H), 4.42 (s, 2H), 4.18 (dd, 1H), 3.82 (dd, 1H), 3.7 (t, 2H), 3.62 (s, 3H), 2.89 (bd, 2H), 2.28 (s, 3H), 1.95 (m, 2H), 1.8 (m, 2H), 1.63 (m, 2H), 1.5-1.3 (m, 3H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3(2(S)-phenylsulfonyl-amino)propionate]-2-[2-N-methylpiperidin-4-yl)ethyl]-3-oxo (17-5)

A solution of 17-4 (0.19 g, 0.35 mmol) in 6N HCl was stirred for 20 h at room temperature and 40°C for 1.5 h, then concentrated to give 17-5 as a yellow solid.

^{1}H NMR (300 MHz, CD_3OD) δ 8.0 (s, 1H), 7.8 (d, 1H), 7.7 (d, 2H), 7.53 (d, 1H), 7.3 (m, 3H), 4.47 (s, 2H), 4.1 (dd, 1H), 3.7-3.6 (m, 2H), 3.42-3.3 (m, 2H), 2.9-2.8 (m, 2H), 2.7 (s, 3H), 2.0 (bd, 2H), 1.7 (m, 2H), 1.5-1.3 (m, 3H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[t-butyl, 3-propionate]-2-[2-N-methylpiperidin-4-yl]ethyl-3-oxo (17-6)

A solution of 17-3 (0.3 g, 1 mmol) in CH_3CN (7 mL) was treated with t-Butyl β alanine hydrochloride (0.18 g, 1 mmol), N-methyl morpholine (0.22 mL, 2 mmol), and BOP reagent (0.44 g, 1 mmol). After 100 h the solution was concentrated and the residue chromatographed (SiO_2, 10:1:1 EtOH/NH_4OH/H_2O) to give 17-6 as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (m, 2H), 7.52 (d, 1H), 6.95 (m, 1H), 4.4 (s, 2H), 3.7 (m, 4H), 2.95 (bd, 2H), 2.6 (t, 2H), 2.32 (s, 3H), 2.0 (m, 2H), 1.9-1.8 (bd, 2H), 1.7-1.6 (m, 2H), 1.45 (s, 9H), 1.4 (m, 3H).

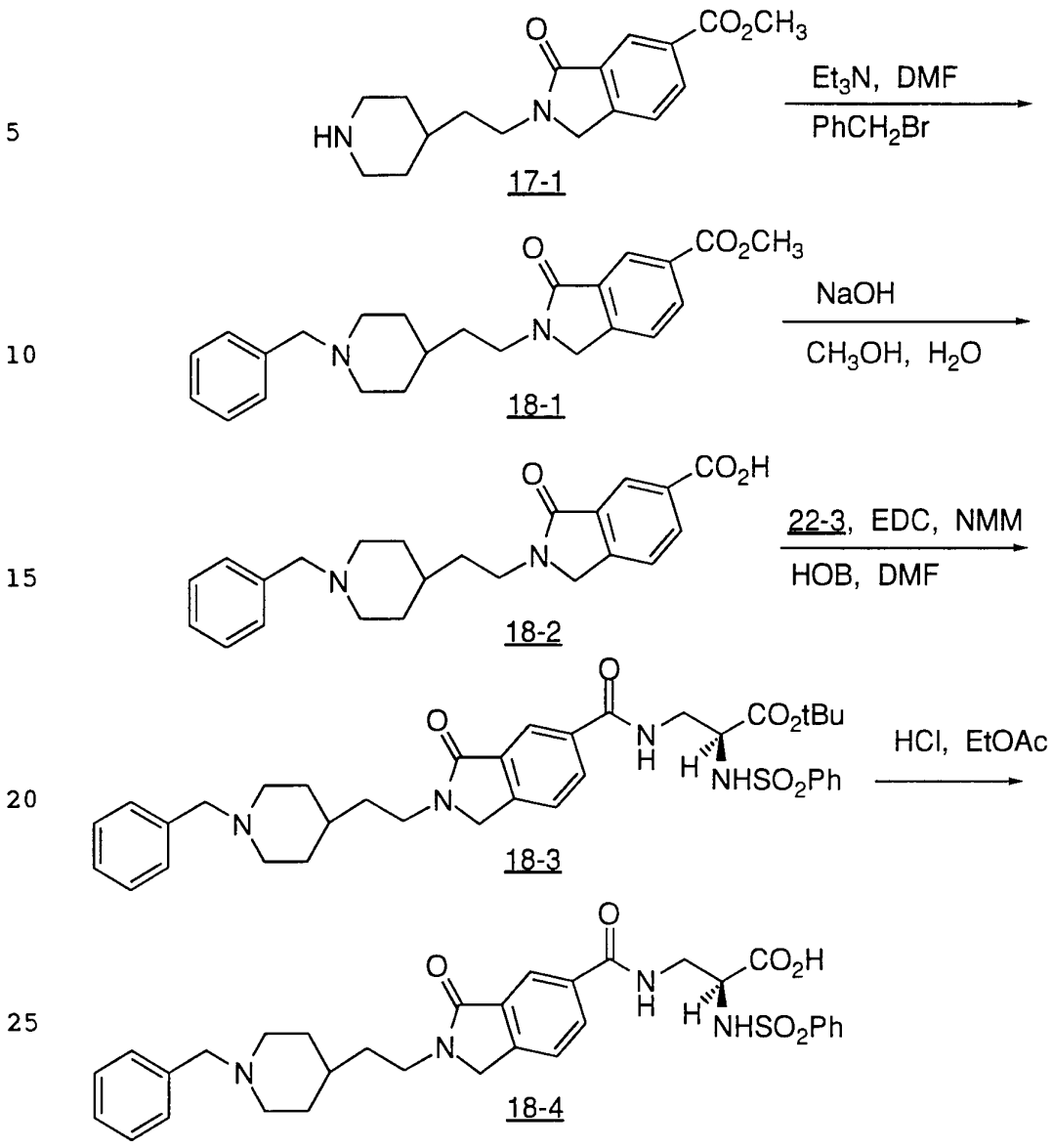
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-propionate]-2-[2-N-methylpiperidin-4-yl]ethyl-3-oxo (17-7)

A solution of 17-6 (0.38 g) was cooled to -40°C and saturated with HCl gas. The solution was warmed to 0°C for 4h, then concentrated to give a greenish residue, which was purified (10:0.3:0.3 EtOH/NH_4OH/H_2O) to give 17-7 as a white solid.

Rf (10:1:1 EtOH/H_2O/NH_4OH) 0.59

^{1}H NMR (400 MHz, CD_3OD) δ 8.2 (s, 1H), 8.1 (d, 1H), 7.65 (d, 1H), 4.6 (s, 2H), 3.68 (m, 4H), 3.45 (d, 2H), 2.9 (m, 2H), 2.8 (s, 3H), 2.58 (m, 2H), 2.05 (bd, 2H), 1.7 (m, 2H), 1.5 (m, 3H).

SCHEME 18



Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2-[2-(N-benzyl-piperidin-4-yl)ethyl]-3-oxo (18-1)

A suspension of 17-1 (0.85 g, 2.5 mmol) in DMF (20 mL) was treated with triethylamine (0.69 mL, 5 mmol) and benzyl bromide (0.43 g, 2.5 mmol). After 20 h the DMF was removed under vacuum and

the residue was dissolved in H_2O, basified to pH 8-9 with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to give 18-1 as a tan solid.

R_f (5% $CH_3OH/CHCl_3$) 0.22

^1H NMR (300 MHz, $CDCl_3$) δ 8.5 (s, 1H), 8.22 (d, 1H), 7.51 (d, 1H), 7.3-7.2 (m, 5H), 4.4 (s, 2H), 3.92 (s, 3H), 3.65 (t, 2H), 3.5 (b, 2H), 2.88 (bd, 2H), 1.95 (m, 2H), 1.7 (m, 2H), 1.6 (m, 2H), 1.4 (m, 3H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[t-butyl, 3(2(S)-phenyl-sulfonylamino)propionate]-2-[2-(N-benzylpiperidin-4-yl)ethyl]-3-oxo (18-3)

A solution of 18-2 (1.0 g, 2.5 mmol) in CH_3OH (20 mL) was treated with 1N NaOH (5.1 mL, 5 mmole) for 20 h. The solvent was evaporated and the residue was chromatographed (SiO_2, 5% NH_4OH/Isopropanol, followed by 10:1:1 $EtOH/H_2O/NH_4OH$) to give 18-2 as a pale yellow solid.

A solution of 18-2 (0.76 g, 2 mmol) in DMF (20 mL) was treated with 22-3 (0.674 g, 2 mmol), HOBt (0.297 g, 2.2 mmol), N-methyl morpholine (0.66 mL, 6 mmol) and EDC (0.46 g, 2.4 mmol) and stirred overnight. The solvent was removed in vacuo, the residue dissolved in 100 mL H_2O, and extracted with EtOAc. The organic layer was extracted with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated. Chromatography (SiO_2, 5% $CH_3OH/CHCl_3$) gave 18-3 as a foam.

Rf (10% $CH_3OH/CHCl_3$) 0.36

1H NMR (300 MHz, CDCl3) d 8.17 (s, 1H), 8.04 (d, 1H), 7.85 (d, 2H), 7.5 (m, 3H), 7.3 (m, 5H), 7.05 (m, 1H), 5.95 (b, 1H), 4.39 (s, 2H), 4.0 (m, 1H), 3.86 (m, 1H), 3.7-3.6 (m, 3H), 3.55 (b, 2H), 2.94 (m, 2H), 2.0 (b, 2H), 1.75 (m, 2H), 1.6 (m, 2H), 1.4 (m, 1H), 1.29 (s, 9H).

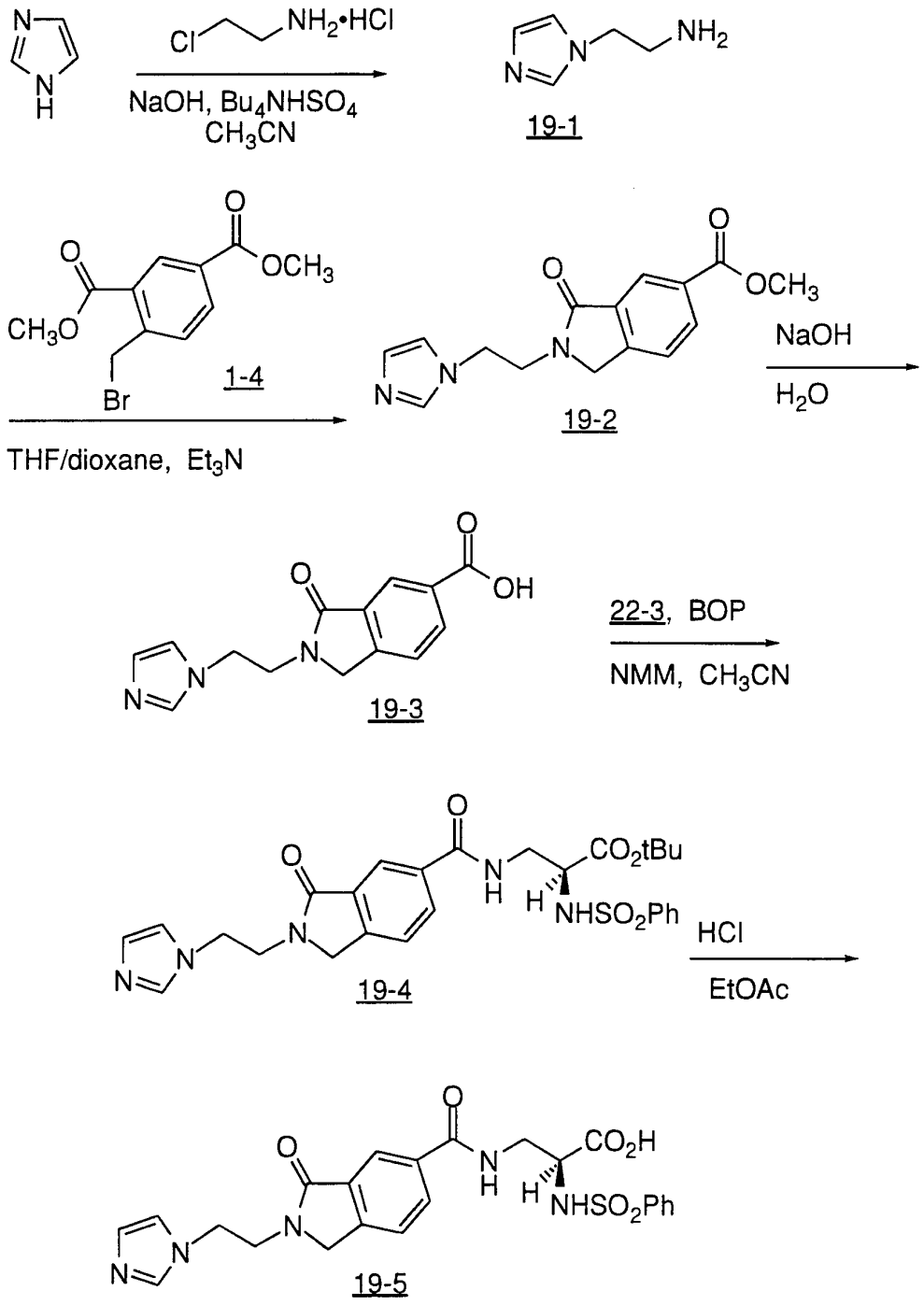
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3(2(S)-phenylsulfonyl-amino)propionate]-2-[2-(N-benzylpiperidin-4-yl)ethyl]-3-oxo (18-4)

A solution of 18-3 (0.39 g, 0.6 mmol) in EtOAc (25 mL) was cooled to -25°C and saturated with HCl gas. The solution was warmed to 0°C for 1h, then degassed with argon and concentrated to give 18-4 as a white solid.

R_f (10:1:1 EtOH/H_2O/NH_4OH) 0.75

^1H NMR (300 MHz, CD_3OD) δ 8.7 (m, 1H), 8.11 (s, 1H), 8.02 (d, 1H), 7.82 (d, 2H), 7.65 (d, 1H), 7.5-7.4 (m, 5H), 4.58 (s, 2H), 4.27 (s, 2H), 4.23 (dd, 1H), 3.8-3.7 (m, 3H), 3.5 (m, 3H), 2.98 (m, 2H), 2.1 (bd, 2H), 1.7 (m, 2H), 1.6-1.4 (m, 3H).

SCHEME 19


NaOH, Bu4NHSO4
CH3CN
19-1
1-4
THF/dioxane, Et3N
19-2
NaOH
H2O
19-3
22-3, BOP
NMM, CH3CN
19-4
HCl
EtOAc
19-5

2-(Imidazole) ethylamine hydrobromide (19-1)

A mixture of imidazole (5.23 g, 76.8 mmol) and NaOH (9.48 g, 237 mmol) in acetonitrile (35 mL) was stirred at room temperature for 0.5 h. Tetra-butyl ammonium hydrogen sulfate (0.896 g, 2.64 mmol) and 2-chloroethylamine monohydrochloride (5.64 g, 70.9 mmol) were added and the mixture was heated to 80°C. After 20 h the reaction was cooled, the solid was removed by filtration and the filtrate was concentrated to give an orange oil, which was treated with an excess of HBr and concentrated to give an off-white solid. This solid was triturated with EtOH to give 19-1 as a white solid.
R_f (10:1:1 EtOH/H_2O/NH_4OH) 0.59
^1H NMR (300 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.0 (b, 2H), 7.78 (m, 1H), 4.45 (t, 2H), 3.4-3.3 (b, 3H).

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2-[2(1-imidazole)-ethyl]-3-oxo (19-2)

A solution of 19-1 (1.98 g, 10.4 mmol) in 1:1 THF/dioxane (50 mL) was treated with 1-4 (3 g, 10.4 mmol) and triethylamine (4.25 mL, 30 mmol), heated to reflux for 3 h, then stirred at room temperature for 20 h. The mixture was concentrated and chromatographed (SiO_2, 10:0.5:0.5 $CHCl_3$/MeOH/NH_4OH) to give 19-2 as a light brown solid.
R_f (10% CH_3OH/$CHCl_3$ saturated with NH_3) 0.54
^1H NMR (300 MHz, CD_3OD) δ 8.02 (s, 1H), 7.94 (d, 1H), 7.63 (m, 1H), 7.35 (m, 2H), 6.9 (s, 1H), 6.65 (s, 1H), 4.1 (m, 4H), 3.72 (t, 2H), 3.64 (s, 3H).

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-2-[2(1-imidazole)ethyl]-3-oxo (19-3)

A solution of 19-2 (2 g, 8.1 mmol) in H_2O (30 mL) was treated with 1N NaOH (8.1 mL, 8.1 mmol) for 65 h. The solution was concentrated to give 19-3 as an orange solid.
R_f (10:1:1 EtOH/H_2O/NH_4OH) 0.69

^{1}H NMR (300 MHz, CD_3OD) δ 8.2 (s, 1H), 8.0-5 (m, 1H), 7.5 (s, 1H), 7.35 (d, 1H), 7.02 (s, 1H), 6.82 (s, 1H), 4.3-4.2 (m, 2H), 4.15 (s, 2H), 3.9-3.8 (m, 2H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[t-Butyl, 3(2(S)-phenyl-sulfonylamino)propionate]-2[2-(1-imidazole)ethyl]-3-oxo (19-4)

An CH_3CN (15 mL) solution of 19-3 (0.4 g, 1.5 mmol) and 22-3 (0.46 g, 1.5 mmol) was treated with N-methyl morpholine (0.33 mL, 3 mmol) and BOP reagent (0.66 g, 1.5 mmol). After stirring for 100 h, the solution was concentrated and the residue was chromatographed (SiO_2, 1-5% $CH_3OH/CHCl_3$ saturated with NH_3 gradient) to give 19-4 as an off-white solid.

Rf (10% $CH_3OH/CHCl_3$ saturated with NH_3) 0.31

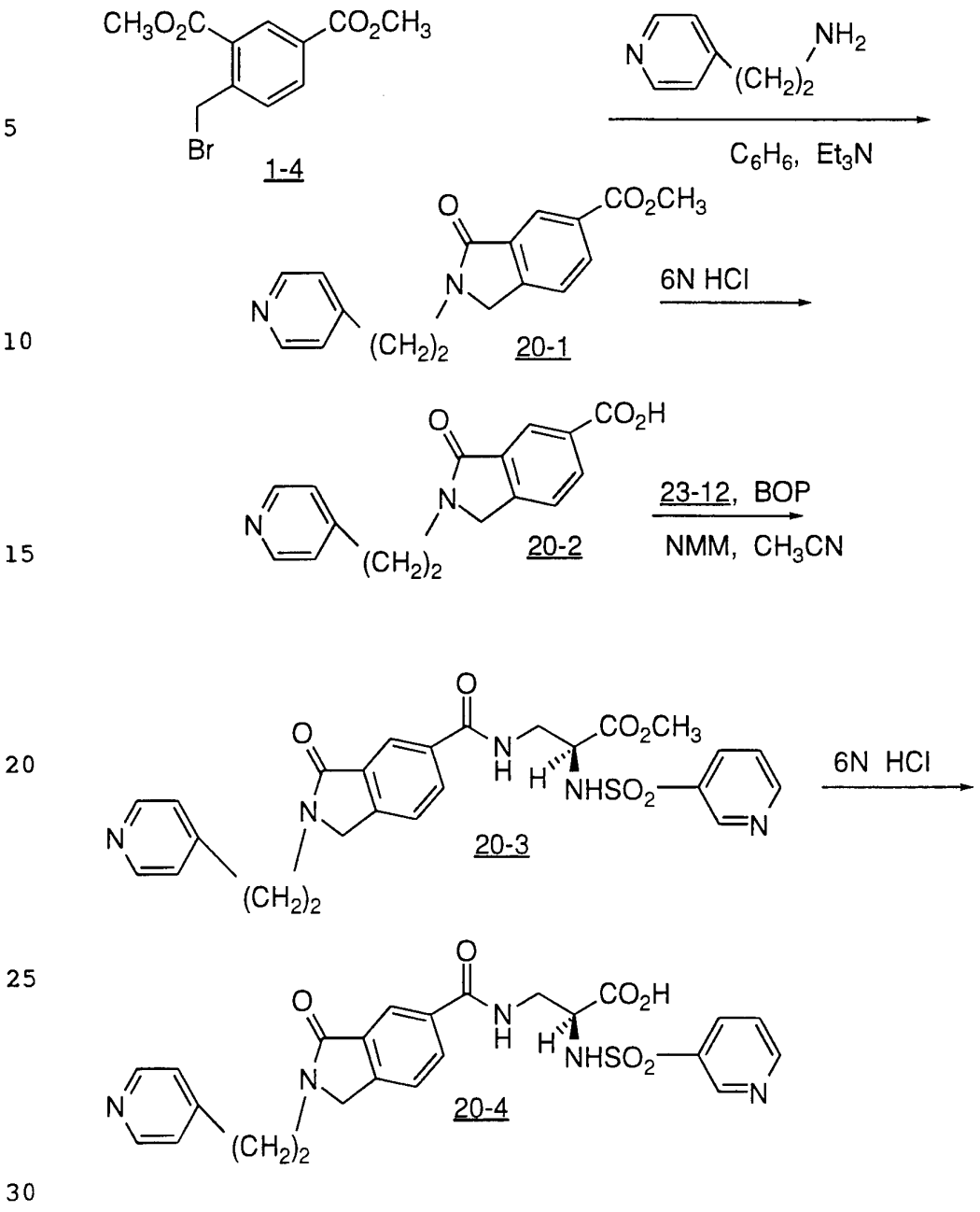
^{1}H NMR (300 MHz, CDCl3) d 8.22 (s, 1H), 8.05 (d, 1H), 7.89 (d, 1H), 7.64 (s, 1H), 7.6-7.4 (m, 5H), 7.1 (s, 1H), 7.0 (s, 1H), 6.15 (bs, 1H), 4.38 (t, 2H), 4.05 (s, 2H), 3.98 (t, 2H), 3.9 (m, 1H), 3.8-3.7 (m, 1H), 1.3 (s, 9H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(2(S)-phenyl sulfonylamino)propionate]-2-[2-(1-imidazole)ethyl]-3-oxo (19-5)

A solution of 19-4 (0.15g, 0.277 mmol) in EtOAc was cooled to -40°C and saturated with HCl gas. The solution was warmed to 0°C for 2h, then concentrated to give 19-5 as a white solid.

1H NMR (400 MHz, CD_3OD) δ 8.28 (s,1H), 7.8-7.75 (m, 2H), 7.55 (d, 2H), 7.36 (d, 1H), 7.2 (s, 1H), 7.15 (m, 2H), 7.07 (s, 1H), 4.28 (s, 2H), 4.23 (t, 2H), 3.85 (dd, 1H), 3.3 (t, 2H), 3.48 (dd, 1H), 3.21 (dd, 1H).

SCHEME 20


CH3O2C
CO2CH3
Br
1-4
NH2
(CH2)2
C6H6, Et3N
CO2CH3
6N HCl
20-1
CO2H
23-12, BOP
NMM, CH3CN
20-2
20-3
6N HCl
20-4

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2-[2-(4-pyridinyl)-ethyl]-3-oxo (20-1)

A solution of 1-4 (2.0 g, 6.9 mmol) in benzene (25 mL) was treated with 4-pyridine ethylamine (0.83 mL, 6.9 mmol) and triethylamine (0.98 mL, 6.9 mmol) and brought to reflux for 2 h. The solvent was removed and the residue was chromatographed (SiO_2, 50% acetone/hexanes) to give 20-1 as a white solid.
^1H NMR (400 MHz, CD_3OD) δ 8.4 (d, 2H), 8.33 (s, 1H), 8.23 (d, 1H), 7.65 (d, 1H), 7.47 (d, 2H), 4.54 (s, 2H), 3.94 (m, 5H), 3.09 (t, 2H).

1-H-Isoindole-5-carboxylic acid, 2,3-dihydro-2-[2-(4-pyridinyl)ethyl-3-oxo (20-2)

A solution of 20-1 (0.6 g, 2 mmol) in 6N HCl (6 mL) was stirred for 72 h at room temperature, then heated to 50°C for 4 h. The solvent was removed to give 20-2 as a white solid.
^1H NMR (400 MHz, CD_3OD) δ 8.71 (d, 2H), 8.3 (s, 1H), 8.26 (d, 1H), 8.06 (d, 1H), 7.7 (d, 1H), 4.7 (s, 2H), 4.19 (t, 2H), 3.4 (t, 2H).

1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[Methyl, 3-[2(S)-(3-pyridyl)sulfonylamino)propionate]-2-[2-(4-pyridinyl)ethyl]-3-oxo (20-3)

A slurry of 20-2 (0.33 g, 1.07 mmol) and 23-12 (0.344 g, 1.04 mmol) in CH_3CN (6 mL) was treated with N-methylmorpholine (0.47 mL, 4.28 mmol), and BOP reagent (0.473 g, 1.07 mmol). After 24 h the reaction was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed (SiO_2, 10% $CH_3OH/CHCl_3$) to give 20-3.
^1H NMR (400 MHz, CD_3OD) δ 8.92 (s, 1H), 8.61 (d, 1H), 8.41 (d, 2H), 8.21 (d, 1H), 8.04 (s, 1H), 8.0 (d, 1H), 7.84 (m, 1H), 7.64 (d, 2H), 7.51 (dd, 1H), 7.48 (d, 2H), 4.55 (s, 2H), 4.33 (m, 1H), 3.96 (t, 2H), 3.74 (dd, 1H), 3.59 (dd, 1H), 3.51 (s, 3H), 3.1 (t, 2H).

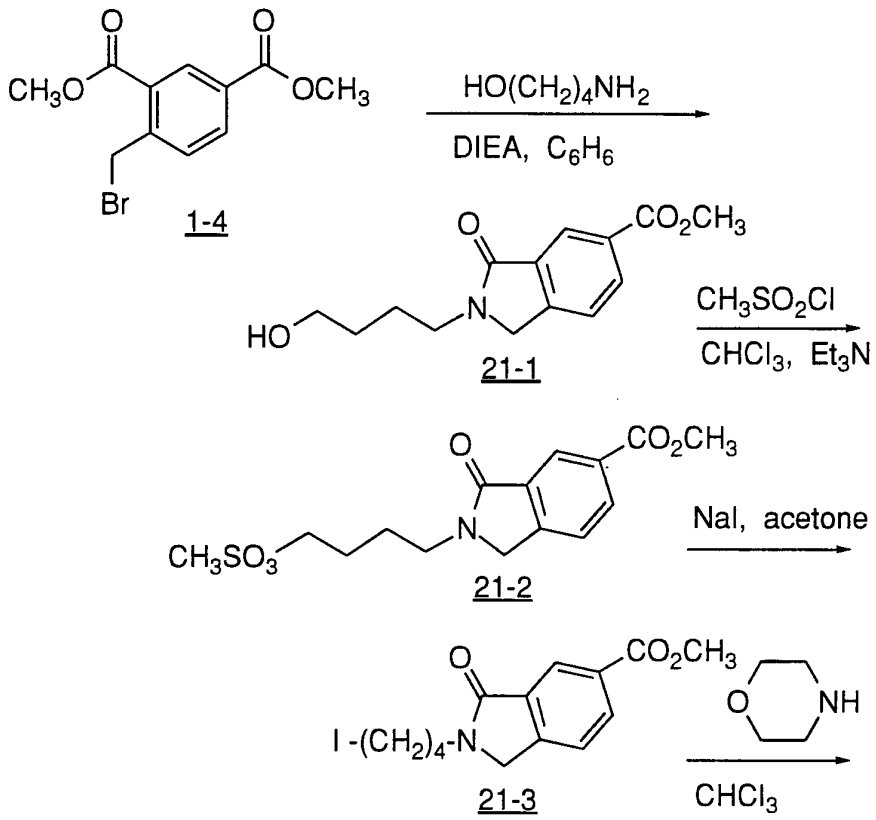
1-H-Isoindole-5-carboxamide, 2,3-dihydro-N-[3-(2-(3-pyridyl)sulfonyl-amino)propionate]-2-[2-(4-pyridyl)ethyl]-3-oxo (20-4)

Compound 20-3 (0.2 g, 0.38 mmol) was treated with 6N HCl for 72 h at room temperature followed by heating at 50°C for 1 h. The solvent was removed and the residue was chromatographed (SiO_2, 10:1:1 EtOH/H_2O/NH_4OH) to give 20-4.

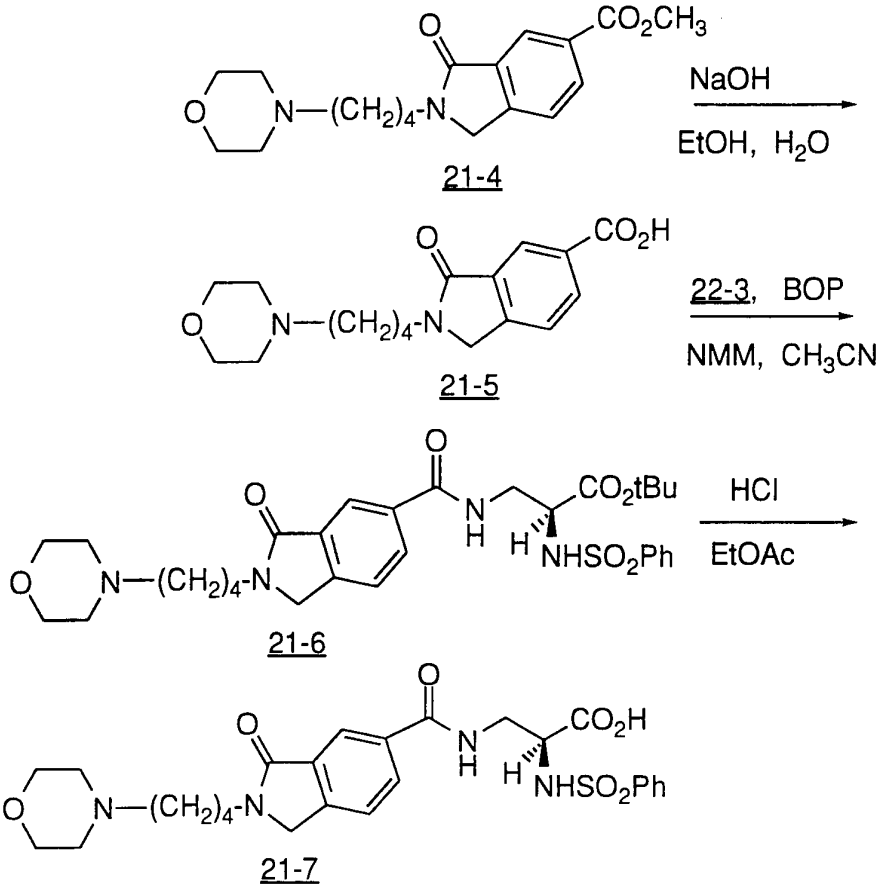
R_f (10:1:1 EtOH/H_2O/NH_4OH) 0.25

^1H NMR (300 MHz, D_2O) δ 8.75 (s, 1H), 8.25 (d, 2H), 8.0 (d, 1H), 7.89 (d, 1H), 7.63 (d, 1H), 7.5 (s, 1H), 7.45 (d, 1H), 7.26 (d, 2H), 7.05 (dd, 1H), 4.4 (s, 2H), 3.91 (dd, 1H,, 3.83 (t, 2H), 3.61 (dd, 1H), 3.3 (dd, 1H), 3.0 (t, 2H).

SCHEME 21


CH3O
O
O
OCH3
Br
1-4
HO(CH2)4NH2
DIEA, C6H6
CO2CH3
HO
21-1
CH3SO2Cl
CHCl3, Et3N
CH3SO3
21-2
NaI, acetone
I -(CH2)4-N
21-3
NH
CHCl3

SCHEME 21 CONT'D



Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2(4-hydroxybutyl)-3-oxo (21-1)

A solution of 1-4 (1.6 g, 5.6 mmol) in benzene (30 mL) was treated with 4-hydroxybutylamine (0.52 mL, 5.6 mmol) and diisopropylethylamine (1.96 mL, 11.2 mmol) and brought to reflux for 5h and stirred at room temperature for 30 h. The reaction was concentrated. Chromatography (SiO_2, 3% $CH_3OH/CHCl_3$) gave 21-1 as a white solid.
R_f (20% $CH_3OH/CHCl_3$) 0.65
^1H NMR (400 MHz, $CDCl_3$) δ 8.5 (s, 1H), 8.23 (dd, 1H), 7.52 (d, 1H), 4.45 (s, 2H), 3.94 (s, 3H), 3.71 (m, 4H), 1.95 (b, 1H), 1.8 (m, 2H), 1.62 (m, 2H).

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2[4-(methanesulfonyl-oxy)butyl]-3-oxo (21-2)

A solution of 21-1 (1.1 g, 4.2 mmol) in $CHCl_3$ (30 mL) was cooled to 0°C and treated with triethylamine (1.05 mL, 7.5 mmol) and methanesulfonyl chloride (0.33 mL, 4.8 mmol). After stirring for 2 h, the solution was washed with H_2O, 10% $KHSO_4$, brine, dried ($MgSO_4$), filtered and evaporated to give 21-2 as a tan solid.
R_f (10% $CH_3OH/CHCl_3$) 0.75
^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.29 (d, 1H), 7.56 (d, 1H), 4.49 (s, 2H), 4.32 (m, 2H), 3.98 (s, 3H), 3.72 (m, 2H), 3.04 (s, 3H), 1.86 (m, 4H).

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2[4-iodobutyl]-3-oxo (21-3)

A solution of 21-2 (1.0 g, 2.93 mmol) in acetone (20 mL) was treated with NaI (0.7 g, 4.4 mmol). After 3 h at room temperature the solution was heated to reflux for 3 h, then allowed to cool to room temperature and stir overnight. The mixture was filtered and the solid washed with acetone. The filtrate was concentrated and chromatographed (SiO_2, 40% EtOAc/Hexanes) to give 21-3 as a pale yellow solid.
R_f (40% EtOAc/Hexanes) 0.25

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.27 (d, 1H), 7.56 (d, 1H), 4.49 (s, 2H), 3.98 (s, 3H), 3.7 (t, 2H), 3.28 (t, 2H), 1.95-1.8 (m, 4H).

Methyl 1-H-Isoindole-5-carboxylate, 2,3-dihydro-2[4-N-(morpholino) butyl]-3-oxo (21-4)

A solution of 21-3 (1.0 g, 2.7 mmol) in $CHCl_3$ (27 mL0 was added to 1.18 mL of morpholine (1.18 mL, 13.5 mmol) and the mixture was heated to reflux for 3h, then concentrated. The residue was chromatographed (SiO_2, 10% $CH_3OH/CHCl_3$) to give 21-4.
R_f (10% CH_3OH/EthylAcetate) 0.19
^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.23 (d, 1H), 7.84 (d, 1H), 4.6 (s, 2H), 3.98 (s, 3H), 3.6 (m, 6H), 2.4 (m, 6H), 1.78 (m, 2H), 1.6 (m, 2H).

1-H-Isoindole-5-carboxylate, 2,3-dihydro-2[4-(N-morpholino)butyl]-3-oxo (21-5)

A solution of 21-4 (0.76 g, 2.3 mmol) in EtOH (11 mL0 was treated with 1N NaOH (2.3 mL, 2.3 mmol) for 120 h, then concentrated to give 21-5 as a white solid.
^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.28 (d, 1H), 7.55 (d, 1H), 4.52 (s, 2H), 3.7-3.6 (m, 6H0, 2.4 (m, 6H), 1.75 (m, 2H), 1.55 (m, 2H).

1-H-Isoindole-5-carboxyamide, 2,3-dihydro-N-[t-butyl, 3(2(S)-phenylsulfonylamino)propionate]-2[4-N-morpholinobutyl]-3-oxo (21-6)

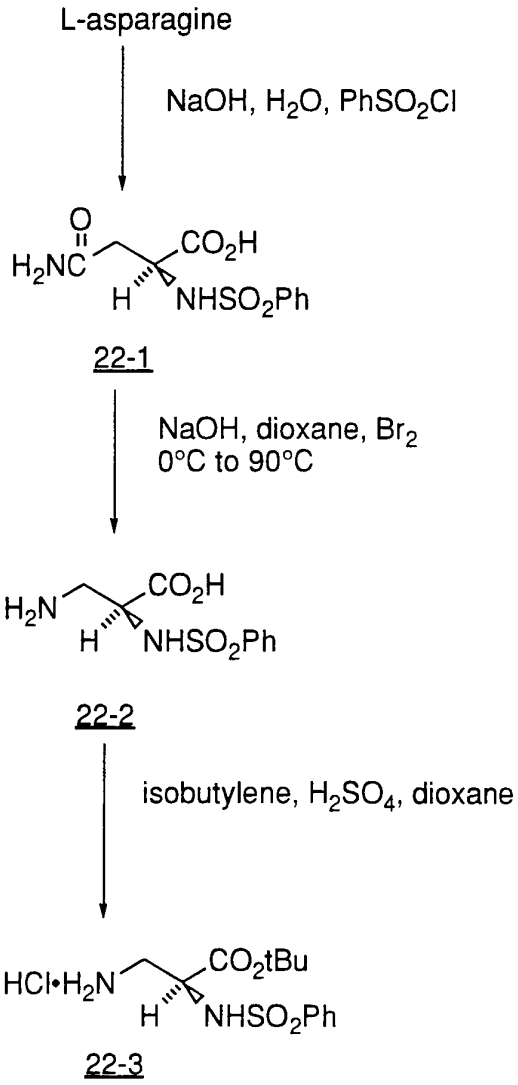
A solution of 21-5 (0.38 g, 1.19 mmol) in CH_3CN (10 mL) was treated with 22-3 (0.36 g, 1.19 mmol), BOP reagent (0.53 g, 1.119 mmol), and N-methyl morpholine (0.26 mL, 2.38 mmol). After 90 h the solution was concentrated and the residue was chromatographed (SiO_2, 5% $CH_3OH/CHCl_3$) to give 21-6 as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.04 (d, 2H), 7.85 (d, 2H), 7.5 (m, 4H), 6.98 (m, 1H), 5.85 (m, 1H), 4.42 (s, 2H), 4.0 (m, 1H), 3.88 (m, 1H), 3.72-3.6 (m, 8H), 2.4 (m, 6H), 1.9 (b, 1H), 1.74 (m, 2H), 1.57 (m, 2H), 1.28 (s, 9H).

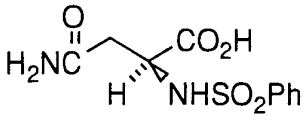
1H-Isoindole-5-carboxamide, 2.3-dihydro-N-[3(2(S)-phenylsulfonyl-amino)propionoate]-2[4-N-methylmorpholinobutyl]-3-oxo 21-7

A solution of 21-6 (0.35 g, 0.58 mmol) in EtOAc (6 mL) was cooled to -40°C and saturated with HCl gas, then warmed to 0°C and stirred for 2 h. The solution was concentrated, and the residue was filtered through a plug of silica gel (eluting with 10:1:1 EtOH/-NH_4OH/H_2O) to give 21-7 as an off-white solid.

^1H NMR (400 MHz, DMSO-d6, of HCl salt before filtration through silica gel plug) d 9.39 (m, 1H), 8.92 (d, 1H), 8.57 (s, 1H), 8.62 (d, 1H), 8.4 (d, 2H), 8.32 (1H), 8.18-8.03 (m, 3H), 5.2 (s, 2H), 4.7-4.6 (m, 2H), 4.58 (d, 2H), 4.27 (t, 2H), 4.2-4.0 (m, 5H), 3.78 (m, 2H), 3.63 (m, 2H), 2.3 (m, 2H), 1.9 (m, 2H).

SCHEME 22

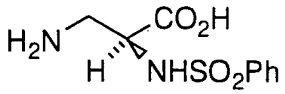

L-asparagine
NaOH, H_2O, $PhSO_2Cl$
H_2NC
O
CO_2H
H
$NHSO_2Ph$
22-1
NaOH, dioxane, Br_2
0°C to 90°C
H_2N
CO_2H
H
$NHSO_2Ph$
22-2
isobutylene, H_2SO_4, dioxane
$HCl•H_2N$
CO_2tBu
H
$NHSO_2Ph$
22-3



22-1

N-Phenysulfonyl-L-asparagine (22-1)

To a stirred solution of L-asparagine (Aldrich) (10 g, 76 mmol), NaOH (3.4 g, 85 mmol), H_2O (50 mL), and dioxane (50 mL) at 0°C was added $PhSO_2Cl$ (10.6 mL, 84 mmol). After 1 min, NaOH (3.4 g) in H_2O (50 mL) was added and the reaction mixture stirred for 30 min. The reaction mixture was then concentrated to remove the dioxane then washed with EtOAc. The aqueous phase was then cooled to 0°C and acidified to pH 3 with conc. HCl to effect product precipitation. The resulting solid was collected by filtration, washed with H_2O (20 mL) and dried at 50°C under vacuum to give 22-1 as a white solid.
R_f 0.40 (silica, 10:1:1 ethanol/H_2O/NH_4OH).
1H NMR (300 MHz, D2O) d 7.59 (m, 2H), 7.26 (m, 3H), 3.92 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H).

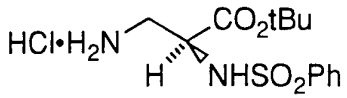


22-2

2(S)-Phenylsulfonylamino-3-aminopropionic acid (22-2)

To a stirred solution of NaOH (15.6 g, 0.4 mol) in H_2O (70 mL), cooled with an icebath, was added bromine (3.6 mL, 0.07 mol) dropwise. After 5 min, a cold solution of 22-1 (14.6 g, 54 mmol) and NaOH (4.3 g, 0.1 mol) in H_2O (50 mL) was added in one portion. The solution was stirred for 20 min at 0°C then 30 min at 90°C. The reaction mixture was re-cooled to 0°C, and the pH adjusted to 7 through dropwise

addition of conc. HCl. The white precipitate that formed was collected by filtration and dried to give 22-2 as a white solid.
^{1}H NMR (300 MHz, D_2O) δ 8.00-7.50 (m, 5H), 3.88 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H).



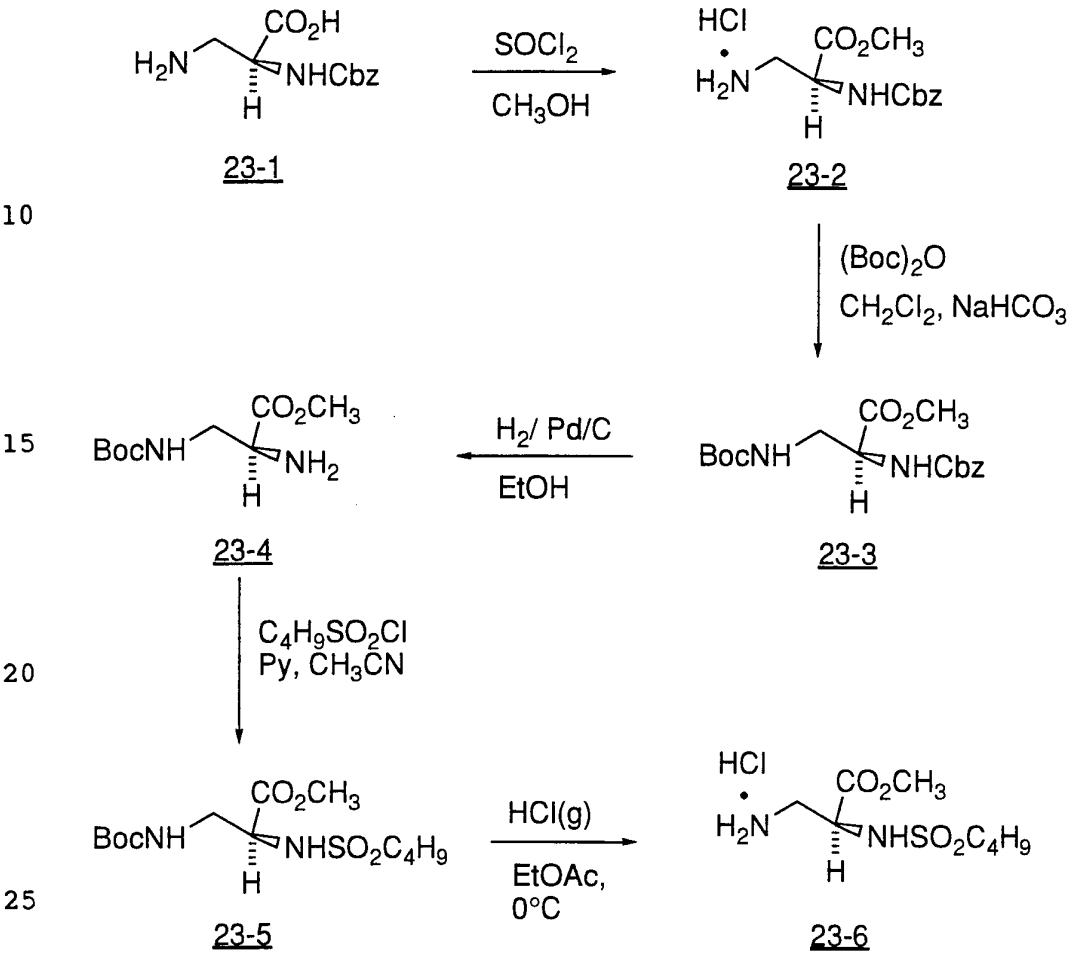
22-3

tert-Butyl 2(S)-Phenylsulfonylamino-3-aminopropionate hydrochloride (22-3)

In a Fischer-Porter tube, a mixture of 22-2 (102 g, 42 mmol) and DME (150 mL) was sequentially treated with H_2SO_4 (6.4 mL, 0.12 mol), cooled to -78°C, and then condensed isobutylene (75 mL). The cooling bath removed. After 2h, ice-water (250 mL) was added followed by washing with ether (2x). The aqueous phase was basified with aq 5N NaOH, then saturated with NaCl, followed by extraction with EtOAc (3x). The combined extracts were washed with brine dried ($MgSO_4$), and concentrated to give a white solid. This was dissolved in $CHCl_3$ then treated with 1N HCl/ether (22 mL) then concentrated to give 22-3 as a glossy yellow solid.
^{1}H NMR (400 MHz, DMSO) δ 8.25-8.00 (m, 4H), 7.85-7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

SCHEME 23

2-Substituted-3-Aminopropionates are prepared in the following manner:



23-1 23-2 23-3 23-4 23-5 23-6

Methyl 2(S)-Benzyloxycarbonylamino-3-aminopropionate hydrochloride (23-2)

To a cooled suspension of 2(S)-benzyloxycarbonylamino-3-aminopropionic acid (Fluka) (23-1) (10g, 0.042 mol) in 150 ml of methanol was added 5.47 g (0.046 mol) of thionyl chloride over 20 minutes. The resulting solution was allowed to stir at room temperature overnight. After ~18 hrs, the solvent was removed in vacuo, and the residual solid was stirred with 150 ml of ether for 0.5 hr. The resulting white solid was collected and air dried to give 23-2.
^{1}H NMR (300 MHz, CD_3OD) δ 3.26 (2H, m), 3.45 (1H, dd), 3.77 (3H, s), 4.25 (1H, m), 5.13 (2H, s), 7.37 (5H, m).

Methyl 2(S)-Benzyloxycarbonylamino-3-(N-t-butyloxycarbonyl)-aminopropionate (23-3)

To a 2-phase mixture of CH_2Cl_2 (500 ml) and saturated $NaHCO_3$ solution (300 ml) was added 28.87 g (0.10 mol) of 23-2. After a few minutes, 21.83 g (0.10 mol) of di-t-butyldicarbonate was added in one portion and the resulting mixture was stirred at room temperature for 4 hrs. The CH_2Cl_2 layer was then separated from the aqueous layer, and the aqueous layer was extracted with 300 ml of CH_2Cl_2. The combined organic extracts were washed with brine, dried and the solvent removed in vacuo to provide the product as a viscous oil. Trituration of this oil with 300 ml of hexane gave 23-3 as a white solid, m.p. 85°-87°.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.50 (4H, m), 1.62 (1H, m), 3.52 (2H, m), 3.75 (3H, s), 4.41 (1H, m), 4.83 (1H, m), 5.12 (2H, s), 5.78 (1H, m), 7.35 (5H, m).

Methyl 2(S)-Amino-3-(N-t-butyloxycarbonyl)aminopropionate (23-4)

To a solution of 6.60 g (0.0187 mol) 23-3 in 150 ml EtOH was added 0.5 g of 10% Pd/C. The resulting mixture was hydrogenated under balloon pressure at r.t. for 4 hrs. The catalyst was filtered off and the solvent removed in vacuo to provide 23-4 as a viscous oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.49 (2H, m), 1.59 (2H, m), 3.25 (1H, m), 3.49 (1H, m), 3.58 (1H,m), 3.75 (3H, s), 5.03 (1H, m).

Methyl 2(S)-Butylsulfonylamino-3-(N-t-butylcarbonyl)aminopropionate (23-5)

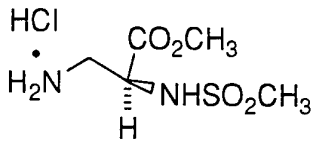
To a solution of 0.400 g (0.00183 mol) of 23-4 in 10 ml of CH_3CN was added 0.226 g (0.00286 mol) pyridine followed by 0.408 g (0.0026 mol) of n-butanesulfonyl chloride. The resulting solution was stirred at room temperature for 2.5 hrs at which time starting material was consumed. The solvent was removed in vacuo and 50 ml of H_2O added to the residual material. This mixture was extracted with 3 x 50 ml portions of ethyl acetate and the combined extracts layer was dried (Na_2SO_4), filtered and concentrated to give 0.5 g of a viscous oil. Trituration to this oil with 25 ml of hexane provided 23-5 as a white, amorphous solid.

^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t), 1.43 (9H, s), 1.48 (2H, m), 1.80 (2H, m), 3.03 (2H, m), 3.52 (2H, t), 3.80 (3H, s), 4.22 (1H, m), 4.99 (1H, bt), 5.48 (1H, bd),

Methyl 2(S)-Butylsulfonylamino-3-aminopropionate hydrochloride (23-6)

A cooled (-20°C) solution of 0.400 g (0.00118 mol) of 23-5 in 25 ml of ethyl acetate was treated with HCl gas for 15 min. The resulting solution was then stoppered and allowed to stir at 0°C for an additional hour. The solvent and excess HCl were removed in vacuo to give 23-6 as a hygroscopic, yellowish foam.

^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t), 1.44 (9H, s), 1.48 (2H, m), 1.80 (2H, m), 3.04 (2H, m), 3.53 (2H, bt), 3.80 (3H, s), 4.22 (1H, m), 4.93 (1H, m), 5.40 (1H, bd).

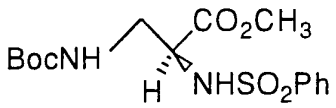


23-7

Methyl 2(S)-Methylsulfonylamino-3-aminopropionate hydrochloride (23-7)

23-7 was prepared as described above for the butylsulfonylamino analog (23-6) using methanesulfonyl chloride at the appropriate stage.

^{1}H NMR (300 MHz, CD_3OD) δ 3.07 (3H, s), 3.13 (1H, m), 3.43 (1H, dd), 3.83 (3H, s), 4.96 (1H, m).



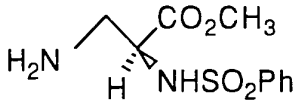
23-8

Methyl 2(S)-Phenylsulfonylamino-3-(t-butyloxycarbonylamino)-propionate acid (23-8)

A solution of 23-4 (19.6 g, 90.1 mmol) in CH_2Cl_2 (150 mL) was treated with benzenesulfonyl chloride (17.3 mL, 127 mmol) and pyridine (10.8 mL) as stirred overnight at room temperature. The solvent was removed in vacuo to give a yellow solid which was triturated with 1:1 hexanes/ether to give 23-8 as a white solid.

R_f (30% EtOAc/Hexane) 0.22

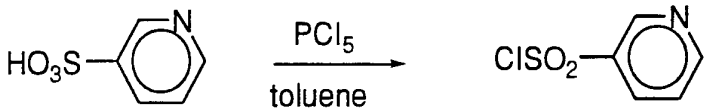
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 2H), 7.6 (m, 1H), 7.56 (m, 2H), 5.6 (bd, 1H), 4.92 (bs, 1H), 4.0 (m, 1H), 3.55 (s, 3H), 3.48 (m, 2H), 1.4 (s, 9H).



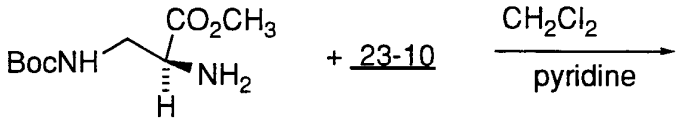
23-9

Methyl 2(S)-Phenylsulfonylamino-3-aminopropionate acid (23-9)

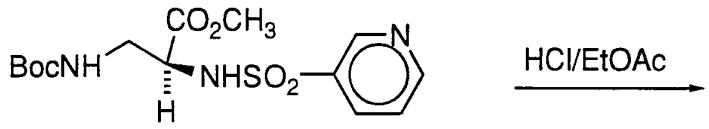
A solution of 23-8 (0.35 g, 0.98 mmol) in EtOAc (5 mL) was cooled to -40°C and saturated with HCl gas. The solution was warmed to 0°C for 2 h, then concentrated to give 23-9 as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.95-7.90 (m, 2H), 7.7-7.5 (m, 3H), 4.22 (dd, 1H), 3.4 (dd, 1H), 3.12 (dd, 1H).



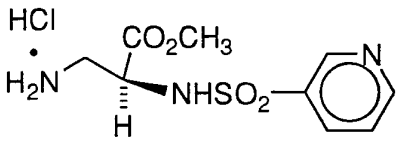
23-10



23-4



23-11



23-12

3-Pyridylsulfonyl chloride (23-10)

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 23-10 as a yellow oil, which was used in the next step without purification.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (1H, s), 8.98 (1H, d, 8.35 (1H, d), 7.62 (1H, dd).

Methyl [2(S)-(3-Pyridylsulfonylamino)-3-(N-t-butyloxycarbonyl)amino] propionate (23-11)

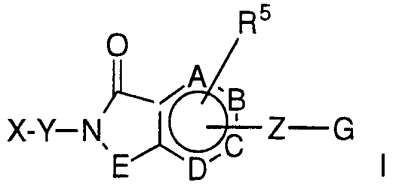
Methyl 2(S)-amino-3-(N-t-butyloxycarbonyl)amino-propionate 23-4 (16.8 g, 0.077 mole) dissolved in 330 mL methylene chloride was treated with sulfonyl chloride 23-10 (20.6 g, 0.116 mole) and pyridine (12.5 mL, 0.154 mole) and the reaction was stirred for 21 hours. The reaction was concentrated, absorbed to silica and chromatographed with a gradient of 30% - 70% acetone/hexanes to give crude 23-11 which was swished with hot EtOAc, cooled and filtered to give 23-11 as a pale yellow solid.
R_f 0.29 (30% acetone/hexanes).
^{1}H 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).

Methyl [2(S)-(3-Pyridylsulfonylamino)-3-amino]propionate (23-12)

Methyl 2(S)-(3-pyridylsulfonyl)amino-3-(N-t-butyloxycarbonyl)aminopropionate 23-11 (17.5 g, 0.049 mole) was suspended in 200 mL EtOAc and cooled to -78°C. HCl gas was 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 23-12 as an off-white solid.
R_f 0.34 (9:1:1 $EtOH/H_2O/NH_4OH$).
^{1}H 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).

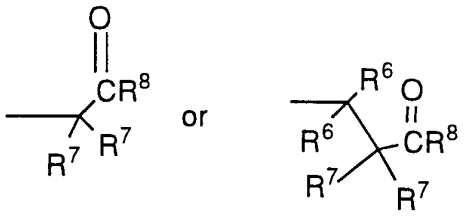
WHAT IS CLAIMED IS:

1. A compound of the following formula and pharmaceutically acceptable salts:



I

wherein G is



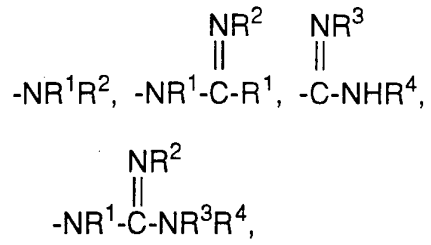
wherein:

A, B, C and D each independently represent a carbon atom or a nitrogen atom;

E is -$(CH_2)_n$-;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

X is



or a 4-membered monocyclic nonaromatic ring system containing 0 or 1 heteroatoms selected from N, 0 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 each independently selected from the group consisting of hydrogen,

C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl,
C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 5- membered monocyclic nonaromatic ring system containing 0 or 1 heteroatoms selected from N, 0 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,

C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,

thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 5- membered monocyclic aromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, 0 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,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 6- membered mono- or polycyclic aromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, 0 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,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,

oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 6- membered mono- or polycyclic nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, 0 and S and 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,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 6- membered mono- or polycyclic nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from 0 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,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,

oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

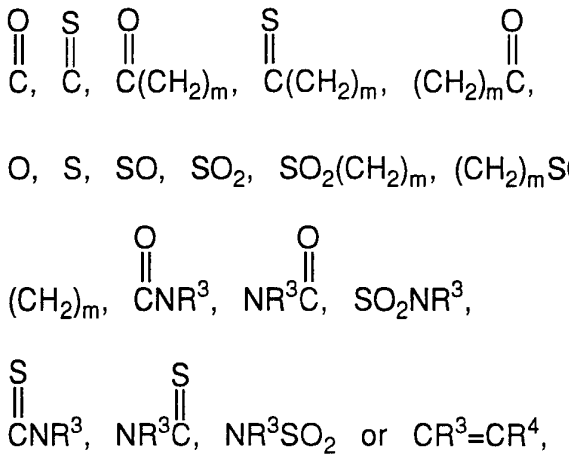
or a 6- membered mono- or polycyclic nonaromatic ring system containing 0, 2, 3 or 4 heteroatoms selected from N, 0 and S and either unsubstituted or substituted with R^1, R^2, R^3 or R^4, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen,
C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

or a 7- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, 0 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,

C_{1-10} alkyl,
aryl C_{0-8} alkyl,
oxo,
thio,
amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
C_{1-6} alkylamino C_{0-8} alkyl,
C_{1-6} dialkylamino C_{0-8} alkyl,
C_{1-4} alkoxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl, C_{1-3} alkoxycarbonyl C_{0-6} alkyl,
carboxy C_{0-6} alkyloxy and
hydroxy C_{0-6} alkyl;

Y is C_{0-8} alkyl,
C_{0-8} alkyl-NR^3-CO-C_{0-8} alkyl,
C_{0-8} alkyl-$CONR^3$-C_{0-8} alkyl,
C_{0-8} alkyl-O-C_{0-8} alkyl,
C_{0-8} alkyl-$S(O_n)$-C_{0-8} alkyl, or
C_{0-8} alkyl-SO_2-NR^3-C_{0-8} alkyl-,
C_{0-8} alkyl-NR^3-SO_2-C_{0-8} alkyl-,
C_{1-8} alkyl-CO-C_{0-8} alkyl;

Z is



wherein m is 0-6;

R5 is

hydrogen
C_{1-6} alkyl,
C_{0-6} alkylcarboxy C_{0-6} alkyl,
C_{0-6} alkyloxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
aryl C_{0-6} alkyl, or
halogen;

R6 is

hydrogen,
C_{1-8} alkyl,
aryl C_{0-6} alkyl,
C_{3-8} cycloalkyl C_{0-6} alkyl,
C_{0-6} alkylcarboxy C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
C_{1-4} alkyloxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,

provided that any of which R6 groups may be substituted or unsubstituted independently with R1 or R2, and provided that,

when two R^6 groups are attached to the same carbon, they may be the same or different;

R^7 is

hydrogen, fluorine
C_{1-8} alkyl,
C_{3-8} cycloalkyl,
aryl C_{0-6} alkyl,
C_{0-6} alkylamino C_{0-6} alkyl,
C_{0-6} dialkylamino C_{0-6} alkyl,
C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonylamino C_{0-6} alkyl,
C_{1-8} alkyloxycarbonylamino C_{0-8}-alkyl,
aryl C_{0-8} alkyloxycarbonylamino C_{0-8} alkyl,
C_{1-8} alkylcarbonylamino C_{0-6} alkyl,
aryl C_{0-6} alkylcarbonylamino C_{0-6} alkyl,
C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
aryl C_{0-8} alkylaminocarbonylamino C_{0-6} alkyl,
C0-6 alkylaminosulfonylamino C0-6 alkyl,
aryl C0-6 alkylaminosulfonylamino C0-6 alkyl,
C_{1-6} alkylsulfonyl C_{0-6} alkyl,
aryl C_{0-6} alkylsulfonyl C_{0-6} alkyl,
C_{1-6} alkylcarbonyl C_{0-6} alkyl
aryl C_{0-6} alkylcarbonyl C_{0-6} alkyl,
C_{1-6} alkylthiocarbonylamino C_{0-6} alkyl
aryl C_{0-6} alkylthiocarbonylamino C_{0-6} alkyl

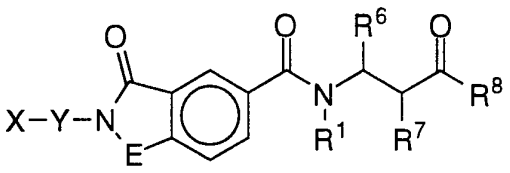
wherein groups may be unsubstituted or substituted with one or more substituents selected from R^1 and R^2, and provided that when two R^7 groups are attached to the same carbon atom, they may be the same or different;

R^8 is

hydroxy,
C_{1-8} alkyloxy,

aryl C_{0-6} alkyloxy,
C_{1-8} alkylcarbonyloxy C_{1-4} alkyloxy,
aryl C_{1-8} alkylcarbonyloxy C_{1-4} 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 C_{1-6} alkyl.

2. The compound of Claim 1, and pharmaceutically acceptable salts, having the formula



II

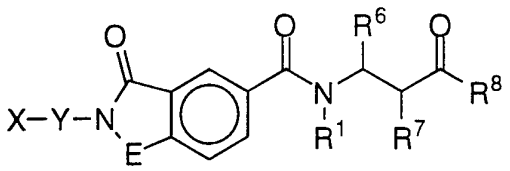
II wherein:

E is -$(CH_2)_n$-;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

and X, Y, R^1, R^6, R^7 and R^8 are as previously defined in Claim 1.

3. A compound of Claim 2, and pharmaceutically acceptable salts, having the formula:



wherein:

E is -$(CH_2)_n$-;
-(C=C)-;
-N-; or
-O-,

wherein n=1-4;

X is

-NR^1R^2

or a 4-membered monocyclic nonaromatic ring system containing 0 or 1 heteroatoms selected from N and 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 5- membered monocyclic nonaromatic ring system containing 0 or 1 heteroatoms selected from N and 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,

C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 5- membered monocyclic aromatic ring system containing 0, 1 or 2 heteroatoms selected from N and 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 6- membered mono- or polycyclic aromatic ring system containing 0, 1 or 2 heteroatoms selected from N or 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 6- membered mono- or polycyclic nonaromatic ring system containing 0, 1 or 2 heteroatoms selected from N and 0 and substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,

carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 6- membered mono- or polycyclic nonaromatic ring system containing 0, 1 or 2 heteroatoms selected from 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 6- membered mono- or polycyclic nonaromatic ring system containing 0 or 2 heteroatoms selected from N or 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,
hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

or a 7- to 10- membered mono- or polycyclic aromatic or nonaromatic ring system containing 0, 1 or 2 heteroatoms selected from N and 0 and either unsubstituted or substituted with R^1 and R^2, wherein R^1 and R^2 are independently selected from the group consisting of hydrogen,
C_{1-6} alkyl,
aryl C_{0-6} alkyl,
carboxy C_{0-6} alkyl,

hydroxy C_{0-6} alkyl,
C_{1-3} alkyloxy C_{0-6} alkyl, or
amino C_{0-6} alkyl;

Y is

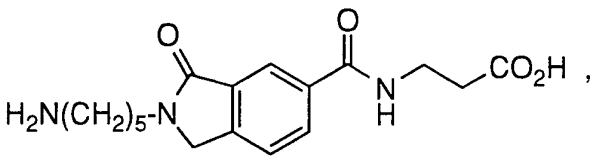
C_{0-6} alkyl,
C_{1-6} alkyl-CO-C_{0-6} alkyl, or
C_{0-6} alkyl-NR^3-CO-C_{0-6} alkyl;

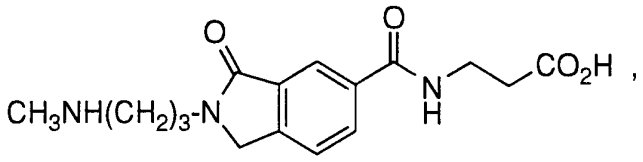
R^6 and R^7 are as previously defined in Claim 1, and

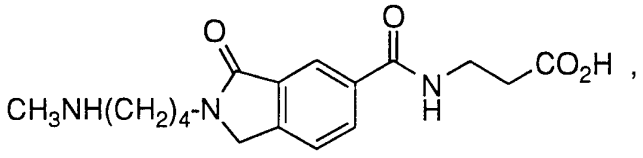
R^8 is

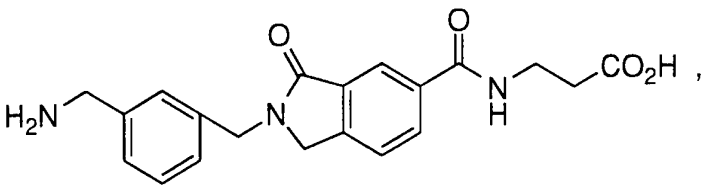
hydroxy,
C_{1-6} alkyloxy,
aryl C_{1-4} alkyloxy, or
C_{1-6} alkylcarbonyloxy C_{1-4} alkyloxy.

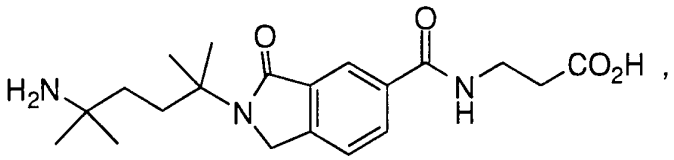
4. The compound of Claim 1, and pharmaceutically acceptable salts, selected from the group of

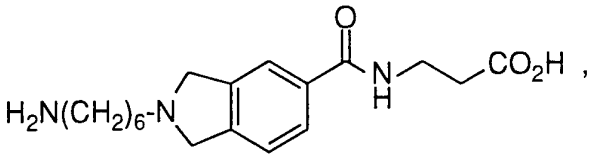


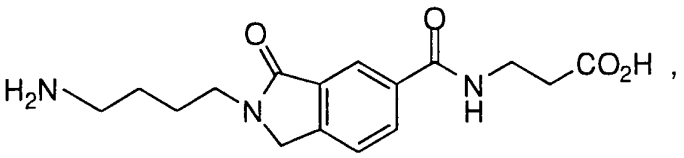


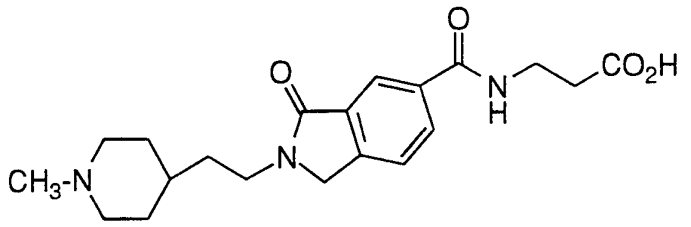




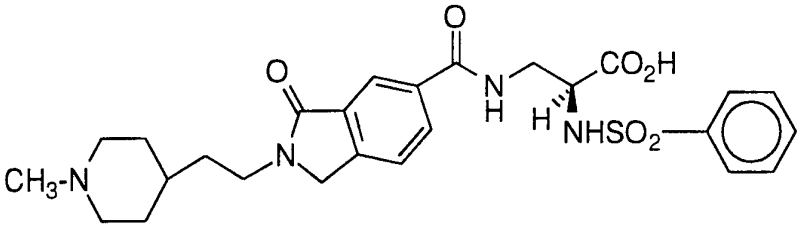




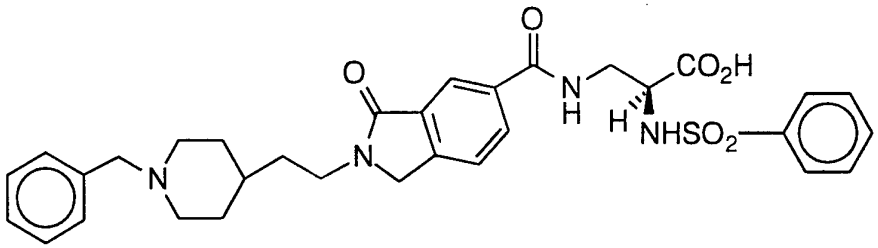




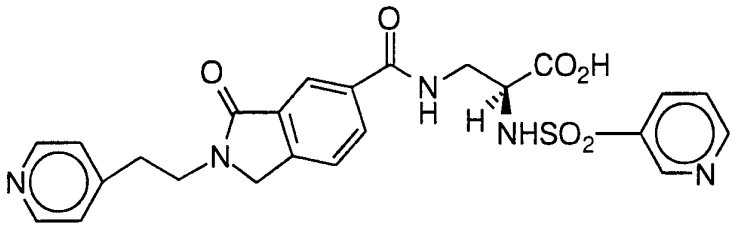
,



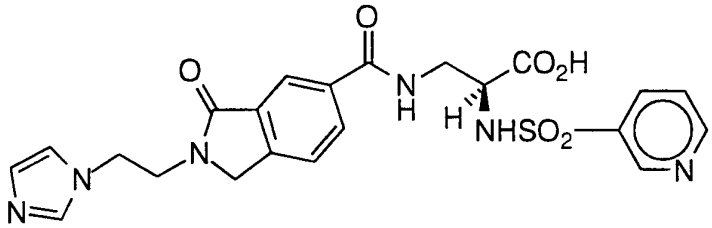
,



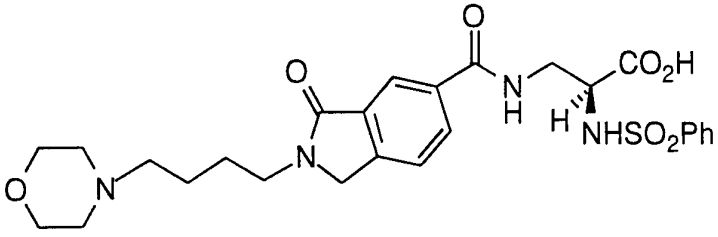
,



,



, and



.

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

6. 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.

7. The composition of Claim 6 wherein the thrombolytic agent is a plasminogen activator or streptokinase.

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

9. The composition of Claim 8, wherein the anticoagulant is heparin or warfarin.

10. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 5.

11. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 6.

12. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 7.

13. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 8.

14. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to the mammal the composition of Claim 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14706

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. : 546/201, 256; 548/336, 486; 544/ 144; 514/235.2, 320, 333, 397, 419

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

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

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A, 0,540,334 (HARTMAN ET AL) 05 MAY 1993, ENTIRE DOCUMENT	1-10

☐ 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)	"&"	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 23 MARCH 1995	Date of mailing of the international search report 12 APR 1995
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 PHYLLIS SPIVACK tcj Telephone No. (703) 308-1235

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

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US94/14706

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

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

Please See Extra Sheet.

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10 (compound of formula I)

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14706

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 413/06, 401/06, 401/14, 209/14, 209/34; A61K 31/405, 31/415, 31/44, 31/445, 31/535;

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/235.2, 320, 333, 397, 419; 544/144; 546/201, 256; 548/336, 486

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

1. This International Search Authority has found 30 inventions claimed in the International Application covered by the claims indicated below:

I.Claims 1 to 9, and 10 drawn to a compound of formula I that is indole, compositions and a method for inhibiting the aggregation of blood platelets, classified in Class 548, subclasses 470+.

II.Claims 1 to 9, drawn to a compound of formula I wherein E is -N- or -O- and A,B,C,D are all carbon, and compositions, classified in Class 548, subclass 453.

III. Claims 1 to 3 and 5 to 9, drawn to a compound of formula I wherein n = 3 or 4, and compositions, in various subclasses of Class 540.

IV. Claims 1 and 5 to 9, drawn to a compound of formula I wherein n = 1-3 and two of A,B,C and D are nitrogen, and compositions, classified in 544, subclass 224+.

V. Claims 1 and 5 to 9, drawn to a compound of formula I wherein n = 1-3 and three or four of A,B,C and D are nitrogen, and compositions, classified in Class 544, subclass 179+.

VI. Claims 1 and 5 to 9, drawn to a compound of formula I wherein n = 1-3 and one of A,B,C and D is nitrogen and compositions, classified in Class 546, subclass 113+.

VII. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I that is indole.

VIII. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I where E is -N- or -O- and A,B,C,D are all carbon.

IX. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I where n = 3 or 4.

X. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I where n = 1-3 and two of A,B,C and D are nitrogen.

XI. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I where n = 1-3 and three or four of A,B,C and D are nitrogen.

XII. Claims 11, 12, drawn to a method for inhibiting the aggregation of blood platelets in combination with streptokinase comprising administering a compound of formula I where n = 1-3 and one of A,B,C and D is nitrogen.XIII. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparin comprising administering a compound of formula I that is indole.

XIV. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparin comprising administering a compound of formula I where E is -N- or -O- and A,B,C,D are all carbon.

XV. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparin comprising administering a compound of formula I where n = 3 or 4.

XVI. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparin comprising administering a compound of formula I where n = 1-3 and two of A,B,C and D are nitrogen.

XVII. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparin comprising administering a compound of formula I where n = 1-3 and three or four of A,B,C and D are nitrogen.

XVIII. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with heparincomprising administering a compound of formula I where n = 1-3 and one of A,B,C and D is nitrogen.

XIX. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with warfarin comprising administering a compound of formula I that is indole.

XX. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with warfarin comprising administering a compound of formula I where E is -N- or -O- and A,B,C,D are all carbon.

XXI. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with warfarin comprising administering a compound of formula I where n = 3 or 4.

XXII. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with warfarin comprising administering a compound of formula I where n = 1-3 and two of A,B,C and D are nitrogen.

XXIII. Claims 13, 14, drawn to method for inhibiting the aggregation of blood platelets in combination with warfarin comprising administering a compound of formula I where n = 1-3 and three or four of A,B,C and D are nitrogen.XXIV. Claims 13, 14, drawn to a method for inhibiting the aggregation of blood platelets in combination with. warfarin comprising administering a compound of formula I where n = 1-3 and one of A,B,C and D is nitrogen.

XXV. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formula I that is indole.

XXVI. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formula I where E is -N- or -O- and A,B,C,D are all carbon.

XXVII. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formula I where n = 3 or 4.

XXVIII. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formula I where n = 1-3 and two of A,B,C,D are nitrogen.

XXIX. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formula I where n = 1-3 and three or four of A,B,C and D are nitrogen.
XXX. Claim 10, drawn to a method for inhibiting the aggregation of blood platelets comprising administering a compound of formulal where n = 1-3 and one of A,B,C and D is nitrogen.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

PCT Rule 13.1 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept "requirement of unity of invention".

PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Annex B, Part 1(a), indicates that the application should relate to only one invention, or if there is more than one invention, inclusion is permitted if they are so linked to form a single general inventive concept.

Annex B, Part 1(b), indicates that "special technical features" means those technical features as a whole define a contribution over the prior art.

Annex B, Part 1(c), further defines independent and dependent claims. Unity of invention only is concerned in relation to independent claims. Dependent claims are defined as a claim which contains all the features of another claim and is

in the same category as the other claim. The category of a claim refers to the classification of claims according to subject matter, e.g., product, process, use, apparatus, means, etc.Annex B, Part 1(e), indicates the permissible combinations of differentcategories of claims. Part 1(e(i)) states that inclusion of an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product is permissible.

Annex B, Part 1(f) indicates the "Markush practice" of alternatives in a single claim. Part 1(f(i)) indicates the technical interrelationship and the same or corresponding special technical feature is considered to be met when: (A) all alternatives have a common property or activity, and (B) a common structure is present or all alternatives belong to a recognized class of chemical compounds. Further defining (B) in Annex B, Part 1(f)(i-iii), the common structure must; a) occupy a large portion of their structure, or b) the common structure constitutes a structurally distinctive portion, or c) where the structures are equivalent and therefore a recognized class of chemical compounds, each member could be substituted for one another with the same intended result. That is, with a common or equivalent structure, there is an expectation from knowledge in the art that all members will behave in the same way. Thus, the technical relationship and the corresponding special technical feature result from a common (or equivalent) structure which is responsible for the common activity (or property). Part 1(f(iv)) indicates that when all alternatives of a Markush grouping can be differently classified, it shall not, taken alone, be considered justification for finding a lack of unity. Part 1 (f(v))indicates that when dealing with alternatives, it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered, but does not imply that an objection shall be raised.

Herein, as shown by the myriad of compounds encompassed within instant formula I, a lack of unity of invention exists.