



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/38, 31/405, 31/445, C07D 209/90, 471/02, 495/16, 513/16</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/18464</p> <p>(43) International Publication Date: 7 May 1998 (07.05.98)</p>
<p>(21) International Application Number: PCT/US97/19183</p> <p>(22) International Filing Date: 23 October 1997 (23.10.97)</p> <p>(30) Priority Data: 60/029,849 30 October 1996 (30.10.96) US</p> <p>(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BACH, Nicholas, J. [US/US]; 7215 South Meridian Street, Indianapolis, IN 46217 (US). DILLARD, Robert, D. [US/US]; 7243 West 92nd Street, Zionsville, IN 46077 (US). DRAHEIM, Susan, E. [US/US]; 6125 Burlington Avenue, Indianapolis, IN 46220 (US). MORIN, John, M., Jr. [US/US]; 9 Roselawn Avenue, Brownsburg, IN 46112 (US).</p> <p>(74) Agents: PALMBERG, Arleen et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).</p>	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: SUBSTITUTED TRICYCLICS</p>		
<p>(57) Abstract</p> <p>A class of novel tricyclics is disclosed together with the use of such compounds for inhibiting sPLA₂ mediated release of fatty acids for treatment of conditions such as septic shock.</p>		

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Title

SUBSTITUTED TRICYCLICS

5

BACKGROUND OF THE INVENTION

Field of the Invention

10 This invention relates to novel substituted tricyclic organic compounds useful for inhibiting sPLA₂ mediated release of fatty acids for conditions such as septic shock.

Background Information

15

The structure and physical properties of human non-pancreatic secretory phospholipase A₂ (hereinafter called, "sPLA₂") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A₂ Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5335-
20 5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A₂" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky,
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R. Blake; The Journal of Biological Chemistry, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

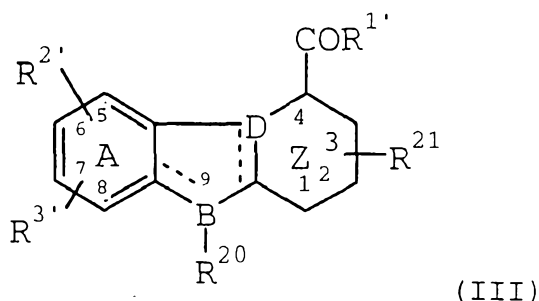
It is believed that sPLA₂ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit sPLA₂ mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of sPLA₂ such as septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, etc.

It is desirable to develop new compounds and treatments for sPLA₂ induced diseases.

Alexander, et al., United States Patent Nos. 3,939,177 and 3,979,391, disclose 1,2,3,4-tetrahydrocarbazoles useful as antibacterial agents.

20 Summary of the Invention

This invention provides tricyclic compounds as depicted in the general formula (III) below:



25 wherein ;

A is phenyl or pyridyl wherein the nitrogen is at the 5-, 6-, 7- or 8-position;

one of B or D is nitrogen and the other is carbon;

30 Z is cyclohexenyl, phenyl, pyridyl, wherein the nitrogen is at the 1-, 2-, or 3-position, or a 6-membered

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heterocyclic ring having one heteroatom selected from the group consisting of sulfur or oxygen at the 1-, 2- or 3-position, and nitrogen at the 1-, 2-, 3- or 4-position;

--- is a double or single bond;

5 R^{20} is selected from groups (a), (b) and (c) where;

(a) is $-(C_5-C_{20})$ alkyl, $-(C_5-C_{20})$ alkenyl, $-(C_5-C_{20})$ alkynyl, carbocyclic radicals, or heterocyclic radicals, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents;

10 or

(c) is the group $-(L)-R^{80}$; where, $-(L)-$ is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein

15 the combination of atoms in $-(L)-$ are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one sulfur only, and (vi) and carbon, hydrogen, and oxygen

20 only; and where R^{80} is a group selected from (a) or (b);

R^{21} is a non-interfering substituent;

$R^{1'}$ is $-NHNH_2$ or $-NH_2$;

$R^{2'}$ is selected from the group $-OH$, $-O(CH_2)_tR^5$ where R^5 is CN or phenyl, or $-(L_a)-(\text{acidic group})$; wherein

25 $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;

$R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;

30

or a pharmaceutically acceptable salt, racemate, solvate, tautomer, optical isomer or prodrug derivative thereof;

35 provided that when $R^{3'}$ is H, R^{20} is benzyl and m is 1 or 2, $R^{2'}$ cannot be $-O(CH_2)_mH$;

and when D is nitrogen, the heteroatom of Z is selected from the group consisting of sulfur or oxygen at the 1-, 2- or 3-position and nitrogen at the 1-, 2-, 3- or 4-position.

5 These substituted tricyclics are effective in inhibiting human sPLA₂ mediated release of fatty acids.

 This invention is also a pharmaceutical formulation comprising a compound of formula III in association with one or more pharmaceutically acceptable
10 diluents, carriers and excipients.

 This invention is also a method of inhibiting sPLA₂ comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula III.

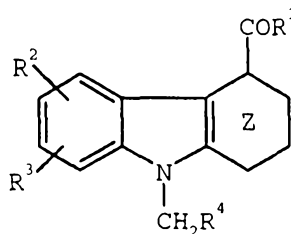
15 According to a further aspect of the present invention, there is provided a method of selectively inhibiting sPLA₂ in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of formula III.

20 This invention also provides a method of alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid
25 arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy
30 or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis
35 nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell

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arteritis, calcium crystal deposition arthropathris, pseudo
 gout, non-articular rheumatism, bursitis, tenosynovitis,
 epicondylitis (tennis elbow), carpal tunnel syndrome,
 repetitive use injury (typing), miscellaneous forms of
 5 arthritis, neuropathic joint disease (charco and joint),
 hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura,
 hypertrophic osteoarthropathy, multicentric
 reticulohistiocytosis, arthritis associated with certain
 diseases, surcoilosis, hemochromatosis, sickle cell disease
 10 and other hemoglobinopathries, hyperlipoproteineimia,
 hypogammaglobulinemia, hyperparathyroidism, acromegaly,
 familial Mediterranean fever, Behat's Disease, systemic
 lupus erythrematosis, or relapsing polychondritis and
 related diseases which comprises administering to a mammal
 15 in need of such treatment a therapeutically effective amount
 of the compound of formula III in an amount sufficient to
 inhibit sPLA₂ mediated release of fatty acid and to thereby
 inhibit or prevent the arachidonic acid cascade and its
 deleterious products.

20 This invention provides, in addition, a process of
 preparing compounds of formula



wherein

- 25 R¹ is -NHNH₂, or -NH₂;
 R² is -OH, or -O(CH₂)_mR⁵ where
 R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl),
 $\begin{array}{c} \text{O} \\ \parallel \\ -\text{P}(\text{R}^6\text{R}^7) \end{array}$, phenyl, or phenyl substituted with
 -CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are

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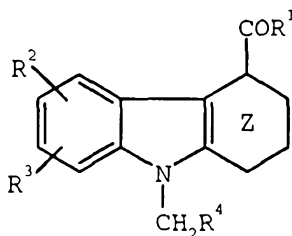
each independently -OH or -O(C₁-C₄ alkyl) and m is 1-3;

R³ is H, -O(C₁-C₄ alkyl), or -(CH₂)_nR⁸ where

R⁸ is H, -NR⁹R¹⁰, $\overset{\text{O}}{\parallel}\text{C}\text{NH}_2$, -CN, or phenyl where R⁹ and R¹⁰ are independently -(C₁-C₄)alkyl, or -phenyl(C₁-C₄)alkyl and n is 1-8;

R⁴ is H, -(C₅-C₁₄)alkyl, -(C₃-C₁₄)cycloalkyl, phenyl, or phenyl substituted with 1 or 2 substituents selected from the group consisting of -(C₁-C₄)alkyl, -(C₁-C₄)alkoxy, -phenyl(C₁-C₄)alkyl, -(C₁-C₄)alkylthio, halo or phenyl; and

Z is phenyl comprising dehydrogenating a compound of the formula



wherein

R¹ is -NHNH₂, or -NH₂;

R² is -OH, or -O(CH₂)_mR⁵ where

R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl),

$\overset{\text{O}}{\parallel}\text{P}(\text{R}^6\text{R}^7)$, phenyl, or phenyl substituted with -CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are each independently -OH or -O(C₁-C₄ alkyl) and m is 1-3;

R³ is H, -O(C₁-C₄ alkyl), or -(CH₂)_nR⁸ where

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R^8 is H, $-NR^9R^{10}$, $-\overset{\text{O}}{\parallel}{C}NH_2$, $-CN$, or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)$ alkyl, or $-\text{phenyl}(C_1-C_4)$ alkyl and n is 1-8;

R^4 is H, $-(C_5-C_{14})$ alkyl, $-(C_3-C_{14})$ cycloalkyl, phenyl, or phenyl substituted with 1 or 2 substituents selected from the group consisting of $-(C_1-C_4)$ alkyl, $-(C_1-C_4)$ alkoxy, $-\text{phenyl}(C_1-C_4)$ alkyl, $-(C_1-C_4)$ alkylthio, halo or phenyl; and

Z is cyclohexenyl.

Other objects, features and advantages of the present invention will become apparent from the subsequent description and the appended claims.

Detailed Description of the Invention

Definitions:

As used herein, the term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, isobutyl, sec-butyl, tert butyl, n-pentyl, isopentyl, neopentyl, heptyl, hexyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and the like. The term "alkyl" includes $-(C_1-C_2)$ alkyl, $-(C_1-C_4)$ alkyl, $-(C_1-C_6)$ alkyl, $-(C_5-C_{14})$ alkyl, and $-(C_1-C_{10})$ alkyl.

The term "alkenyl" as used herein represents an olefinically unsaturated branched or linear group having at least one double bond. Examples of such groups include radicals such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl,

5-heptenyl, 6-heptenyl as well as dienes and trienes of straight and branched chains.

The term "alkynyl" denotes such radicals as ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl as well as di- and tri-ynes.

The term "halo" means chloro, fluoro, bromo or iodo.

The term "-(C₁-C₄)alkoxy", as used herein, denotes a group such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups, attached to the remainder of the molecule by the oxygen atom.

The term "phenyl(C₁-C₄)alkyl" refers to a straight or branched chain alkyl group having from one to four carbon atoms attached to a phenyl ring which chain is attached to the remainder of the molecule. Typical phenylalkyl groups include benzyl, phenylethyl, phenylpropyl, phenylisopropyl, and phenylbutyl.

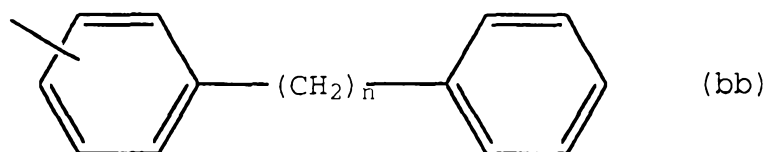
The term "-(C₁-C₄)alkylthio" defines a straight or branched alkyl chain having one to four carbon atoms attached to the remainder of the molecule by a sulfur atom. Typical -(C₁-C₄)alkylthio groups include methylthio, ethylthio, propylthio, butylthio and the like.

The term "-(C₃-C₁₄)cycloalkyl" includes groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclotridecyl, cyclotetradecyl and the like. The term "-(C₃-C₁₄)cycloalkyl" includes and -(C₃-C₇)cycloalkyl.

The term, "heterocyclic radical", refers to radicals derived from monocyclic or polycyclic, saturated or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl, carbazolyl, norharmanyl,

azaindolyl, benzofuranyl, dibenzofuranyl, thianaphthenyl,
 dibenzothiophenyl, indazolyl, imidazo(1.2-A)pyridinyl,
 benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl,
 benzoxazolyl, benzothiazolyl, purinyl, pyridinyl,
 5 dipyridyl, phenylpyridinyl, benzylpyridinyl, pyrimidinyl,
 phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl,
 phthalazinyl, quinazolinyl, and quinoxalinyl.

The term "carbocyclic radical" refers to radicals
 derived from a saturated or unsaturated, substituted or
 10 unsubstituted 5 to 14 membered organic nucleus whose ring
 forming atoms (other than hydrogen) are solely carbon atoms.
 Typical carbocyclic radicals are cycloalkyl, cycloalkenyl,
 phenyl, naphthyl, norbornanyl, bicycloheptadienyl, toluyl,
 xylenyl, indenyl, stilbenyl, terphenyl, diphenylethylenyl,
 15 phenylcyclohexenyl, acenaphthylenyl, and anthracenyl,
 biphenyl, bibenzyl and related bibenzyl homologues
 represented by the formula (bb),



20

where n is an integer from 1 to 8.

The term, "non-interfering substituent", refers to
 radicals suitable for substitution at positions 1, 2, 3, 7
 and/or 8 on the tricyclic nucleus (as depicted in Formula
 25 III) and radical(s) suitable for substitution on the
 heterocyclic radical and carbocyclic radical as defined
 above. Illustrative non-interfering radicals are hydrogen,
 -(C₁-C₁₂)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,
 -(C₇-C₁₂)aralkyl, -(C₇-C₁₂)alkaryl, -(C₃-C₈)cycloalkyl,
 30 -(C₃-C₈)cycloalkenyl, phenyl, toluyl, xylenyl, biphenyl,
 -(C₁-C₆)alkoxy, -(C₂-C₆)alkenyloxy, -(C₂-C₆)alkynyloxy,
 -(C₁-C₁₂)alkoxyalkyl, -(C₁-C₁₂)alkoxyalkyloxy,
 -(C₁-C₁₂)alkylcarbonyl, -(C₁-C₁₂)alkylcarbonylamino,
 -(C₁-C₁₂)alkoxyamino, -(C₁-C₁₂)alkoxyaminocarbonyl,

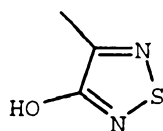
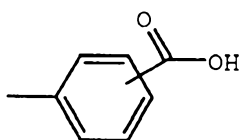
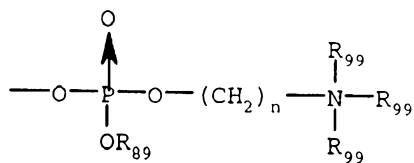
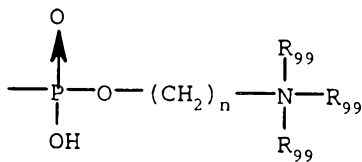
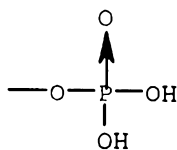
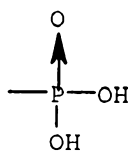
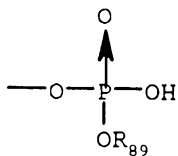
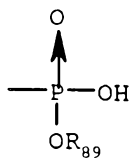
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-(C₁-C₁₂)alkylamino, -(C₁-C₆)alkylthio,
 -(C₁-C₁₂)alkylthiocarbonyl, -(C₁-C₆)alkylsulfinyl,
 -(C₁-C₆)alkylsulfonyl, -(C₁-C₆)haloalkoxy,
 -(C₁-C₆)haloalkylsulfonyl, -(C₁-C₆)haloalkyl,
 5 -(C₁-C₆)hydroxyalkyl, -(CH₂)_nCN, -(CH₂)_nNR⁹R¹⁰, -C(O)O(C₁-C₆
 alkyl), -(CH₂)_nO(C₁-C₆ alkyl), benzyloxy, phenoxy,
 phenylthio, -(CONHSO₂R), -CHO, amino, amidino, halo,
 carbamyl, carboxyl, carbalkoxy, -(CH₂)_nCO₂H, cyano,
 cyanoguanidiny, guanidino, hydrazide, hydrazino, hydrazido,
 10 hydroxy, hydroxyamino, nitro, phosphono, -SO₃H, thioacetal,
 thiocarbonyl, and (C₁-C₆)alkylcarbonyl; where n is from 1 to
 8 and R⁹ and R¹⁰ are independently -(C₁-C₄)alkyl or
 phenyl(C₁-C₄)alkyl. A preferred group of non-interfering
 substituents include hydrogen, halo, -(C₁-C₃)alkyl,
 15 -(C₃-C₄)cycloalkyl, -(C₃-C₄)cycloalkenyl, -O(C₁-C₂)alkyl or
 -S(C₁-C₂)alkyl.

The term, "acidic group" means an organic group
 which when attached to a tricyclic nucleus, through
 suitable linking atoms (hereinafter defined as the "acid
 20 linker"), acts as a proton donor capable of hydrogen
 bonding. Illustrative of an acidic group are the
 following:

-CO₂H,
 25 -5-tetrazolyl,
 -SO₃H,

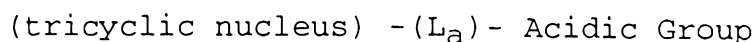
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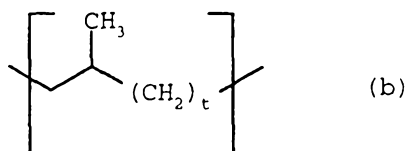
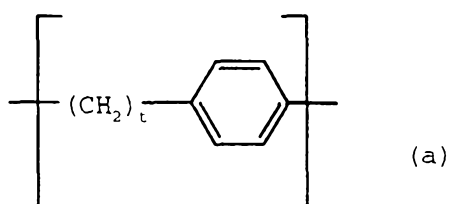
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where n is 1 to 8, R₈₉ is a metal or -(C₁-C₁₀)alkyl, and R₉₉ is hydrogen or -(C₁-C₁₀)alkyl.

The words, "acid linker" refer to a divalent linking group symbolized as, -(L_a)-, which has the function of joining the 5 or 6 position of the tricyclic nucleus to an acidic group in the general relationship:

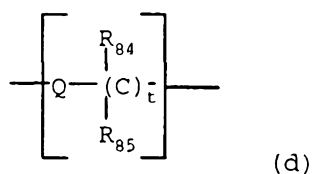
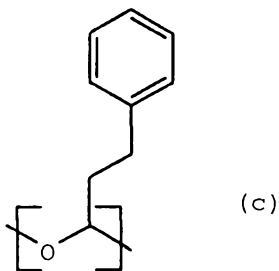


The words, "acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group -(L_a)- that connects the 5 or 6 position of the tricyclic nucleus with the acidic group. The presence of a carbocyclic ring in -(L_a)- counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of -(L_a)-. Illustrative acid linker groups are;



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where t is 1 to 5, Q is selected from the group $-(CH_2)-$,
 $-O-$, $-NH-$, and $-S-$, and R₈₄ and R₈₅ are each independently
 5 selected from hydrogen, $-(C_1-C_{10})$ alkyl, aryl,
 $-(C_1-C_{10})$ alkaryl, $-(C_1-C_{10})$ aralkyl, carboxy, carbalkoxy, and
 halo, when t is one (1), groups (a), (b), (c) and (d) have
 acid linker lengths of 3, 3, 2, and 2, respectively.

The salts of the above tricyclics are an
 10 additional aspect of the invention. In those instances
 where the compounds of the invention possess acidic
 functional groups various salts may be formed which are
 more water soluble and physiologically suitable than the
 parent compound. Representative pharmaceutically
 15 acceptable salts include but are not limited to the alkali
 and alkaline earth salts such as lithium, sodium,
 potassium, calcium, magnesium, aluminum and the like.
 Salts are conveniently prepared from the free acid by
 treating the acid in solution with a base or by exposing
 20 the acid to an ion exchange resin.

Included within the definition of
 pharmaceutically acceptable salts are the relatively non-
 toxic, inorganic and organic base addition salts of
 compounds of the present invention, for example, ammonium,
 25 quaternary ammonium, and amine cations, derived from
 nitrogenous bases of sufficient basicity to form salts

with the compounds of this invention (see, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)).

Compounds of the invention may have chiral
5 centers and exist in optically active forms. R- and S-
isomers and racemic mixtures are contemplated by this
invention. A particular stereoisomer may be prepared by
known methods using stereospecific reactions with starting
materials containing asymmetric centers already resolved
10 or, alternatively, by subsequent resolution of mixtures of
stereoisomers using known methods.

Prodrugs are derivatives of the compounds of the
invention which have chemically or metabolically cleavable
groups and become by solvolysis or under physiological
15 conditions the compounds of the invention which are
pharmaceutically active in vivo. Derivatives of the
compounds of this invention have activity in both their
acid and base derivative forms, but the acid derivative
form often offers advantages of solubility, tissue
20 compatibility, or delayed release in a mammalian organism
(see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24,
Elsevier, Amsterdam 1985). Prodrugs include acid
derivatives, such as, esters prepared by reaction of the
parent acidic compound with a suitable alcohol, or amides
25 prepared by reaction of the parent acid compound with a
suitable amine. Simple aliphatic esters (e.g., methyl,
ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl) or
aromatic esters derived from acidic groups pendent on the
compounds of this invention are preferred prodrugs. In
30 some cases it is desirable to prepare double ester type
prodrugs such as (acyloxy) alkyl esters or
((alkoxycarbonyl)oxy)alkyl esters. Preferred esters
include morpholinoethoxy and
diethylaminocarbonylmethoxy.

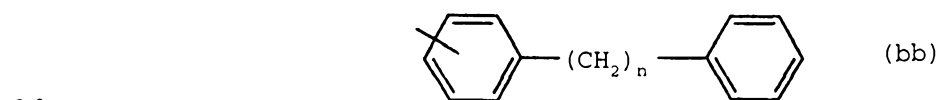
Preferred Compounds of the Invention

Preferred Subgroups of Compounds of Formula (III):

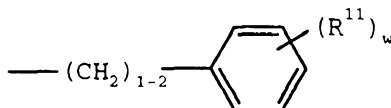
Another preferred subclass of compounds of formula
 5 (III) are those wherein R^{21} is selected from the group hydrogen, halo, $-(C_1-C_3)$ alkyl, $-(C_3-C_4)$ cycloalkyl, $-(C_3-C_4)$ cycloalkenyl, $-O(C_1-C_2)$ alkyl and $-S(C_1-C_2)$ alkyl.

Another preferred subclass of compounds of formula
 10 (III) are those wherein for $R^{2'}$, $-(L)-$ is an alkyl chain of 1 or 2 carbon atoms.

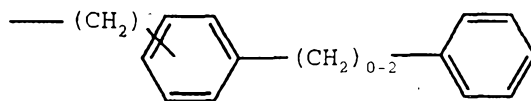
Another preferred subclass of compounds of formula
 (III) are those wherein for R^{20} , group R_{80} is selected
 from the group consisting of cycloalkyl, cycloalkenyl,
 phenyl, naphthyl, norbornanyl, bicycloheptadienyl,
 15 tolulyl, xylenyl, indenyl, stilbenyl, terphenyl,
 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl,
 and anthracenyl, biphenyl, bibenzyl and related
 bibenzyl homologues represented by the formula (bb),



where n is a number from 1 to 8. Particularly preferred are
 compounds wherein R^{20} is selected from the group consisting
 of



and



25

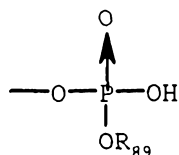
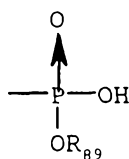
where R^{11} is a radical independently selected from halo,
 $-(C_1-C_{10})$ alkyl, $-(C_1-C_{10})$ alkoxy, $-S-(C_1-C_{10})$ alkyl, and
 $-(C_1-C_{10})$ haloalkyl, and w is a number from 0 to 5.

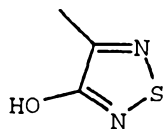
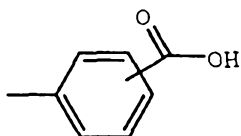
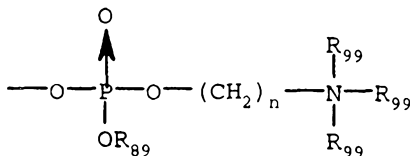
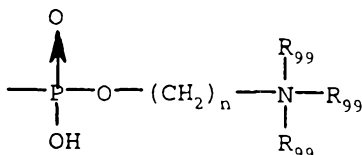
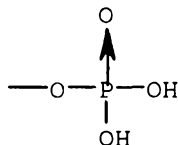
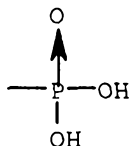
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Another preferred subclass of compounds of formula (III) are those wherein R^{2'} is a substituent having an acid linker with an acid linker length of 2 or 3. Most preferred are compounds where the acidic group is selected from

10

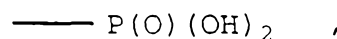
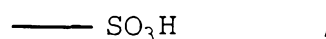
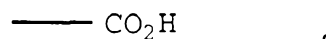
-CO₂H
-5-tetrazolyl,
-SO₃H,





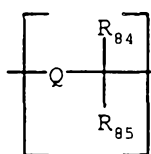
where n is 1 to 8, R₈₉ is a metal or -(C₁-C₁₀)alkyl, and R₉₉ is hydrogen or -(C₁-C₁₀)alkyl. Particularly preferred
 5 are compounds wherein the acidic group of R^{2'} is selected from;

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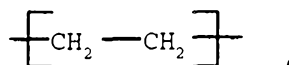
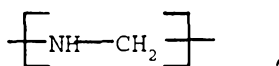
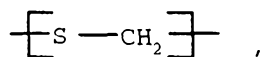
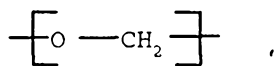
or salt, and prodrug (e.g., ester) derivatives thereof.

Another preferred subclass of compounds of formula
 5 (III) are those wherein $R^{2'}$ is a substituent having an acid linker with an acid linker length of 2 or 3 and the acid linker group, $-(L_a)-$, for $R^{2'}$ is selected from a group represented by the formula;

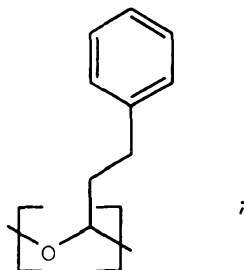
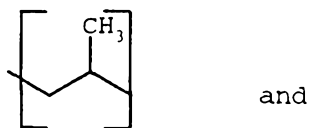


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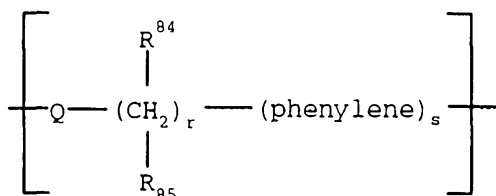
where Q is selected from the group $-(\text{CH}_2)-$, $-\text{O}-$, $-\text{NH}-$, and $-\text{S}-$, and R_{84} and R_{85} are each independently selected from hydrogen, $-(\text{C}_1\text{-C}_{10})$ alkyl, aryl, $-(\text{C}_1\text{-C}_{10})$ alkylaryl,
 15 $-\text{aryl}(\text{C}_1\text{-C}_{10})$ alkyl, carboxy, carbalkoxy, and halo. Most preferred are compounds where the acid linker, $-(L_a)-$, for $R^{2'}$ is selected from the specific groups;



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Another preferred subclass of compounds of formula (III) are those wherein $R^{2'}$ is a substituent having an acid linker with an acid linker length of 3 to 8 atoms and the acid linker group, $-(L_a)-$, for $R^{2'}$ is selected from;



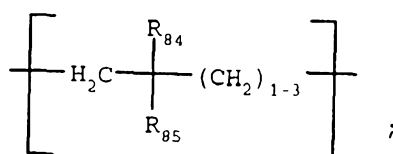
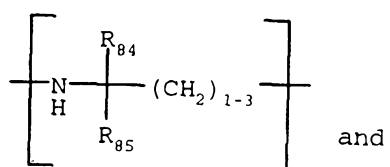
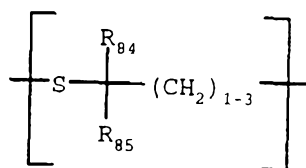
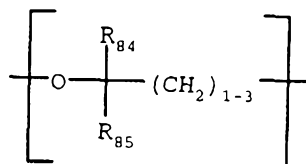
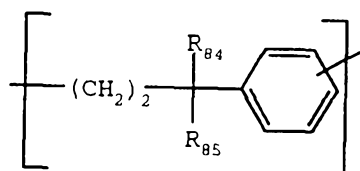
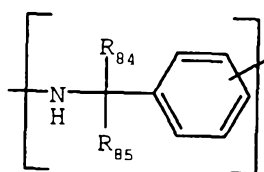
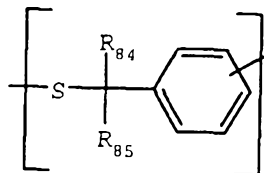
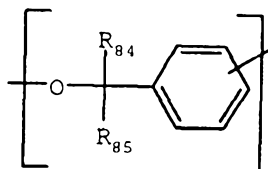
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where r is a number from 2 to 7, s is 0 or 1, and Q is selected from the group $-(\text{CH}_2)-$, $-\text{O}-$, $-\text{NH}-$, and $-\text{S}-$, and R^{84} and R^{85} are each independently selected from hydrogen, $-(\text{C}_1-\text{C}_{10})$ alkyl, aryl, $-(\text{C}_1-\text{C}_{10})$ alkylaryl,

15 $-\text{aryl}(\text{C}_1-\text{C}_{10})$ alkyl, carboxy, carbalkoxy, and halo.

Most preferred are compounds where the acid linker, $-(L_a)-$, for $R^{2'}$ is selected from the specific groups;

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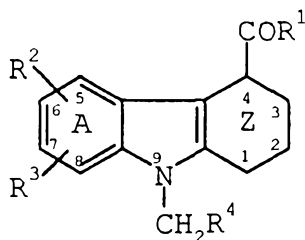
-21-

wherein R₈₄ and R₈₅ are each independently selected from hydrogen, -(C₁-C₁₀)alkyl, aryl, -(C₁-C₁₀)alkaryl, -(C₁-C₁₀)aralkyl, carboxy, carbalkoxy, and halo.

Another preferred subclass of compounds of formula
 5 (III) are those wherein R^{3'} is selected from hydrogen and non-interfering substituents, with the non-interfering substituents being selected from the group consisting of hydrogen, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl,
 10 -(C₇-C₁₂)aralkyl, -(C₇-C₁₂)alkaryl, -(C₃-C₈)cycloalkyl, -(C₃-C₈)cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, -(C₁-C₆)alkoxy, -(C₂-C₆)alkenyloxy -(C₂-C₆)alkynyloxy, -(C₁-C₁₂)alkoxyalkyl, -(C₁-C₁₂)alkoxyalkyloxy,
 15 -(C₁-C₁₂)alkylcarbonyl, -(C₁-C₁₂)alkylcarbonylamino, -(C₁-C₁₂)alkoxyamino, -(C₁-C₁₂)alkoxyaminocarbonyl, -(C₁-C₁₂)alkylamino, -(C₁-C₆)alkylthio,
 -(C₁-C₁₂)alkylthiocarbonyl, -(C₁-C₆)alkylsulfinyl, -(C₁-C₆)alkylsulfonyl, -(C₁-C₆)haloalkoxy,
 -(C₁-C₆)haloalkylsulfonyl, -(C₁-C₆)haloalkyl,
 -(C₁-C₆)hydroxyalkyl, -C(O)O(C₁-C₆ alkyl), -(CH₂)_nO(C₁-C₆
 20 alkyl), benzyloxy, halo, phenylthio, -(CH₂)_nCN, -(CH₂)_nNR⁹R¹⁰, where R⁹ and R¹⁰ are independently -(C₁-C₄)alkyl or -phenyl(C₁-C₄)alkyl, -(CONHSO₂R), -CHO, amino, amidino, carbamyl, carboxyl, carbalkoxy, -(CH₂)_nCO₂H, cyano, cyanoguanidiny, guanidino, hydrazide, hydrazino,
 25 hydrazido, hydroxy, hydroxyamino, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, and -(C₁-C₆)alkylcarbonyl; where n is from 1 to 8.

Preferred compounds of the invention are those having the general formula (II)

30



(II)

wherein:

R¹ is -NHNH₂, or -NH₂;

5 R² is -OH, or -O(CH₂)_mR⁵ where

R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl),



(R⁶R⁷), -NHSO₂(C₁-C₆)alkyl,

-CONHSO₂(C₁-C₆)alkyl, -CN, tetrazolyl, phenyl,

10 or phenyl substituted with -CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are each independently -OH or -O(C₁-C₄ alkyl) and m is 1-3;

R³ is H, -O(C₁-C₄ alkyl), or -(CH₂)_nR⁸ where



R⁸ is H, -NR⁹R¹⁰, -C^{||}NH₂, -CN, or phenyl where

15 R⁹ and R¹⁰ are independently -(C₁-C₄)alkyl, or -phenyl(C₁-C₄)alkyl and n is 1-8;

R⁴ is H, -(C₅-C₁₄)alkyl, -(C₃-C₁₄)cycloalkyl, phenyl,

or phenyl substituted with 1 or 2 substituents selected from the group consisting of

20 -(C₁-C₄)alkyl, -(C₁-C₄)alkoxy, -phenyl(C₁-C₄)alkyl, -(C₁-C₄)alkylthio, halo or phenyl; and

Z is cyclohexenyl, phenyl, pyridyl wherein the nitrogen is at the 1-, 2- or 3-position or a 6-membered heterocyclic ring having one heteroatom selected from the group consisting of sulfur or oxygen at the 1-, 2- or 3-position and nitrogen at the 1-, 2-, 3- or 4-position, or wherein one carbon on the heterocyclic ring is optionally substituted with =O

30 A is phenyl or pyridyl wherein the nitrogen is at the 5-, 6-, 7- or 8-position;

or a pharmaceutically acceptable salt, racemate, solvate, tautomer, optical isomer or prodrug derivative thereof;

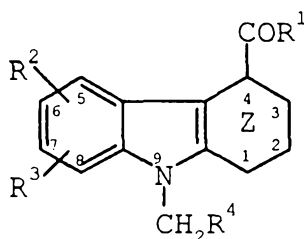
-23-

provided that when R^3 is H, R^4 is phenyl, m is 1 or 2 and R^2 is substituted at the 6 position, R^5 cannot be H; and

when R^1 is NHNH_2 , R^8 cannot be $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{NH}_2$.

5

Another preferred group are compounds of the formula (I)



(I)

10

wherein:

R^1 is -NHNH_2 , or -NH_2 ;

R^2 is -OH , or $\text{-O(CH}_2\text{)}_m\text{R}^5$ where

R^5 is H, $\text{-CO}_2\text{H}$, $\text{-CO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$,

15 $\text{-}\overset{\text{O}}{\parallel}\text{P}(\text{R}^6\text{R}^7)$, phenyl, or phenyl substituted with $\text{-CO}_2\text{H}$ or $\text{-CO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$ where R^6 and R^7 are each independently -OH or $\text{-O(C}_1\text{-C}_4 \text{ alkyl)}$ and m is 1-3;

R^3 is H, $\text{-O(C}_1\text{-C}_4 \text{ alkyl)}$, or $\text{-(CH}_2\text{)}_n\text{R}^8$ where

20 R^8 is H, $\text{-NR}^9\text{R}^{10}$, $\text{-}\overset{\text{O}}{\parallel}\text{C}\text{NH}_2$, -CN , or phenyl where R^9 and R^{10} are independently $\text{-(C}_1\text{-C}_4\text{)alkyl}$, or $\text{-phenyl(C}_1\text{-C}_4\text{)alkyl}$ and n is 1-8;

25 R^4 is H, $\text{-(C}_5\text{-C}_{14}\text{)alkyl}$, $\text{-(C}_3\text{-C}_{14}\text{)cycloalkyl}$, phenyl, or phenyl substituted with 1 or 2 substituents selected from the group consisting of $\text{-(C}_1\text{-C}_4\text{)alkyl}$, $\text{-(C}_1\text{-C}_4\text{)alkoxy}$,

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-phenyl(C₁-C₄)alkyl, -(C₁-C₄)alkylthio, halo or phenyl; and

Z is cyclohexenyl or phenyl;

or a pharmaceutically acceptable salt, racemate,
5 optical isomer, solvate, tautomer or prodrug derivative thereof;

provided that when R³ is H, R⁴ is phenyl, m is 1 or 2 and R² is substituted at the 6 position, R⁵ cannot be H; and

10 when R¹ is NHNH₂, R⁸ cannot be $\overset{\text{O}}{\parallel}{\text{C}}\text{NH}_2$.

Preferred substituents of compounds of formula I and II include the following:

- 15 (a) R¹ is -NH₂, -NHNH₂;
 (b) R¹ is -NH₂;
 (c) R² is -O(CH₂)_mR⁵ where R⁵ is -H, -CO₂H or $\overset{\text{O}}{\parallel}{\text{P}}(\text{R}^6\text{R}^7)$, where R⁶ and R⁷ are -OH;
- 20 (d) R² is -OH;
 (e) R² is -O(CH₂)_mR⁵ where R⁵ is -H, -CO₂(C₁-C₄ alkyl), phenyl or phenyl substituted with -CO₂H or -CO₂(C₁-C₄ alkyl);
- 25 (f) R² is -O(CH₂)_mR⁵ where R⁵ is $\overset{\text{O}}{\parallel}{\text{P}}(\text{R}^6\text{R}^7)$ and R⁶ and R⁷ are -O(C₁-C₄ alkyl), or when one of R⁶ and R⁷ is -O(C₁-C₄ alkyl), the other is -OH;
 (g) R³ is -H, -O(C₁-C₄ alkyl) or -(CH₂)_nR⁸ where n = 2 and R⁸ is H or phenyl;
 (h) R³ is H, or -O(C₁-C₄ alkyl);
- 30 (i) R³ is -(CH₂)_nR⁸ where R⁸ is -NR⁹R¹⁰, $\overset{\text{O}}{\parallel}{\text{C}}\text{NH}_2$ or -CN where R⁹ and R¹⁰ are -(C₁-C₄)alkyl;

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- (j) R⁴ is phenyl;
- (k) R⁴ is phenyl substituted at the 2- and 6-position of the phenyl ring with -(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo or phenyl;
- 5 (l) R⁴ is phenyl substituted at the 2- or 6-position of the phenyl ring with -(C₁-C₄)alkyl, -(C₁-C₄)alkoxy, halo or phenyl;
- (m) R⁴ is phenyl substituted at the 3- or 5-position of the phenyl ring with -(C₁-C₄)alkyl,
- 10 -(C₁-C₄)alkoxy, halo or phenyl;
- (n) R⁴ is -(C₆-C₁₄)alkyl or -(C₆-C₁₄)cycloalkyl;
- (o) Z is cyclohexenyl;
- (p) R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl), $\overset{\text{O}}{\parallel}{\text{P}}(\text{R}^6\text{R}^7)$,
 -NHSO₂(C₁-C₆)alkyl, -CONHSO₂(C₁-C₆)alkyl,
 15 tetrazolyl, phenyl, or phenyl substituted with -CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are each independently -OH or -O(C₁-C₄ alkyl) and m is 1-3;
- (q) R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl), $\overset{\text{O}}{\parallel}{\text{P}}(\text{R}^6\text{R}^7)$,
 20 phenyl, or phenyl substituted with -CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are each independently -OH or -O(C₁-C₄ alkyl) and m is 1-3;
- (r) Z is cyclohexenyl, phenyl, pyridyl wherein the
 25 nitrogen is at the 1-, 2- or 3-position or a 6-membered heterocyclic ring having one heteroatom selected from the group consisting of sulfur or oxygen at the 1-, 2- or 3-position and nitrogen at the 1-, 2-, 3- or 4-position wherein
 30 one carbon on the heterocyclic ring is
 optionally substituted with $\overset{\text{O}}{\parallel}{\text{C}}$
- (s) Z is cyclohexenyl or phenyl; or a pharmaceutically acceptable salt, racemate or

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optical isomer thereof; provided that when R³ is H, R⁴ is phenyl, m is 1 or 2 and R² is substituted at the 6 position, R⁵ cannot be H;

and when R¹ is NHNH₂, R⁸ cannot be $\overset{\text{O}}{\parallel}{\text{C}}\text{NH}_2$.

- 5 (t) A is phenyl; and
 (u) A is pyridyl wherein the nitrogen is at the 5-, 6-, 7- or 8-position.

Further typical examples of compounds of formula I which are useful in the present invention include:

- 10 5-hydroxy-7-(5-cyanopentyl)-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 6-(2-carboxyethoxy)-8-methoxy-9-cyclopentylmethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 15 5-(3-phenylpropoxy)-7-ethoxy-9-butyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 6-(2-phosphonoethoxy)-8-phenylhexyl-9-(cyclotetradecyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 20 5-ethoxycarbonylmethoxy-8-(5-carbamoylpent-1-yl)-9-(3,5-dipropylphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 6-(diethoxyphosphonyl)methoxy-9-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-
 25 carboxamide;
 6-(3-(4-carboxyphenyl)prop-1-yl)oxy-8-heptyl-9-(3-phenylethyl)phenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 6-(2-propoxycarbonyl)ethoxy-8-(3-(N,N-
 30 dimethylamino)prop-1-yl)-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
 5-(di-t-butoxyphosphonyl)methoxy-7-nonyl-9-(3-propylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;

- 5-(2-(3-methoxycarbonyl)phenyl)ethoxy-7-pentyl-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 6-hydroxy-8-(4-(N,N-diethylamino)but-1-yl)-9-(3-fluorophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 5 6-(2-phenylethoxy)-9-(2-phenylphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- (S)-6-((3-carboxy)prop-1-yl)oxy-8-propoxy-9-(7-cyanohept-1-yl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 10 5-(propoxycarbonyl)methoxy-9-cyclopentylmethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- (S)-5-(2-ethoxyphosphonyl)ethoxy-(4-carbamoyl)but-1-yl-9-(3-methylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 15 5-(3-(ethoxycarbonyl)prop-1-yl)oxy-7-propoxy-9-(cyclononyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 5-(3-phosphonoprop-1-yl)oxy-8-heptyl-9-(4-chlorophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 20 6-methoxycarbonylmethoxy-7-(5-cyanopent-1-yl)-9-tridecylmethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- (S)-6-propoxycarbonylmethoxy-9-(3-isopropyl-5-methoxy)phenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 25 (S)-6-dimethoxyphosphonoethoxy-8-(6-(N,N-dimethylamino)hex-1-yl)-9-(3,5-dimethoxyphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide;
- 5-hydroxy-7-(5-cyanopentyl)-9-methylcarbazole-4-carboxamide;
- 30 6-(2-carboxyethoxy)-8-methoxy-9-cyclopentylmethylcarbazole-4-carboxamide;
- 5-(3-phenylprop-1-yl)oxy-7-ethoxy-9-butylcarbazole-4-carboxamide;
- 35 6-(2-phosphonoethoxy)-8-phenylhexyl-9-(cyclotetradecyl)methylcarbazole-4-carboxamide;

- 5-ethoxycarbonylmethoxy-8-(5-carbamoylpent-1-yl)-9-(3,5-dipropylphenyl)methylcarbazole-4-carboxamide;
6-(diethoxyphosphonyl)methoxy-9-(4-methoxyphenyl)methylcarbazole-4-carboxamide;
- 5 6-(3-(4-carboxyphenyl)prop-1-yl)oxy-8-heptyl-9-(3-phenylethyl)phenyl)methylcarbazole-4-carboxamide;
6-(2-propoxycarbonyl)ethoxy-8-(3-(N,N-dimethylamino)prop-1-yl)-9-methylcarbazole-4-carboxamide;
- 10 5-((di-t-butoxyphosphonyl)methoxy-7-nonyl-9-(3-propylthiophenyl)methylcarbazole-4-carboxamide;
(S)-5-(2-(3-methoxycarbonyl)phenyl)ethoxy-7-pentyl-9-methylcarbazole-4-carboxamide;
(S)-6-hydroxy-8-(4-(N,N-diethylamino)but-1-yl)-9-(3-fluorophenyl)methylcarbazole-4-carboxamide;
- 15 (S)-6-(2-phenylethoxy)-9-((2-phenyl)phenyl)methylcarbazole-4-carboxamide;
6-((3-carboxy)prop-1-yl)oxy-8-propoxy-9-(7-cyanohept-1-yl)-carbazole-4-carboxamide;
- 20 5-(propoxycarbonyl)methoxy-9-cyclopentylmethylcarbazole-4-carboxamide;
5-(2-ethoxyphosphonyl)ethoxy-(4-carbamoyl)but-1-yl-9-(3-methylthiophenyl)methylcarbazole-4-carboxamide;
- 25 5-((3-ethoxycarbonyl)prop-1-yl)oxy-7-propoxy-9-(cyclononyl)methylcarbazole-4-carboxamide;
(S)-5-(3-phosphonoprop-1-yl)oxy-8-heptyl-9-(4-chlorophenyl)methylcarbazole-4-carboxamide;
- (S)-6-methoxycarbonylmethoxy-7-(5-cyanopent-1-yl)-9-tridecylmethylcarbazole-4-carboxamide;
- 30 6-(propoxycarbonyl)methoxy-9-(3-isopropyl-5-methoxy)phenyl)methylcarbazole-4-carboxamide;
6-dimethoxyphosphonoethoxy-8-(6-(N,N-dimethylamino)hex-1-yl)-9-(3,5-dimethoxyphenyl)methylcarbazole-4-carboxamide;
- 35 5-hydroxy-7-(5-cyanopentyl)-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
6-(2-carboxyethoxy-8-methoxy-9-cyclopentyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

5-(3-phenylprop-1-yl)oxy-7-ethoxy-9-butyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

6-(2-phosphonoethoxy)-8-phenylhexyl-9-(cyclotetradecyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

5-ethoxycarbonylmethoxy-8-(5-carbamoylpent-1-yl)-9-(3,5-dipropylphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

(S)-6-(diethoxyphosphonyl)methoxy-9-(4-methoxyphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

6-(3-(4-carboxyphenyl)prop-1-yl)oxy-8-heptyl-9-(3-phenylethyl)phenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

(S)-6-(2-propoxycarbonyl)ethoxy-8-(3-(N,N-dimethylamino)prop-1-yl)-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

5-(di-t-butoxyphosphonyl)methoxy-7-nonyl-9-(3-propylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

(S)-5-(2-(3-methoxycarbonyl)phenyl)ethoxy-7-pentyl-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

6-hydroxy-8-(4-(N,N-diethylamino)but-1-yl)-9-(3-fluorophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

(S)-6-(2-phenylethoxy)-9-(2-phenylphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

6-((3-carboxy)prop-1-yl)oxy-8-propoxy-9-(7-cyanohept-1-yl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

5-(propoxycarbonyl)methoxy-9-cyclopentylmethyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

5-(2-ethoxyphosphonyl)ethoxy-(4-carbamoyl)but-1-yl-9-(3-methylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;

- 5-((3-(ethoxycarbonyl)prop-1-yl)oxy-7-propoxy-9-(cyclononyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
- 5 5-(3-phosphonoprop-1-yl)oxy-8-heptyl-9-(4-chlorophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
- 6-methoxycarbonylmethoxy-7-(5-cyanopent-1-yl)-9-tridecyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
- 10 6-propoxycarbonylmethoxy-9-(3-isopropyl-5-methoxyphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
- 6-dimethoxyphosphonoethoxy-8-(6-(N,N-dimethylamino)hex-1-yl-9-(3,5-dimethoxyphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide;
- 15 5-hydroxy-7-(5-cyanopentyl)-9-methylcarbazole-4-carboxylic acid hydrazide;
- 6-(2-carboxyethyloxy)-8-methoxy-9-cyclopentylmethylcarbazole-4-carboxylic acid hydrazide;
- 20 5-(3-phenylprop-1-yl)oxy-7-ethoxy-9-butylcarbazole-4-carboxylic acid hydrazide;
- 6-(2-phosphonoethoxy-8-phenylhexyl-9-(cyclotetradecyl)methylcarbazole-4-carboxylic acid hydrazide;
- 25 5-ethoxycarbonylmethoxy-8-(5-carbamoylpent-1-yl)-9-(3,5-dipropylphenyl)methylcarbazole-4-carboxylic acid hydrazide;
- 6-(diethoxyphosphonyl)methoxy-9-(4-methoxyphenyl)methylcarbazole-4-carboxylic acid hydrazide;
- 30 6-(3-(4-carboxyphenyl)prop-1-yl)oxy-8-heptyl-9-(3-phenylethyl)phenyl)methylcarbazole-4-carboxylic acid hydrazide;
- 6-(2-propoxycarbonyl)ethoxy-8-(3-(N,N-dimethylamino)prop-1-yl)-9-methylcarbazole-4-carboxylic acid hydrazide;
- 35

5-(di-t-butoxyphosphonyl)methoxy-7-nonyl-9-(3-propylthiophenyl)methylcarbazole-4-carboxylic acid hydrazide;

5 5-(2-(3-methoxycarbonyl)phenyl)ethoxy-7-pentyl-9-methylcarbazole-4-carboxylic acid hydrazide;

6-hydroxy-8-(4-(N,N-diethylamino)but-1-yl)-9-(3-fluorophenyl)methylcarbazole-4-carboxylic acid hydrazide;

6-(2-phenylethoxy)-9-(2-phenylphenyl)methylcarbazole-4-carboxylic acid hydrazide;

10 6-((3-carboxy)prop-1-yl)oxy-8-propoxy-9-(7-cyanohept-1-yl)-carbazole-4-carboxylic acid hydrazide;

(S)-5-(propoxycarbonyl)methoxy-9-cyclopentylmethylcarbazole-4-carboxylic acid hydrazide;

15 5-(2-ethoxyphosphonyl)ethoxy-(4-carbamoyl)but-1-yl-9-(3-methylthiophenyl)methylcarbazole-4-carboxylic acid hydrazide;

(S)-5-(3-(ethoxycarbonyl)prop-1-yl)oxy-7-propoxy-9-(cyclononyl)methylcarbazole-4-carboxylic acid hydrazide;

20 5-(3-phosphonoprop-1-yl)oxy-8-heptyl-9-(4-chlorophenyl)methylcarbazole-4-carboxylic acid hydrazide;

6-methoxycarbonylmethoxy-7-(5-cyanopent-1-yl)-9-tridecylcarbazole-4-carboxylic acid hydrazide;

25 6-propoxycarbonylmethoxy-9-((3-isopropyl-5-methoxy)phenyl)methylcarbazole-4-carboxylic acid hydrazide;

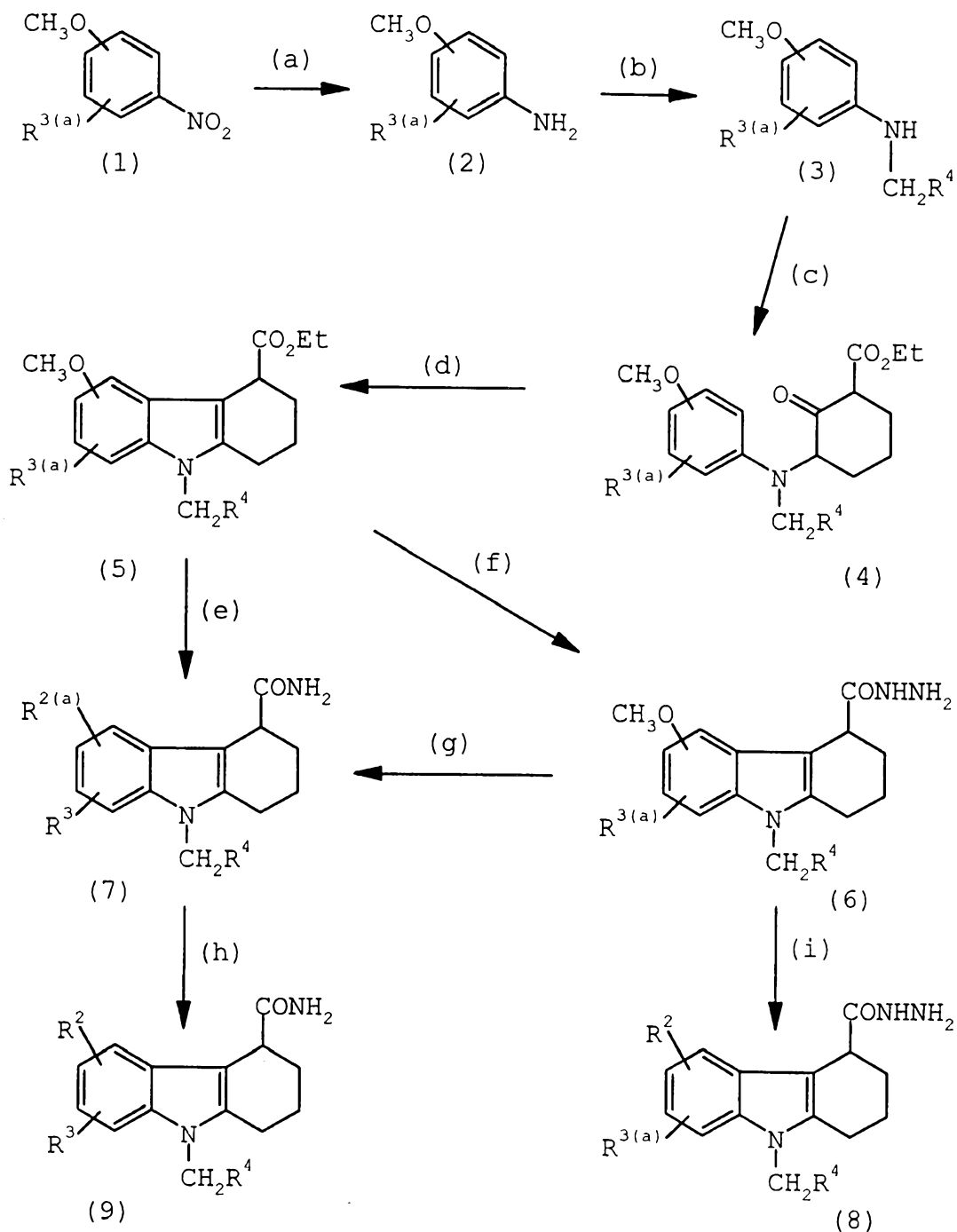
(S)-6-dimethoxyphosphonoethoxy-8-(6-(N,N-dimethylamino)hex-1-yl)-9-(3,5-dimethoxyphenyl)methylcarbazole-4-carboxylic acid hydrazide.

30

Synthesis Methods

The compounds of formula I where Z is cyclohexene are prepared according to the following reaction Schemes I(a) and (c).

Scheme I (a)



5

When R^1 is $-NH_2$, $R^{3(a)}$ is H, $-O(C1-C4 \text{ alkyl})$ or $-(CH_2)_nR^8$
 where R^8 is H, $-NR^9R^{10}$, $-CN$, $-\overset{O}{\parallel}C(O(C1-C4 \text{ alkyl}) \text{ or phenyl})$

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where R^9 and R^{10} are independently $-(C_1-C_4)$ alkyl or $-(C_1-C_4)$ alkylphenyl and n is 1-8 when R^1 is $-NH_2$; when R^1 is $-NHNH_2$, $R^{3(a)}$ is H, $-O(C_1-C_4)$ alkyl or $(CH_2)_nR^8$ where R^8 is H, NR^9R^{10} , $-CN$ or phenyl
 5 where R^9 and R^{10} are independently $-(C_1-C_4)$ alkyl or $-(C_1-C_4)$ alkylphenyl and n is 1-8;
 $R^{2(a)}$ is $-OCH_3$ or $-OH$.

An appropriately substituted aldehyde is treated with
 10 Wittig reagent to prepare the appropriately substituted nitrobenzene (1) which can be reduced to the aniline (2) by treatment with a reducing agent, such as hydrogen in the presence of Pd/C, preferably at room temperature.

Compound (2) is N-alkylated at temperatures of from
 15 about 0 to 20°C using an alkylating agent such as an appropriately substituted aldehyde and sodium cyanoborohydride to form (3). Alternately, an appropriately substituted benzyl halide may be used for the first alkylation step. The resulting intermediate is
 20 further N-alkylated by treatment with 2-carbethoxy-6-bromocyclohexanone, preferably at temperatures of about 80°C to yield (4).

The product (4) is cyclized to the tetrahydrocarbazole (5) by refluxing with $ZnCl_2$ in
 25 benzene for from about 1 to 2 days, preferably at 80°C. (Ref 1). Compound (5) is converted to the hydrazide (6) by treatment with hydrazine at temperatures of about 100°C, or to the amide (7) by reacting with methylchloroaluminum amide in benzene. (Ref 2)
 30 Alternatively, (7) may be produced by treatment of (6) with Raney nickel active catalyst.

It will be readily appreciated that when $R^{3(a)}$ is

$$-(CH_2)_n \overset{\overset{O}{\parallel}}{C} O(C_1-C_4 \text{ alkyl}),$$
 conversion to the amide will also be achieved in this procedure.

Compounds (6) and (7) may be dealkylated, preferably at 0°C to room temperature, with a dealkylating agent, such as boron tribromide or sodium thioethoxide, to give compound (7) where R^{2(a)} is -OH, which may then be further
5 converted to compound (9), by realkylating with a base, such as sodium hydride, and an alkylating agent, such as Br(CH₂)_mR⁵, where R⁵ is the carboxylate or phosphonic diester or nitrile as defined above. Conversion of R² to the carboxylic acid may be accomplished by treatment with
10 an aqueous base. When R² is nitrile, conversion to the tetrazole may be achieved by reacting with tri-butyl tin azide. When R² is the phosphonic diester, conversion to the acid may be achieved by reacting with a dealkylating agent such as trimethylsilyl bromide. The monoester may
15 be accomplished by reacting the diester with an aqueous base.

When R² and R³ are both methoxy, selective demethylation can be achieved by treating with sodium ethanethiolate in dimethylformamide at 100°C.

20

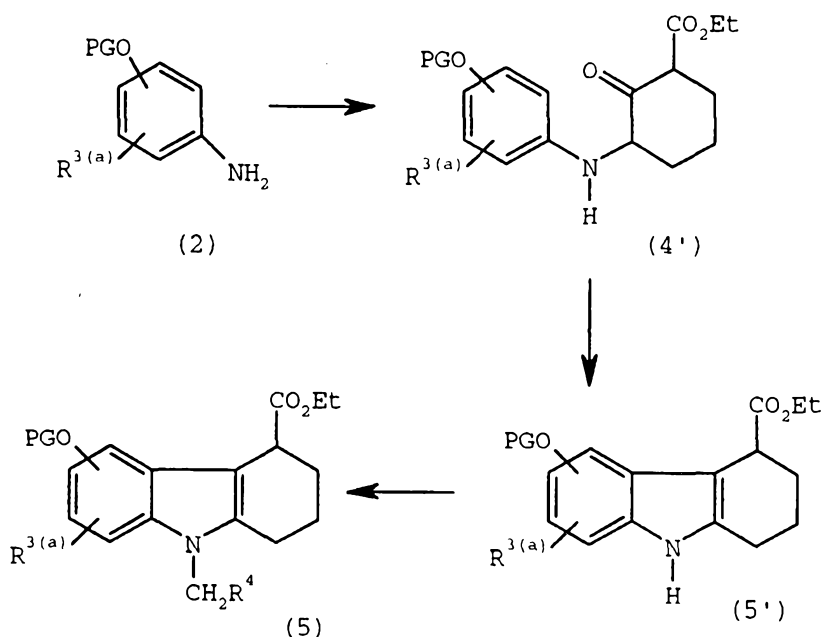
Ref 1 Julia, M.; Lenzi, J. Preparation d'acides tetrahydro-1,2,3,4-carbazole-1 ou -4. *Bull.Soc.Chim.France*, **1962**, 2262-2263.

25 Ref 2 Levin, J.I.; Turos, E.; Weinreb, S.M. An alternative procedure for the aluminum-mediated conversion of esters to amides. *Syn.Comm.*, **1982**, 12, 989-993.

30 An alternative synthesis of intermediate (5) is shown in Scheme I(b), as follows.

-35-

Scheme I (b)



5

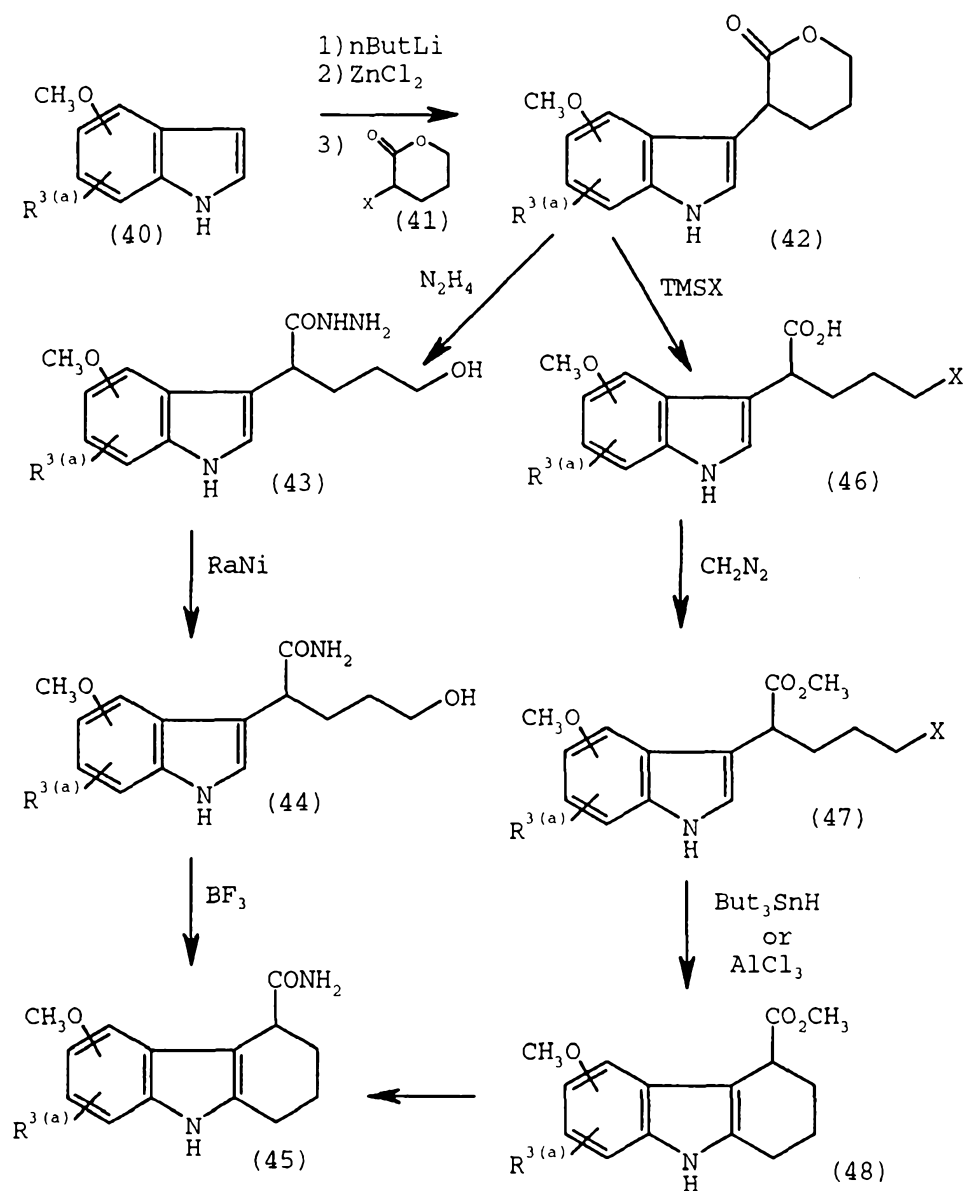
PG is a protecting group

R^{3a} is as defined in Scheme 1, above.

The aniline (2) is N-alkylated with 2-carbethoxy-6-bromocyclohexanone in dimethyl formamide in the presence of sodium bicarbonate for 8-24 hours at 50°C. Preferred protecting groups include methyl, carbonate, and silyl groups, such as t-butyldimethylsilyl. The reaction product (4') is cyclized to (5') using the ZnCl₂ in benzene conditions described in Scheme I(a), above. N-alkylation of (5') to yield (5) is accomplished by treatment with sodium hydride and the appropriate alkyl halide in dimethylformamide at room temperature for 4-8 hours.

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Scheme I (c)



5

X is halo

 $\text{R}^3(\text{a})$ is as defined in Scheme I (a)

The zinc salt of α -methoxyindole (40) is alkylated by α -bromovalerolactone (41) to give (42) which are ring opened to (46) by trimethylsilyl halides to give the omega-haloacids (47) which are esterified and then cyclized to the

-37-

tetrahydrocarbazoles (48) by Lewis acids (eg. aluminum chloride) or radical initiators (eg. tributyltin hydride).

Alternatively, (42) can be ring opened by hydrazine to give hydrazides (43) which are cleaved to amides (44)
5 by Raney nickel catalyst and cyclized by acids to the tetrahydrocarbazoles (45).

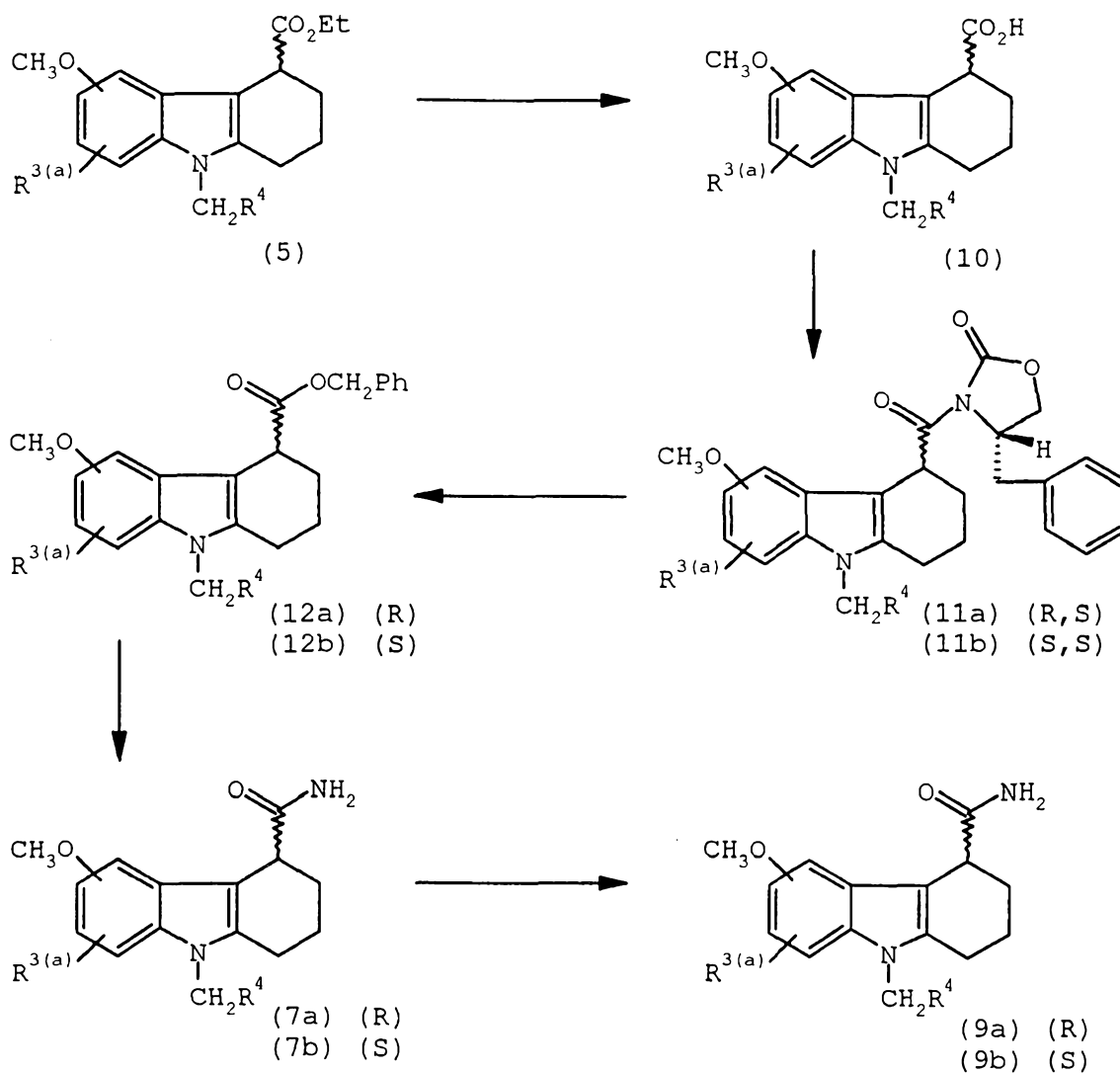
N-alkylation is accomplished by treatment with sodium hydride and the appropriate alkyl halide, XCH_2R^4 , in diethylformamide as described above.

10 Tetrahydro derivatives may be dehydrogenation with palladium on carbon in refluxing carbitol as described below to prepare the desired carbazoles (see Scheme III(a)).

Racemates of the compounds of formula I may be
15 converted to their respective enantiomers as described in Scheme II below.

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Scheme II



5

$\text{R}^{3(a)}$ is as defined in Scheme I.

As discussed in Scheme I above, carbazole (5) is hydrolyzed to the carboxylic acid (10) by treatment with an aqueous base, preferably at room temperature to about 100°C. The intermediate is then converted to an acid chloride utilizing, for example, oxalyl chloride and dimethylformamide, and then further reacted with a lithium salt of (S) or (R)-4-alkyl-2-oxazolidine at a temperature of about -75°C, to give (11a) and (11b), which are separable by chromatography.

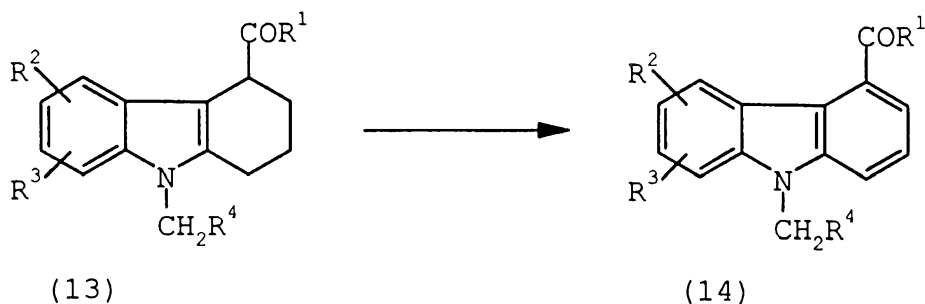
The diastereomers are converted to the corresponding enantiomeric benzyl esters (12) by brief treatment at temperatures of about 0°C to room temperature with lithium benzyl oxide. (Ref 3) The esters (12) are then converted
5 to (7) preferably by treatment with methylchloroaluminum amide (Ref 2, above) or, alternately, by hydrogenation using, for example, hydrogen and palladium on carbon, as described above, to make the acid and then reacting with
10 by treatment with ammonia. Using the procedure described above in Scheme I, compound (9a) or (9b) may be accomplished.

Ref 3 Evans, D.A.; Ennis, M.D.; Mathre, D.J. Asymmetric
15 alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of *alpha*-substituted carboxylic acid derivatives. *J.Am.Chem.Soc.*, **1982**, 104, 1737-1738.

20 Compounds of formula I where Z is phenyl can be prepared as follows in Schemes III(a) - (d), below.

-40-

Scheme III (a)



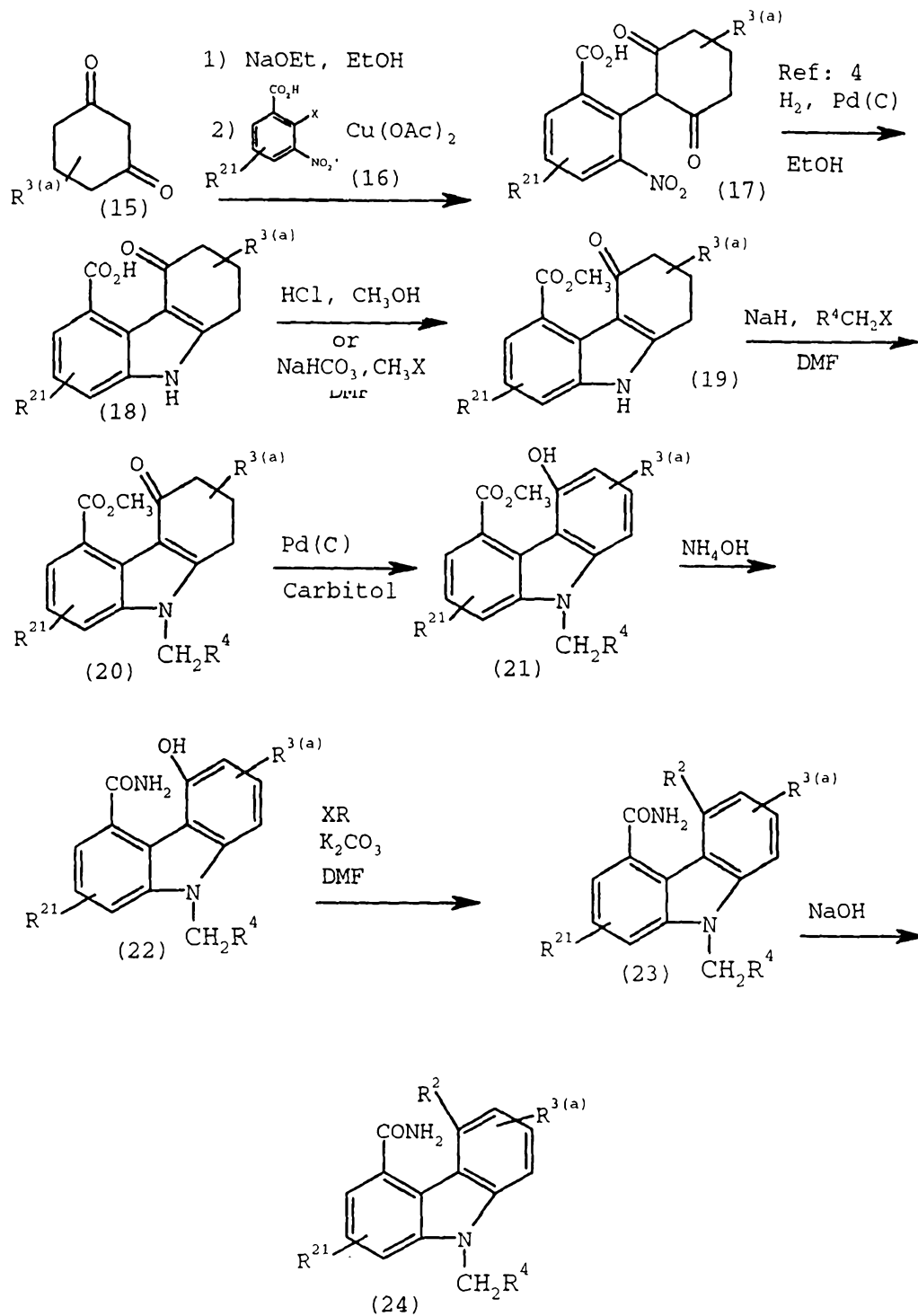
5 A 1,2,3,4-tetrahydrocarbazole-4-carboxamide or 4-carboxhydrazide (13) is dehydrogenated by refluxing in a solvent such as carbitol in the presence of Pd/C to produce the carbazole-4-carboxamide.

10 The intermediates and final products may be isolated and purified by conventional techniques, for example by concentration of the solvents, followed by washing of the residue with water, then purification by conventional techniques, such as chromatography or recrystallization.

15 It will be readily appreciated by the skilled artisan that the starting materials are either commercially available or can be readily prepared by known techniques from commercially available starting materials. All other reactants used to prepare the compounds in the instant invention are commercially available.

20

Scheme III(b)



5

$R^{3(a)}$ is as defined in Scheme I(a), above;
 R is $-(\text{CH}_2)_m\text{R}^5$; and
 X is halo.

The Dione (15) and benzoic acid derivative (16) are condensed according to the general procedure of Ames and Ribiero (Ref 1), in a noninterfering solvent, preferably ethanol, in the presence of a base, preferably sodium ethoxide, and a copper salt, preferably copper (II) acetate to afford the coupled product (17). Other solvents, such as methanol, propanol, isopropanol, t-butanol, and the like can be used. Other bases, such as the potassium, sodium, and lithium salts of the corresponding alcoholic solvents can also be used.

Reduction of the nitro group with a reducing agent, such as hydrogen in the presence of palladium on carbon, in a noninterfering solvent, such as ethanol, at 1 to 60 atmospheres, at a temperature of 0 to 60°C affords the cyclized product (18) (Ref 1). The acid (18) is converted to the methyl ester (19) by treatment with methanol in the presence of an acid, such as hydrochloric acid. Alternately, the acid (18) can be converted to the ester (19) by treatment with methyl iodide in the presence of a base, such as potassium carbonate or sodium carbonate, in an inert solvent, such as dimethylformamide or dimethylsulfoxide.

Compound (19) is N-alkylated with an appropriately substituted halide in the presence of a base, such as sodium hydride or potassium carbonate, in a noninterfering solvent, such as dimethylformamide or dimethylsulfoxide to afford ketone (20).

Ketone (20) is dehydrogenated by treatment with palladium on carbon in a noninterfering solvent, such as carbitol or cymene, to produce the phenolic derivative (21).

Ester (21) is converted to the corresponding amide (22) under standard conditions with ammonia or an ammonium salt, such as ammonium acetate, in an inert solvent, such as water

or alcohol, or with MeClAlNH_2 in an inert solvent, such as toluene, at a temperature between 0 to 110°C .

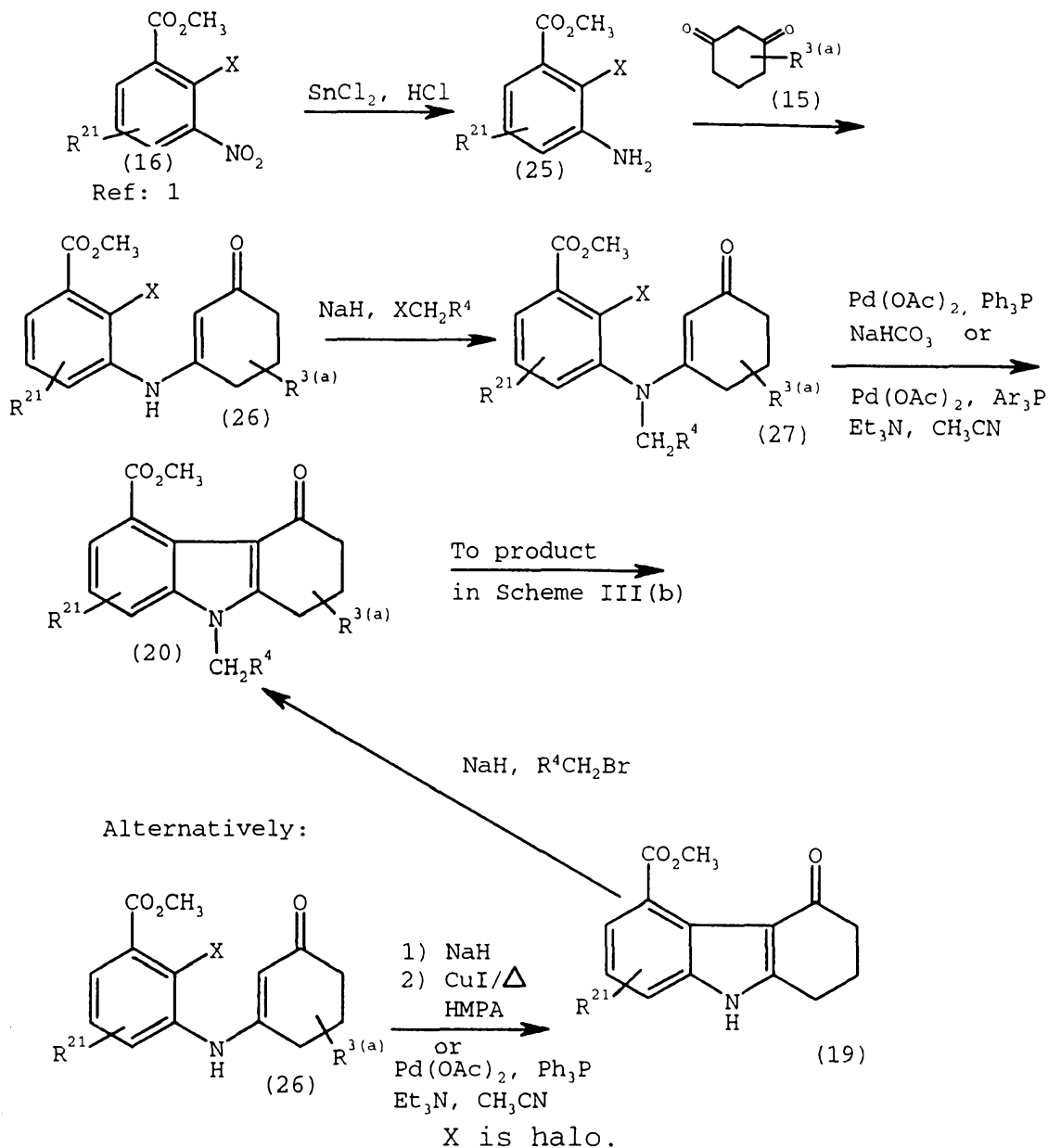
Alkylation of the phenolic oxygen of compound (22) with an appropriate haloester, such as methyl bromoacetate, in the presence of a base, such as potassium carbonate or sodium carbonate, in an inert solvent, such as dimethylformamide or dimethylsulfoxide affords the ester-amide (23). Other haloesters, such as ethyl bromoacetate, propyl bromoacetate, butyl bromoacetate, and the like can also be used to prepare the corresponding esters.

Saponification of compound (23), with sodium hydroxide in an inert solvent, such as methanol-water, affords carbazole (24). The intermediate and final products may be isolated and purified by conventional techniques such as chromatography or recrystallization. Regioisomeric products and intermediates can be separated by standard methods, such as, recrystallization or chromatography.

Reference:

4) D. E. Ames and O. Ribiero, J. Chem. Soc., Perkin Trans. I, 1073 (1976)

Scheme III(c)



5

Benzoic acid derivatives (16) (X= Cl, Br, or I), described above, are reduced to the corresponding anilines (25) with a reducing agent, such as SnCl₂ in hydrochloric acid in an inert solvent, such as ethanol.

The aniline (25) and dione (15) are condensed under dehydrating conditions, for example, using the general procedure of Iida, et al., (Ref 5), with or without a

noninterfering solvent, such as toluene, with or without a catalytic amount of an acid, such as p-toluenesulfonic acid, to afford the coupled product (26).

Compound (26) is N-alkylated with an appropriately substituted alkyl or aryl halide in the presence of a base, such as sodium hydride, in a noninterfering solvent, such as toluene, dimethylformamide, or dimethylsulfoxide to afford ketone (27).

Ketone (27) is cyclized according to the general procedure of Iida et al (Ref 5) or Kashara, et al., (Ref 6) in the presence of a palladium catalyst, such as Pd(OAc)₂, a triarylphosphine, such as tri-o-tolylphosphine, a base, such as sodium bicarbonate or triethylamine, in an inert solvent, such as acetonitrile or triethylamine to afford compound (20). Compound (20) can be processed as described in Scheme III(b) above, to the carbazole product (24). Alternatively, intermediate (26) can be cyclized to compound (19) using the palladium catalyzed conditions described for the procedures to convert compound (27) to (20) above.

Alternatively, intermediate (26) can be cyclized to compound (19) using the general procedure of Osuka, et al., (Ref 7) utilizing a base, such as sodium hydride, and a copper salt, such as copper (I) iodide, in an inert solvent, such as, hexamethylphosphoric triamide. Compound (19) can be converted to product carbazole product (24) as described in Scheme III(b), above.

The intermediate and final products may be isolated and purified by conventional techniques such as chromatography or recrystallization. Regioisomeric products and intermediates can be separated by standard methods, such as, recrystallization or chromatography.

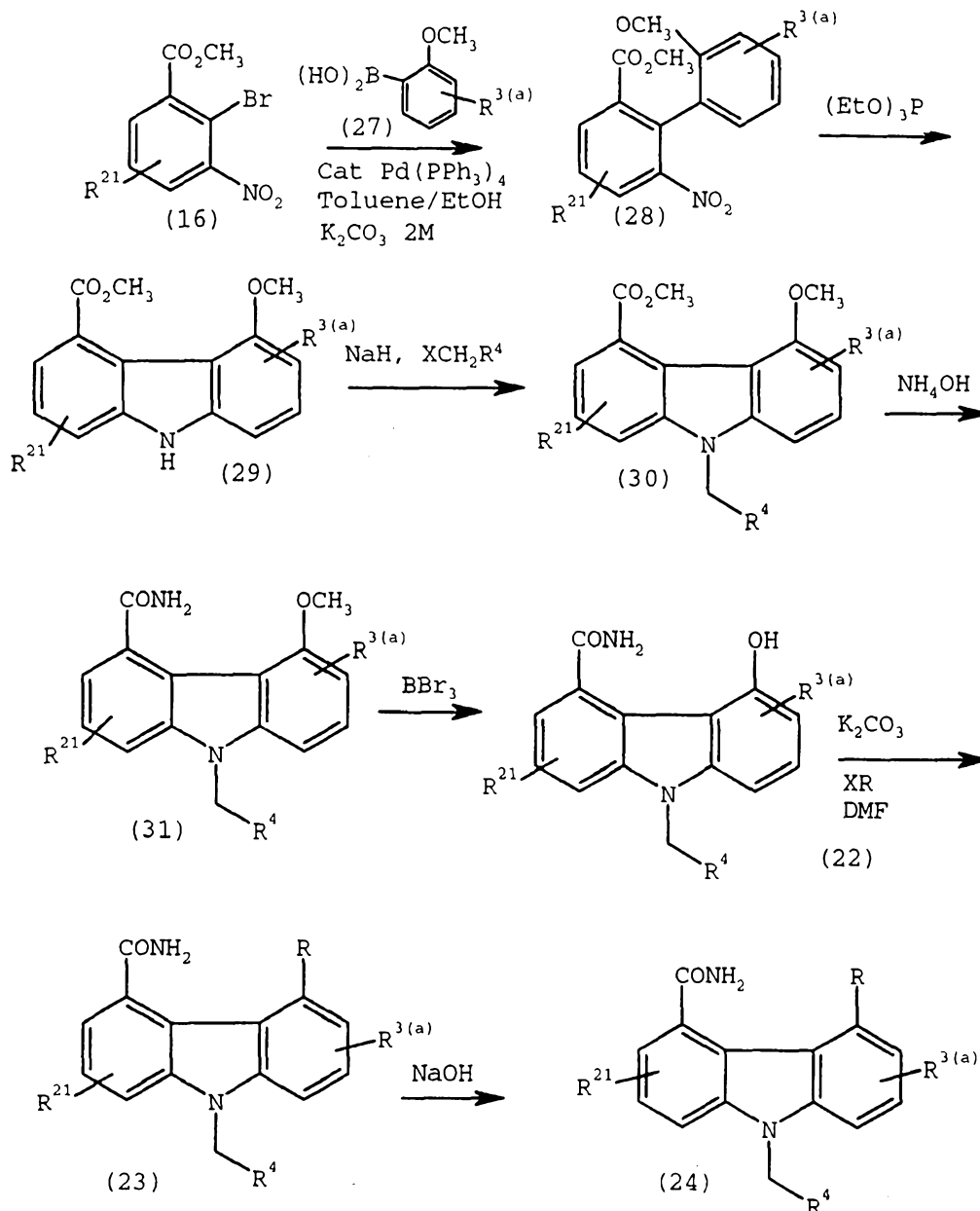
References:

- 5) H. Iida et al., J. Org. Chem., 45, 2938 (1980)
- 6) A. Kasahara et al., Bull. Chem. Soc. Jpn., 59, 927 (1986)

7) A. Osuka et al., Chemistry Letters, 2031 (1982)

Scheme III(d)

5



R is as defined in Scheme III(b),
 $\text{R}^{3(a)}$ is as defined in Scheme I(a), above; and
 X is halo.

10

Benzoic acid derivatives (16) ($\text{X} = \text{Cl, Br, or I}$) and boronic acid derivatives (27) (either commercially available or readily prepared by known techniques from

commercially available starting materials) are condensed under the general procedure of Miyaura, et al., (Ref 8a) or Trecourt, et al., (Ref 8b) in the presence of a palladium catalyst, such as $\text{Pd}(\text{Ph}_3\text{P})_4$, a base, such as sodium bicarbonate, in an inert solvent, such as toluene or ethanol, to afford compound (28).

Compound (28) is converted to the carbazole product (29) by treatment with a trialkyl phosphite or phosphine, such as, triethylphosphite or triphenyl phosphine, according to the general procedure of Cadogan, et al. (Ref 6).

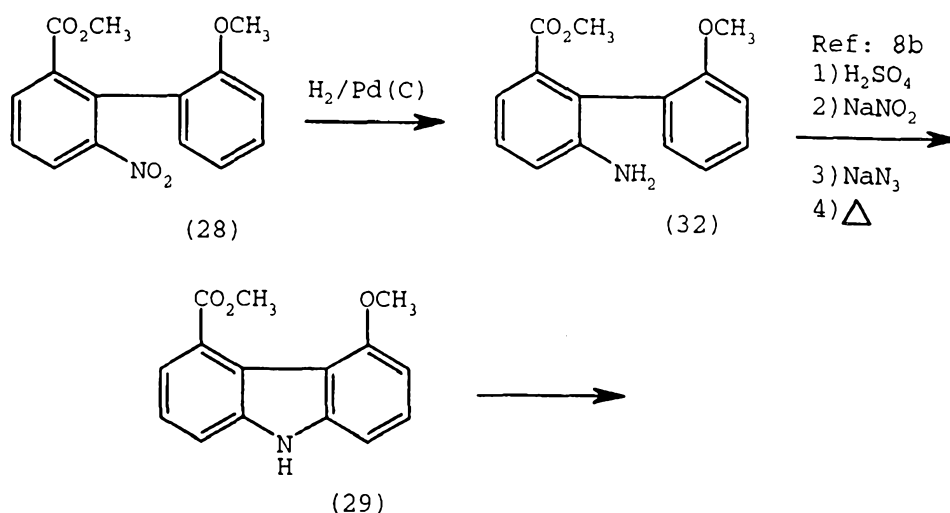
Compound (29) is N-alkylated with an appropriately substituted alkyl or aryl halide in the presence of a base, such as sodium hydride or potassium carbonate, in a noninterfering solvent, such as toluene, dimethylformamide, or dimethylsulfoxide to afford carbazole (30).

Compound (30) is converted to the corresponding amide (31) under standard conditions with ammonia or an ammonium salt, such as ammonium acetate, in an inert solvent, such as water or alcohol, or with methylchloroaluminum amide in an inert solvent, such as toluene, at a temperature between 0 to 110°C.

Compound (31) may be dealkylated with a dealkylating agent, such as boron tribromide or sodium thioethoxide, to give compound (22). Compound (22) can be converted to product carbazole product (24) as described in Scheme III(b) above.

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Scheme III(d)



Alternatively, reduction of the nitro group of compound (28) with a reducing agent, such as hydrogen in the presence of palladium on carbon, in a noninterfering solvent, such as ethanol, at 1 to 60 atmospheres, at a temperature of 0 to 60°C affords the corresponding aniline (32). Compound (32) is converted to the carbazole (29) according to the general procedure described by Trecourt, et al. (Ref 8b). The aniline is treated with sulfuric acid and sodium nitrite, followed by sodium azide to form an intermediate azide which is cyclized to carbazole (29) by heating in an inert solvent, such as toluene. Compound (29) is converted to carbazole product (24) as described previously in Scheme III(b).

References:

- 8) a. N. Miyaura, et al., Synth. Commun. 11, 513 (1981)
 b. F. Trecourt, et al., Tetrahedron, 51, 11743 (1995)
 J. Cadogan et al., J. Chem. Soc., 4831 (1965)

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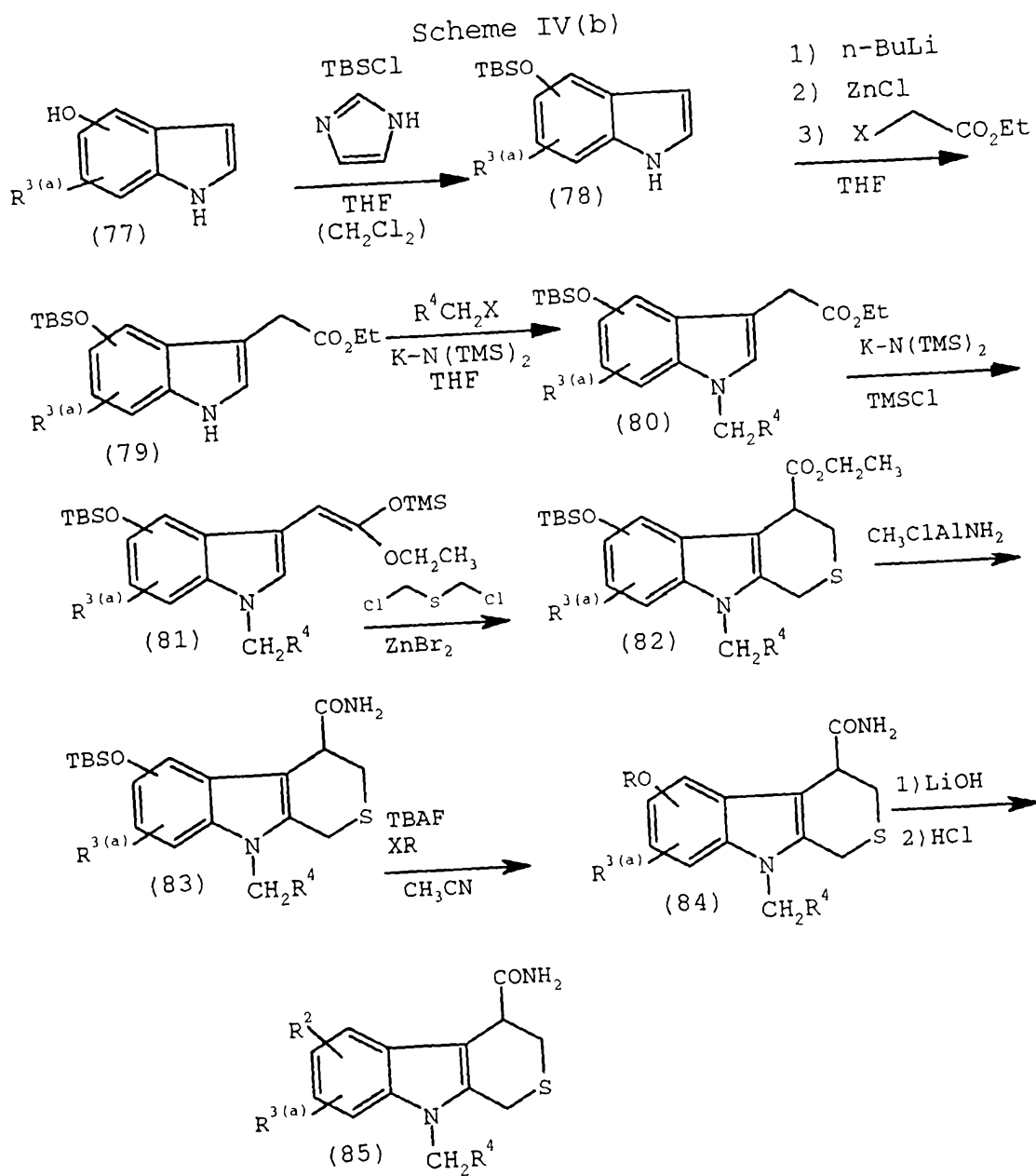
Alternately, treatment with oxalyl chloride and then ammonia may be employed to give the amide which can be used in subsequent steps as well as the ester. Compound (61) is condensed with nitromethane in the presence of a base to
5 give the nitro olefin (61) which is reduced to the amine (62) by, for example, treatment with hydrogen and palladium or carbon. Amine (62) on reaction with an appropriately substituted aldehyde and acid produces the carbolines (63).

Reaction of (60) with the methoxymethylene Wittig
10 reagent gives the enol ether (64) which is hydrolyzed to the aldehyde (65) and reduced with hydride to the alcohol (66). Reaction of this alcohol with aldehyde and acid produces the pyranoindole (69).

Conversion of the hydroxyl function of (66) to a halide
15 or sulfate functionality by treatment with triphenylphosphine and CH_3X (where X is a halogen) to make compounds of formula (67) where X is a halide; or by treatment with triethylamine and methanesulfonyl chloride to make the sulfate (67), followed by displacement with the sodium salt of thiol
20 acetic acid gives (70) which in turn is hydrolyzed by base to the thiol (71) which is reacted with an appropriately substituted aldehyde and acid to produce the thiopyranoindoles (72).

Intermediate (67) may also be reacted with sodium
25 azide to give the azido derivatives (68) which are reduced by hydrogen catalytically to give the amines (63) which are converted to the carbolines (64) as above.

Intermediates (63), (69) and (72) may be N-alkylated as described in Scheme I above, using sodium hydride and
30 an appropriately substituted alkylhalide XCH_2R^4 .



X is halo,
 R^{3(a)} is as defined in Scheme I(a); and
 R is as defined in Scheme III(b).

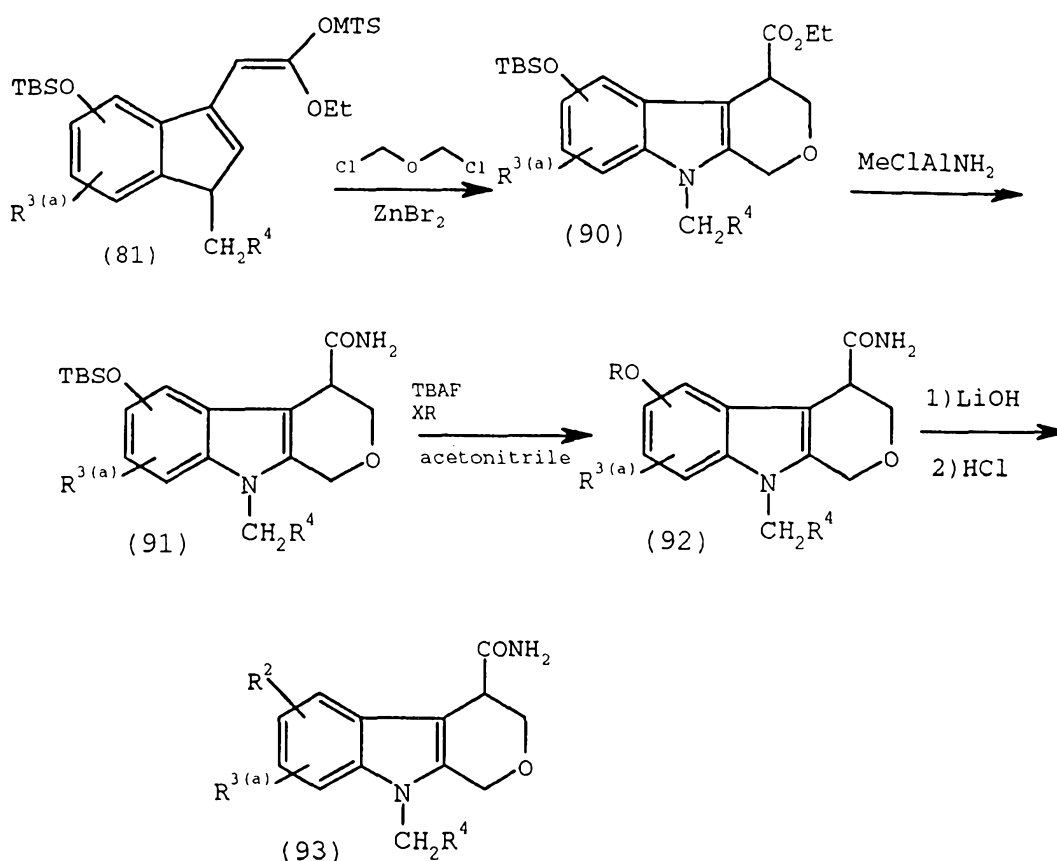
Protection of the oxygen by treatment of (77) with *tert*-butyldimethylsilyl chloride and imidazole in an aprotic polar solvent such as tetrahydrofuran or methylene chloride accomplishes (78).

5 Alkylation at the 3-position of the indole (78) is achieved by treatment with *n*-butyllithium then zinc chloride at temperatures starting at about 10°C and warming to room temperature, followed by reaction with an appropriate haloalkyl ester such as ethyl or bromo
10 acetate. The reaction is preferably conducted at room temperature in an appropriate aprotic polar solvent such as tetrahydrofuran.

Alkylation of the indole-nitrogen can then be achieved by reacting (79) with a suitable alkyl halide in
15 the presence of potassium bis(trimethylsilyl)amide to prepare (80).

The ester functionality of (80) is converted to a trimethylsilylketene acetal (81) by treatment with potassium bis(trimethylsilyl)amide and trimethylsilyl chloride.
20 Treatment of the ketene acetal (81) with bis(chloromethyl)sulfide and zinc bromide in methylene chloride affords the cyclized product (82). Conversion to amide (83) can be accomplished by a Weinreb reaction with methylchloroaluminum amide. Removal of the oxygen
25 protecting group with a fluoride source, such as TBAF, and concomitant reaction of the resulting anion with, for example, ethyl bromoacetate yields the ester (84). Deprotection of the ester yields the desired acid (85).

Scheme IV(d)

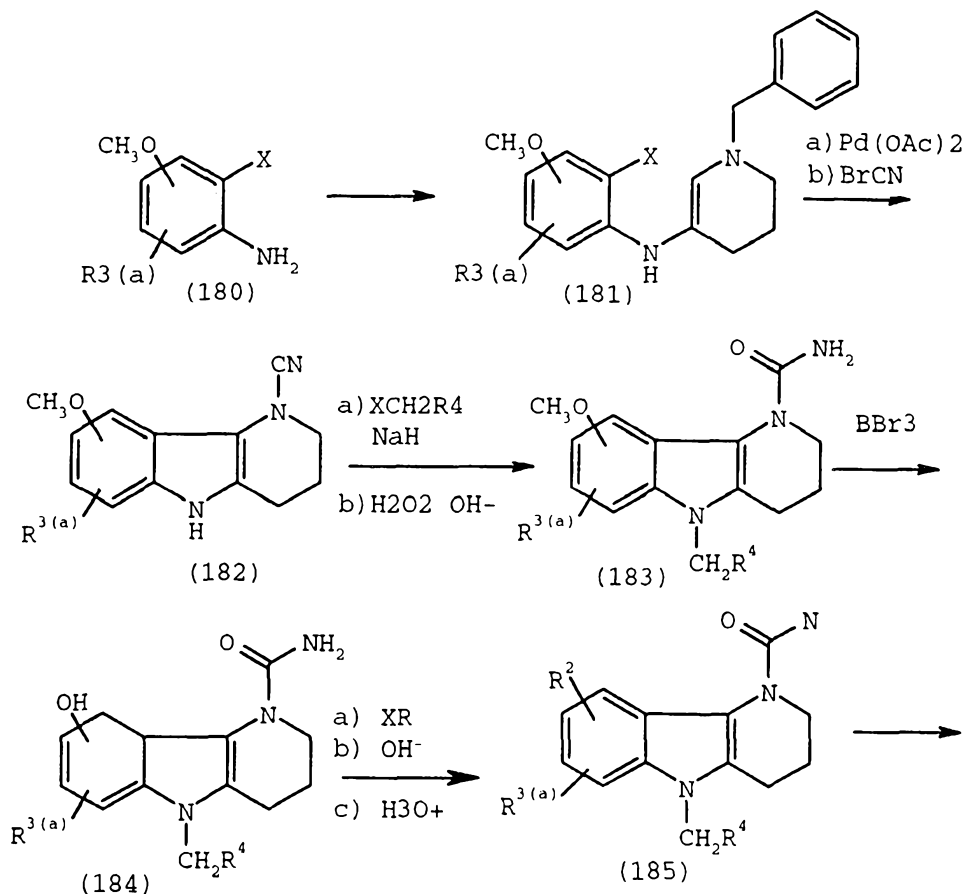


5 $R^{3(a)}$ is as described in Scheme I(a) and
 R is as described in Scheme III(b).

Treatment of the ketene acetal (81) with
 bis(chloromethyl) ether and zinc bromide in methylene
 chloride affords the cyclized product (90). Conversion to
 10 amide (91) can be accomplished by a Weinreb reaction with
 methylchloroaluminum amide. Removal of the oxygen
 protecting group with a fluoride source, such as TBAF, and
 concomitant reaction of the resulting anion with ethyl
 bromoacetate yields the ester (92). Deprotection of the
 15 ester yields the desired acid (93).

Compounds where Z is an aromatic or heterocyclic ring
 containing nitrogen can be prepared as described in
 Schemes V(a)-(e), below.

Scheme V(a)



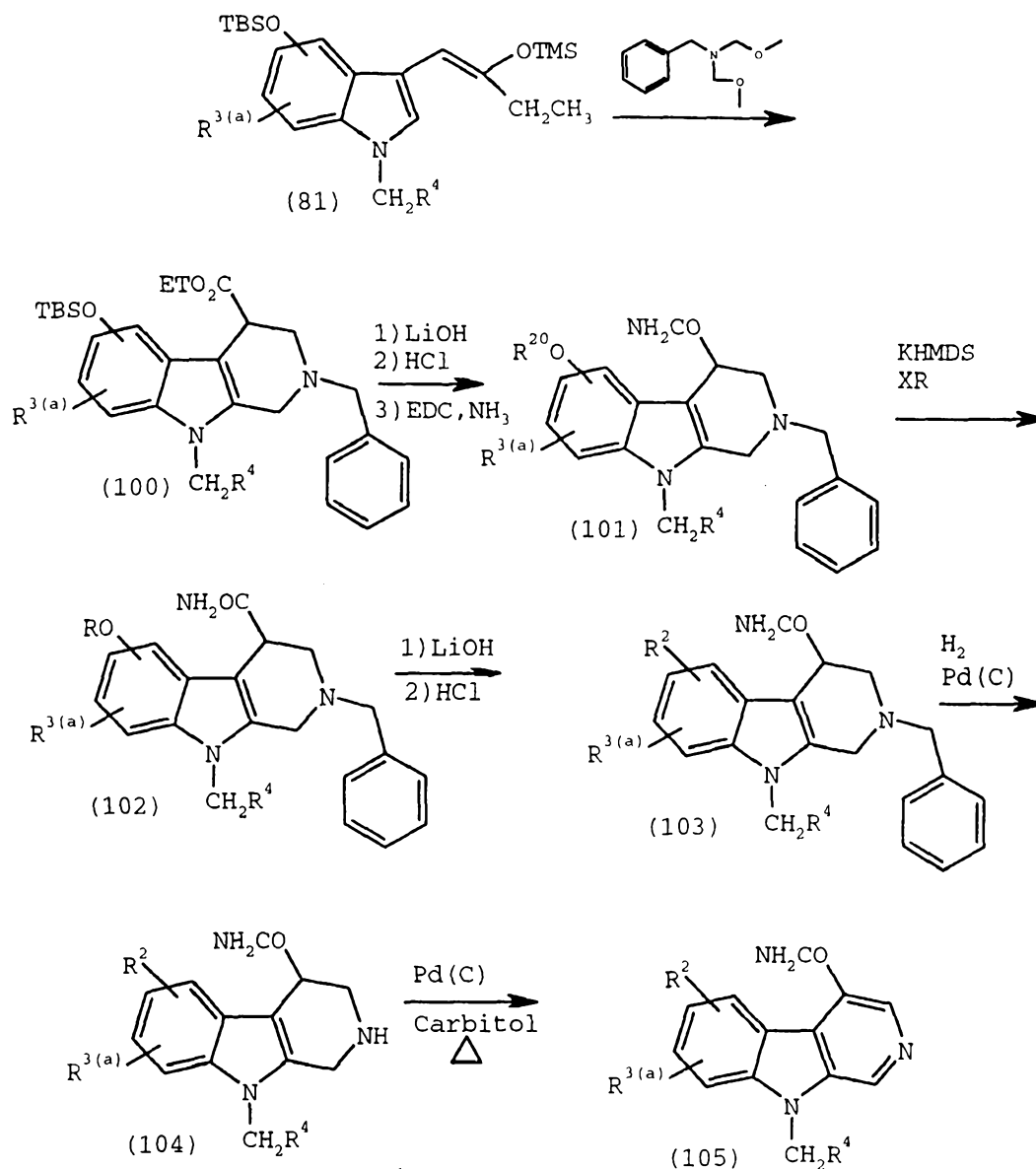
5

Substituted haloaniline (180) is condensed with N-benzyl-3-piperidone to provide enamine (181). Ring closure is effected by treatment of (181) with palladium (II) acetate and the resultant product is converted to (182) by treatment with cyanogen bromide. Alkylation of (182) is accomplished by treatment with the appropriate alkyl bromide using sodium hydride as base. Hydrolysis of this N-alkylated product with basic hydrogen peroxide under standard conditions provides (183). Demethylation of (183) is carried out by treatment with boron tribromide in methylene chloride. The resulting phenol (184) is converted by the standard sequence of O-alkylation with methyl bromoacetate in the presence of a base, hydrolysis with hydroxide to provide the

intermediate salt which is then protonated in aqueous acid to provide desired δ -carboline (185).

Scheme V(b)

5



X is halo,

R is as defined in Scheme III(b), and

$R^{3(a)}$ is as defined in Scheme I(a).

10

Ketene acetal (81), prepared as described in Scheme IV(c), is reacted with benzyl bis(methoxymethyl)amine in the

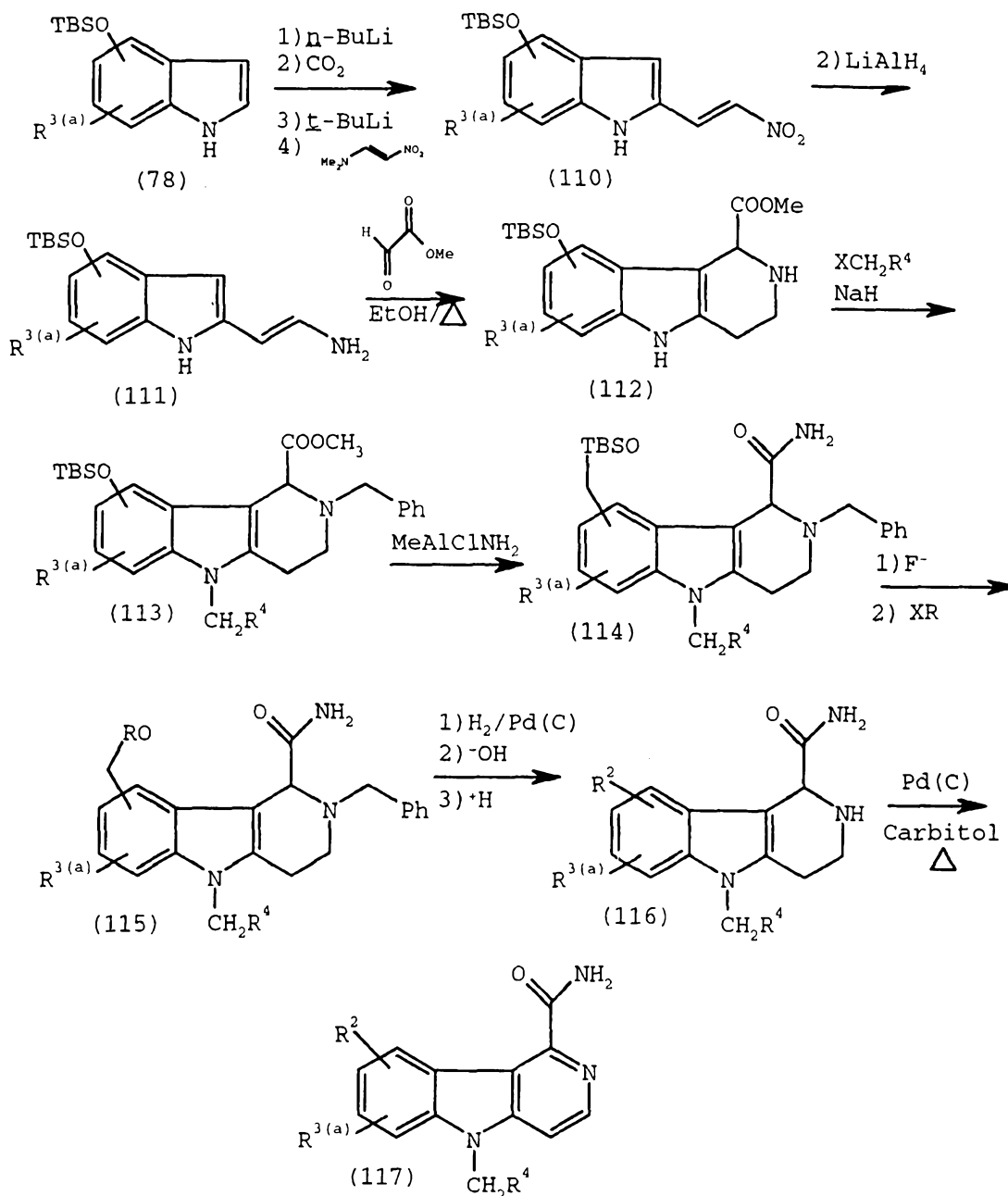
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presence of zinc chloride to give the tetrahydro-beta-carboline (100).

Treatment of (100) with lithium hydroxide, neutralization with hydrochloric acid and subsequent
5 treatment with ethylaluminum dichloride and ammonia provides the desilylated amide (101) where R^{20} is hydrogen, which can be alkylated with, for example, ethylbromoacetate to give ester (102).

Alternatively, treatment of (100) with the
10 appropriate Weinreb reagent provides amide (101) (R^{20} is t-butyldimethylsilyl) which is desilylated with tetra-n-butylammonium fluoride and alkylated with, for example, ethyl bromoacetate to give ester (102). Lithium
hydroxide-mediated hydrolysis gives acid (103), which may
15 be hydrogenated over an appropriate catalyst to give the tetrahydro-beta-carboline (104). Compound (104) may in turn be aromatized by refluxing in carbitol with palladium on carbon to provide beta-carboline (105).

Scheme V(c)



X is halo,

5

R is as defined in Scheme III(b); and

R^{3(a)} is as defined in Scheme I(a).

10 In a one-pot reaction, indole (78) is successively treated with one equivalent *n*-butyllithium, carbon dioxide gas, one equivalent of *t*-butyllithium, and 1-dimethylamino-2-nitroethene to give (110). Nitroalkene

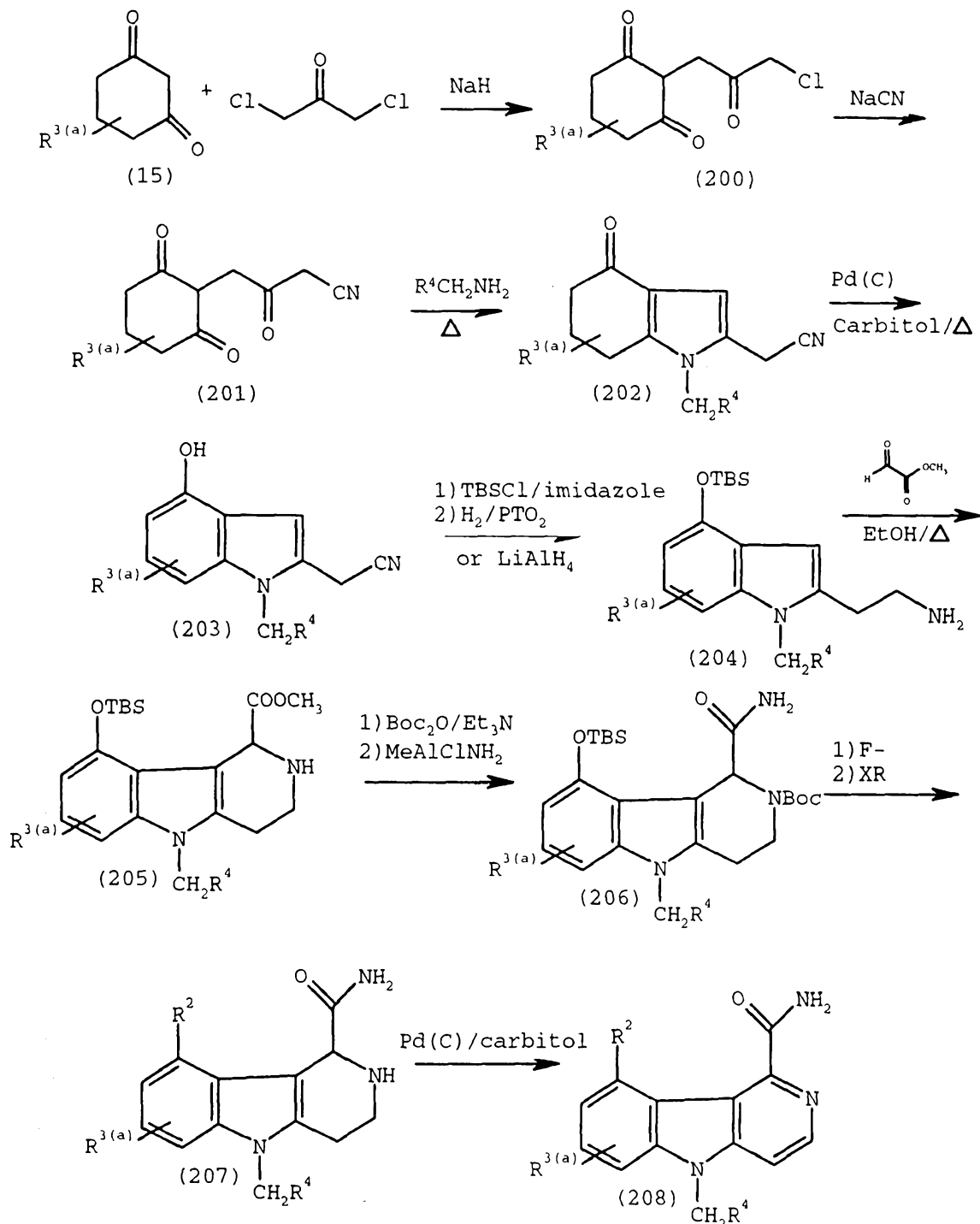
-58-

(110) is reduced with lithium aluminum hydride to amine (111), which is cyclized with methyl glyoxylate (Ref. 9) in refluxing ethanol to give tetrahydrocarboline (112). Alkylation of both nitrogens of (112) leads to
5 intermediate (113), which is treated with the appropriate Weinreb reagent to provide amide (114). Fluoride-assisted desilylation and alkylation with, for example, ethyl iodoacetate gives ester (115), which may be hydrogenated over a suitable catalyst and base-hydrolyzed to give acid
10 (116). Aromatization of (116) to carboline (117) is achieved by refluxing in carbitol in the presence of palladium-on-carbon.

Reference 9:

15 Kelley, T. R.; Schmidt, T. E.; Haggerty, J. G. A convenient preparation of methyl and ethyl glyoxylate, *Synthesis*, **1972**, 544-5.

Scheme V(d)



$\text{R}^{3(a)}$ is as defined in Scheme I(a),

X is halo, and

5

R is as defined in Scheme III(b).

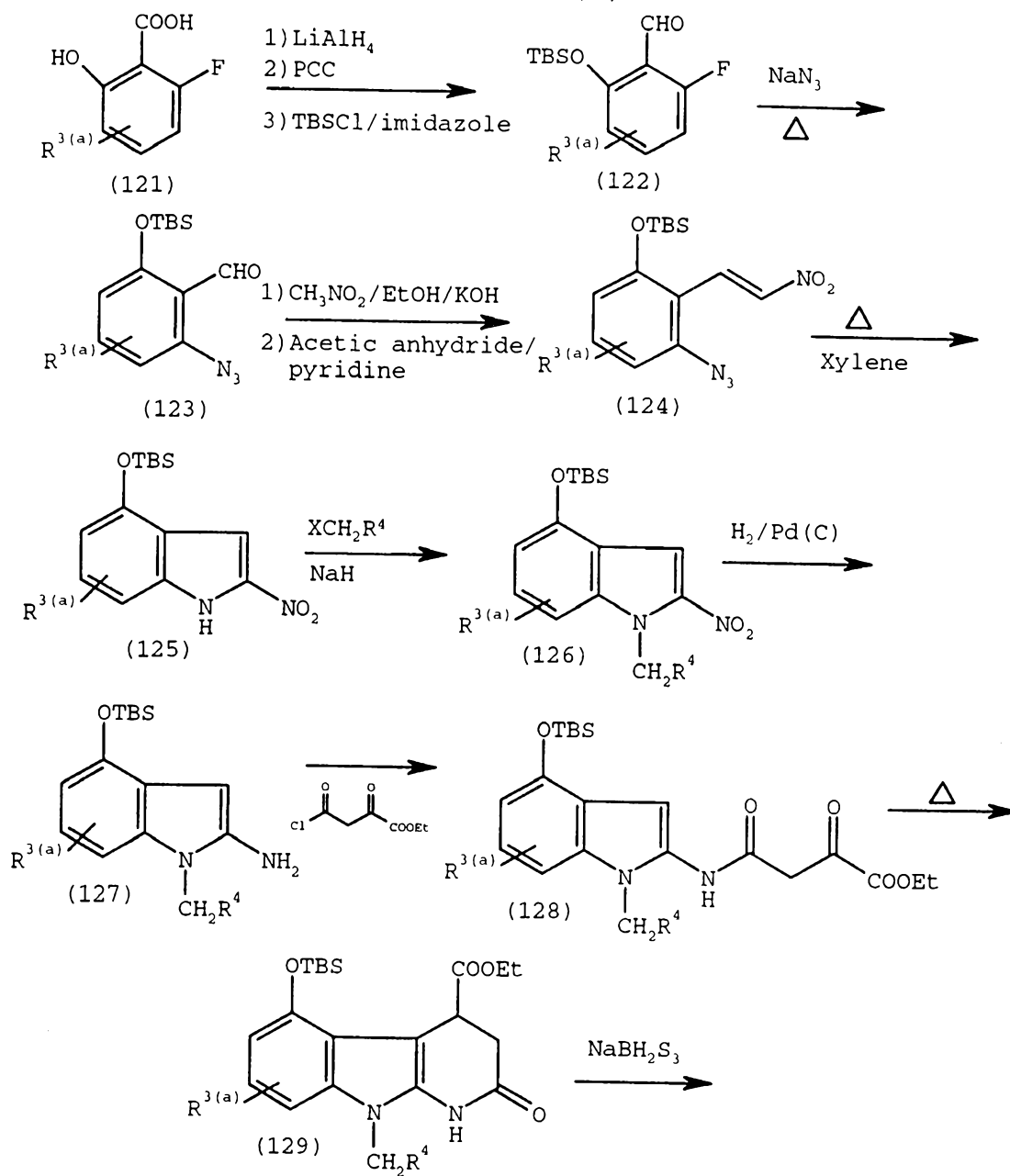
1,3-Cyclohexadione (15) is alkylated with 1,3-dichloroacetone to give chloride (200), which is reacted with sodium cyanide to provide nitrile (201). Cyclization

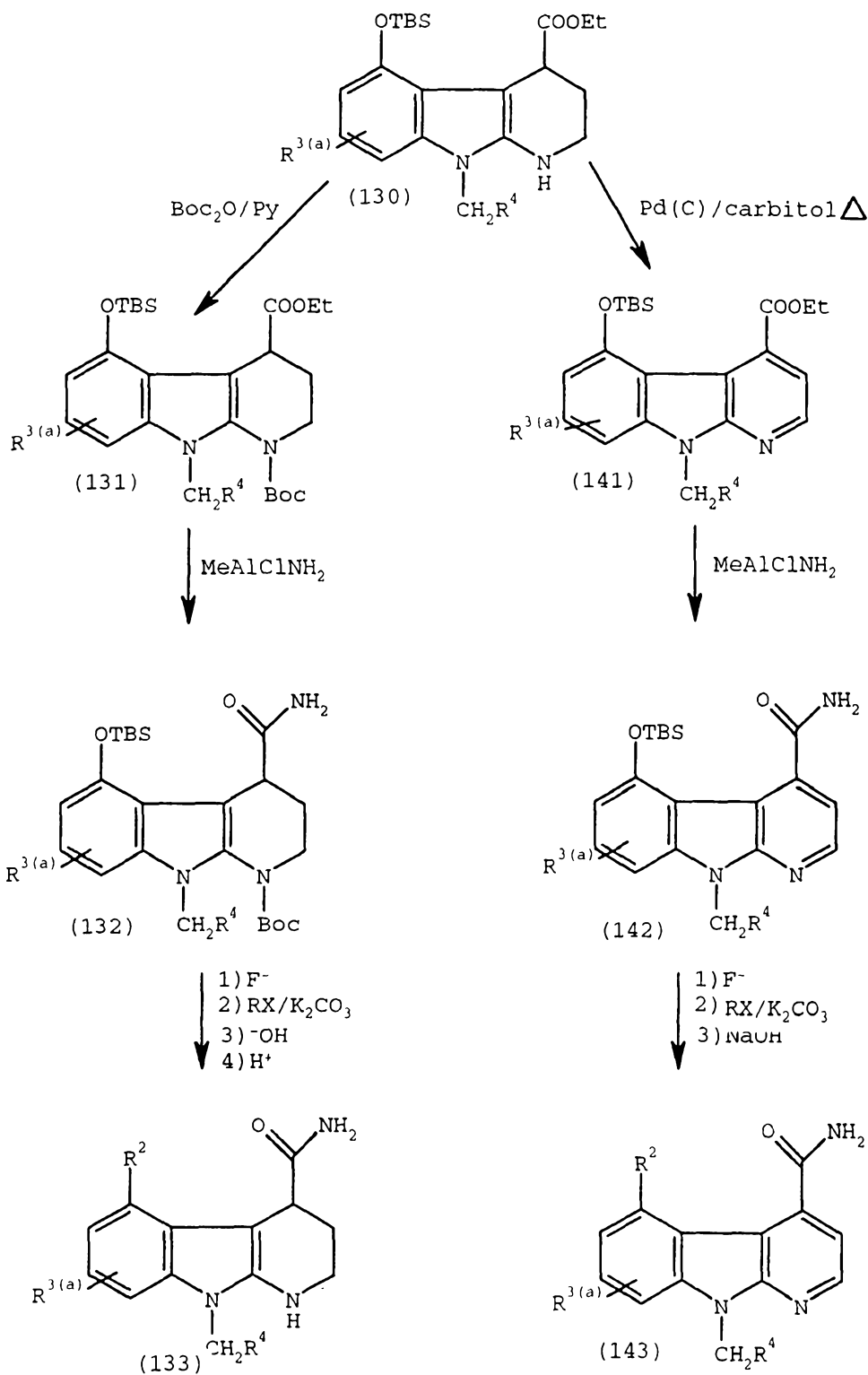
-60-

with, for example, benzyl amine gives pyrrole (202), which is then aromatized by refluxing in carbitol to produce indole (203). Protection of the phenol with t-butyldimethylsilyl chloride followed by reduction of the
5 acetonitrile side chain using lithium aluminum hydride or hydrogen with platinum oxide provides amine (204). Cyclization with methyl glyoxylate in refluxing ethanol gives tetrahydrocarboline (205), which is treated with di-t-butyl dicarbonate and triethylamine followed by the
10 appropriate Weinreb reagent to provide amide (206). Fluoride-assisted desilylation, alkylation with ethyl iodoacetate, and acid hydrolysis gives acid (207), which may be aromatized by refluxing in carbitol or some other suitable high boiling solvent to provide (208).

15

Scheme V(e)





The commercially available acid (121) is reduced with lithium aluminum hydride, oxidized with pyridinium 5 chlorochromate, and silylated with *t*-butyldimethylsilyl

chloride to give (122). Treatment with sodium azide provides azide (123), which is reacted with nitromethane and potassium hydroxide in ethanol, followed by treatment with acetic anhydride and pyridine to give nitroolefin (124).

5 Heating in xylene induces cyclization to produce indole (125). Alkylation with, for example, benzyl iodide and sodium hydride gives (126), which is hydrogenated in the presence of palladium-on-carbon to give amine (127). Acylation with the acid chloride of commercially available
10 oxalacetic acid monoethyl ester gives (128), which is thermally cyclized to lactam (129). Selective reduction of the lactam carbonyl may be accomplished by treatment with NaBH_2S_3 to provide amine (130).

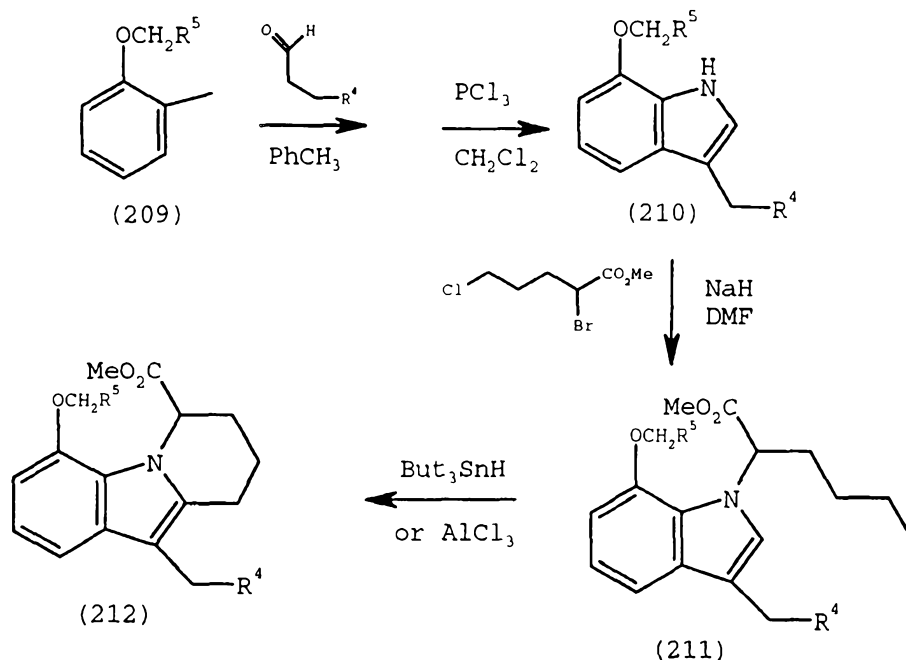
Protection of amine (130) with di-t-butyl dicarbonate
15 and pyridine produces (131), which is converted via the appropriate Weinreb reagent to amide (132). Fluoride-assisted desilylation, alkylation with, for example, ethyl iodoacetate and potassium carbonate, base hydrolysis, and acid hydrolysis produce the tetrahydro-alpha-carboline
20 (133).

Alternatively, amine (130) may be aromatized by refluxing in carbitol or some other suitable high boiling solvent to give alpha-carboline (141), which is converted via the appropriate Weinreb reagent to amide (142).
25 Fluoride-assisted desilylation, alkylation with ethyl iodoacetate and potassium carbonate, and base hydrolysis as described above provides alpha-carboline (143).

Reverse indoles, i.e., compounds where B is carbon and D is nitrogen can be prepared as described in Scheme
30 VI, below.

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Scheme VI



5

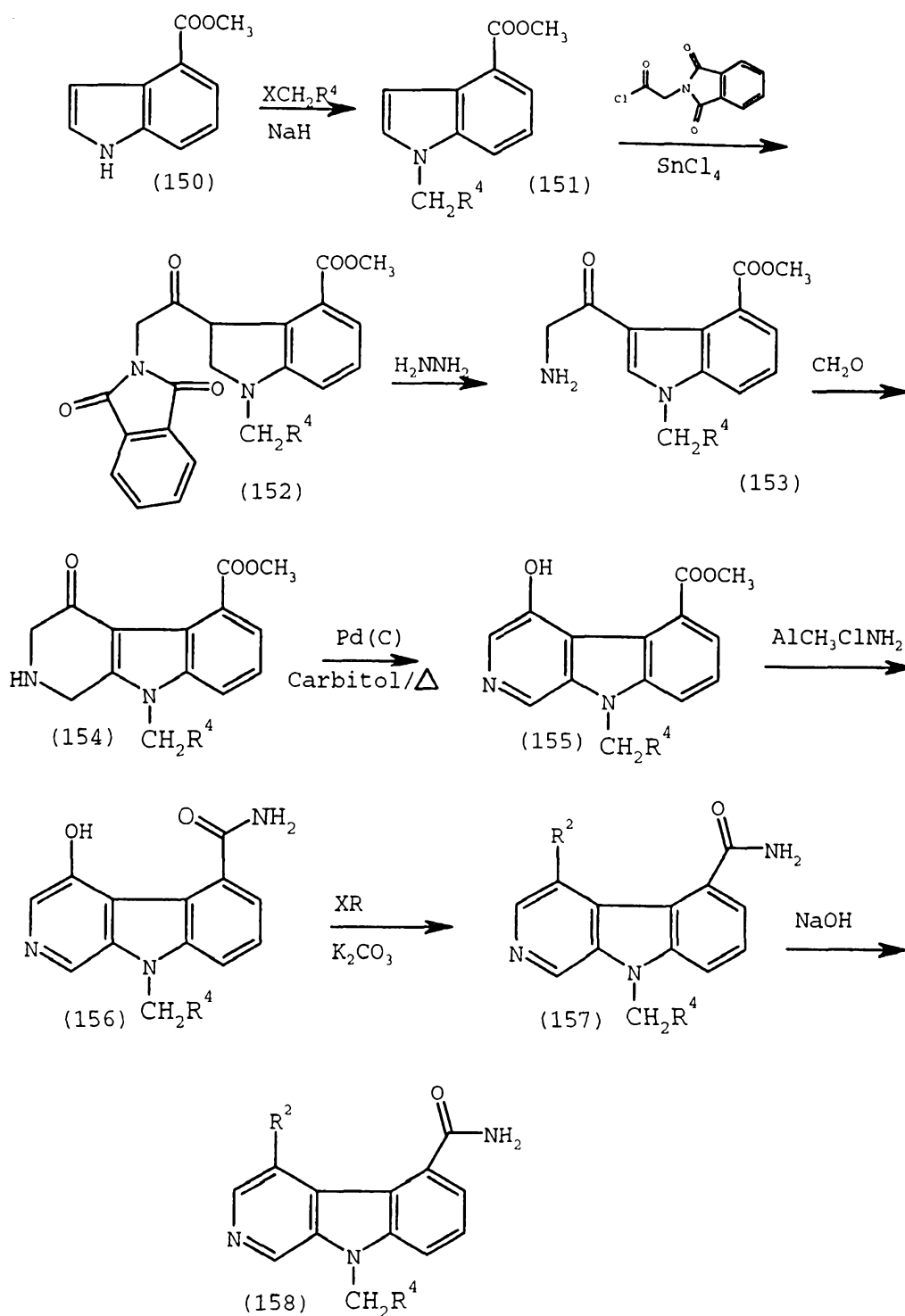
Aryl hydrazines (209) are condensed with substituted propionaldehydes to form hydrazones which are cyclized to indoles (210) by treatment with phosphorous trichloride at room temperature (Ref 1). The indoles are N-alkylated on reaction with a base such as sodium hydride and an α -bromo ester to give indoles (211) which are cyclized to tetrahydrocarbazoles (212) by Lewis acids (e.g., aluminum chloride) or by radical initiators (e.g., tributyltin hydride). Compounds (212) can be converted to carbazoles by the procedures of Scheme III.

15

Compounds of formula III wherein A is pyridyl can be prepared as described in Scheme VIII, below.

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Scheme VIII(a)



R is as defined in Scheme III(b) and X is halo.

5

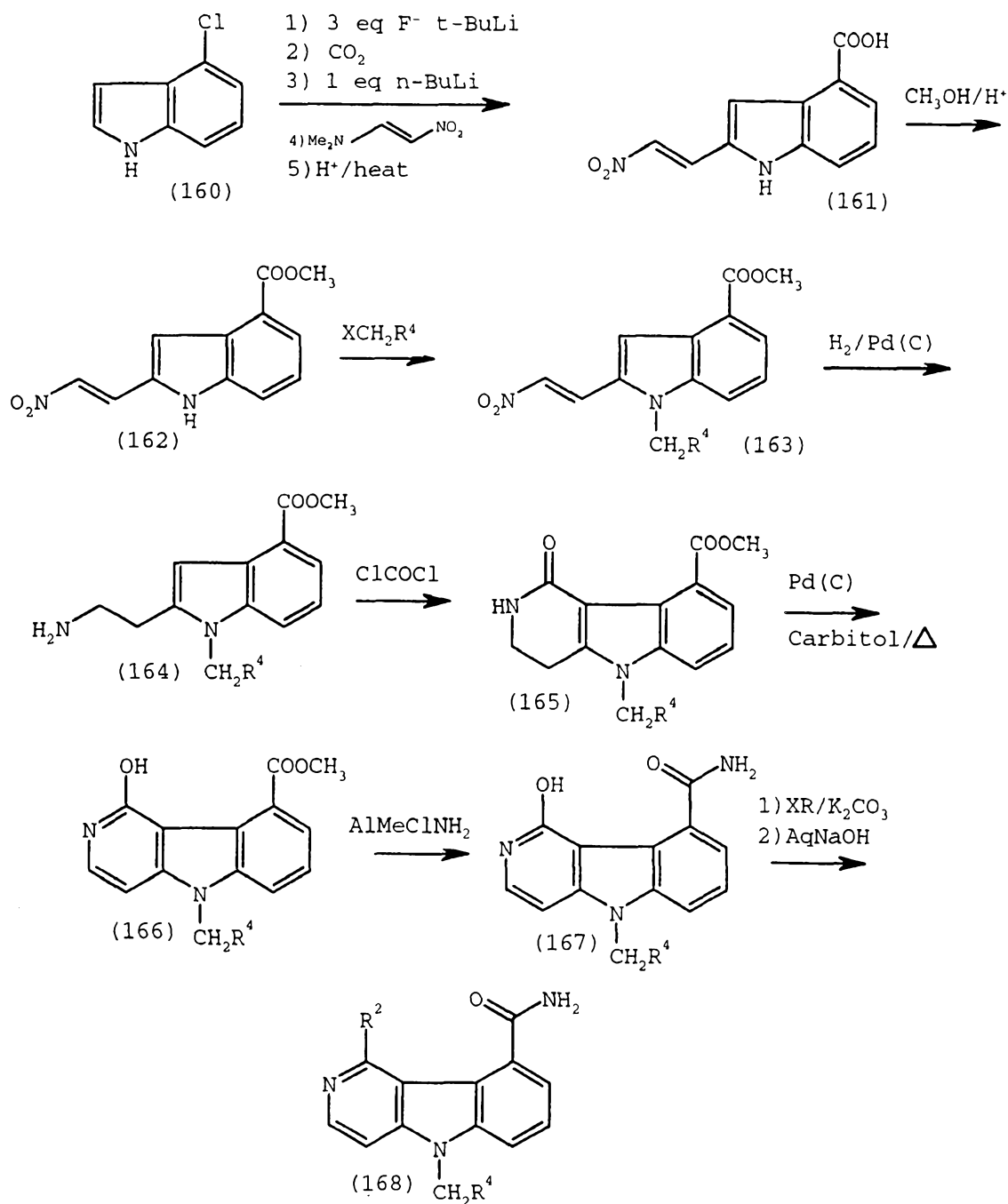
Commercially available 4-carbomethoxyindole (150) with, for example, benzyl iodide and a base such as sodium hydride

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to provide indole (151). Acylation with the acyl chloride of N-phthaloylglycine, catalyzed by a Lewis acid such as stannous tetrachloride, provides intermediate (152), which may be deprotected to give amine (153) by treatment with
5 hydrazine in refluxing ethanol. Pictet-Spengler cyclization of (153) with formaldehyde gives (154), which is then aromatized by refluxing in carbitol or some other suitable high boiling solvent. The resulting beta-carboline (155) is treated with the appropriate Weinreb reagent to provide
10 amide (156), which is alkylated with, for example, ethyl bromoacetate to produce (157) and saponified to give beta-carboline (158).

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Scheme VIII(b)



5

X is halo and
R is as defined in Scheme III(b).

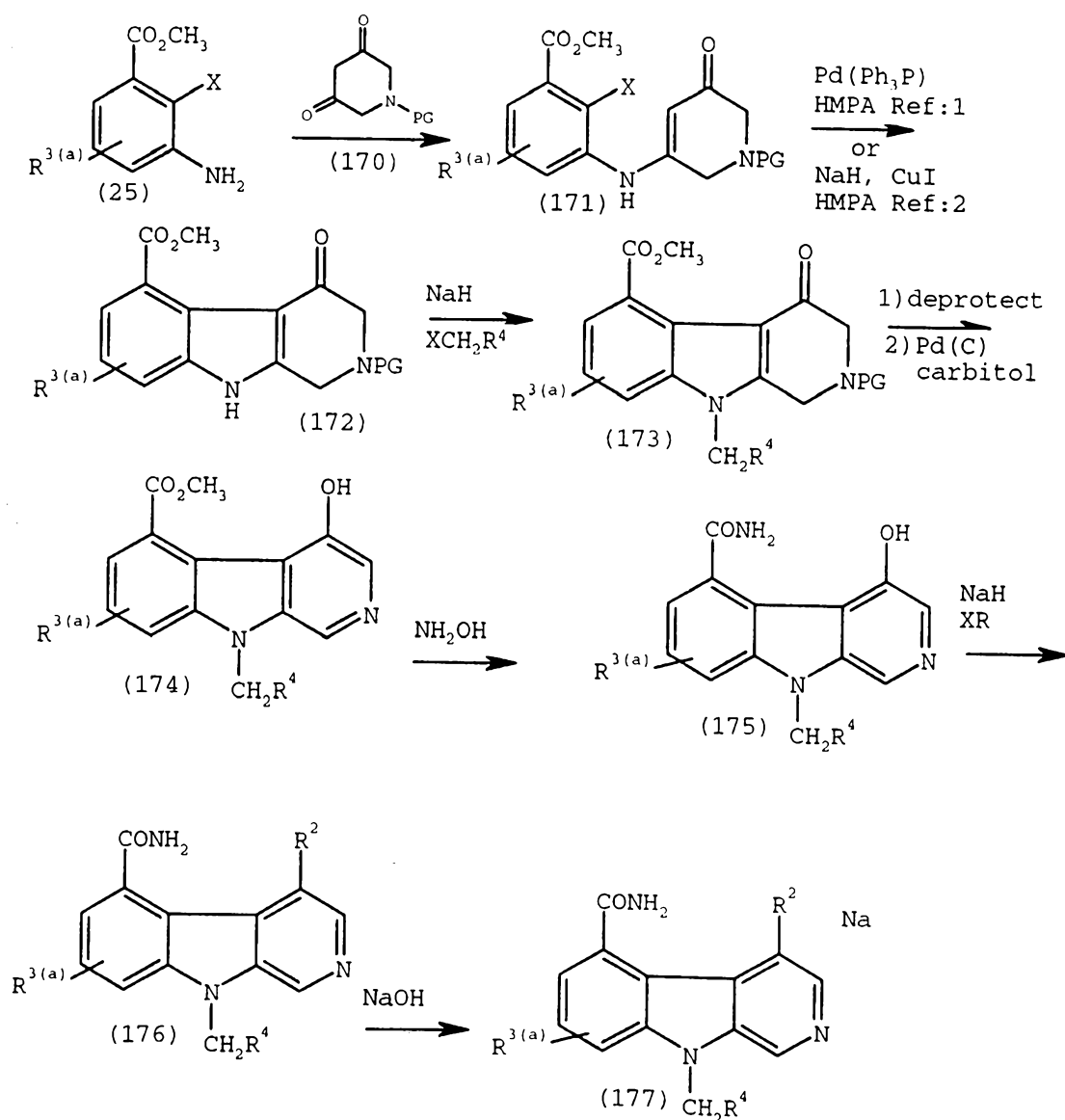
Commercially available 4-chloroindole (160) is treated with 3 equivalents of t-butyllithium followed by carbon dioxide, 1 equivalent of n-butyllithium, 1-dimethylamino-2-nitroethene, and acid to provide carboxylic acid (161),

10

which may be esterified to give (162). Alkylation at the 1-position followed by hydrogenation provides aminoethyl indole (164). Cyclization with phosgene to (165) followed by aromatization gives carboline (166). Treatment of (166) with the appropriate Weinreb reagent provides amide (167), which may be alkylated with, for example, ethyl bromoacetate and saponified with sodium hydroxide to give the carboline (168).

10

Scheme VIII(c)



R^{3(a)} is as defined in Scheme I(a),

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X is halo, and
R is defined in Scheme III(b).

The 1,3-dione structures (170) are either
5 commercially available or readily prepared by known
techniques from commercially available starting materials.
Preparation of the aniline derivatives (25) (X= Cl, Br, or
I) are described in Scheme III(c) above. The amino group
of (170) is protected with an appropriate protecting
10 group, such as the, carboethoxyl, benzyl, CBZ or BOC
protecting group, and the like.

The dione (170) and aniline derivative (25) are
condensed according to the general procedure of Chen, et
al., (Ref 10) or Yang, et al., (Ref 11), with or without a
15 noninterfering solvent, such as methanol, toluene, or
methylene chloride, with or without an acid, such as p-
toluenesulfonic acid or trifluoroacetic acid, with or
without N-chlorosuccinimide and dimethyl sulfide, to
afford the coupled product (172).

20 Compound (171) is cyclized under basic conditions
with a copper (I) salt in an inert solvent according to
the general procedure of Yang, et al., (Ref 8). The
derivative (171) is treated with a base, such as sodium
hydride, in an inert solvent, such as HMPA, at a
25 temperature between 0 and 25°C. A copper (I) salt, such
as copper (I) iodide, is added and the resultant mixture
stirred at a temperature between 25 and 150°C for 1 to 48
hours to afford compound (173).

30 Compound (171) may also be cyclized according to the
general procedure of Chen, et al., (Ref 10). The
derivative (171) is treated with a base, such as sodium
bicarbonate, and a palladium catalyst, such as Pd(PPh₃)₄,
in an inert solvent, such as HMPA, at a temperature
between 25 and 150°C to afford compound (172).

35 Compound (172) is N-alkylated with an appropriately
substituted benzyl halide in the presence of a base, such
as sodium hydride or potassium carbonate, in a

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noninterfering solvent, such as dimethylformamide or dimethylsulfoxide to afford ketone (173). The nitrogen protecting group of (172) is removed under standard conditions and the resulting ketone is dehydrogenated by
5 treatment with palladium on carbon in a noninterfering solvent, such as carbitol or cymene, to produce the phenolic derivative (174).

The ester (174) is converted to the corresponding amide (175) under standard conditions with ammonia or an
10 ammonium salt, such as ammonium acetate, in an inert solvent, such as water or alcohol, or with MeClAlNH_2 in an inert solvent, such as toluene, at a temperature between 0 to 110°C . Alkylation of the phenolic oxygen of compound 38 with an appropriate haloester, such as methyl
15 bromoacetate, in the presence of a base, such as potassium or sodium carbonate, in an inert solvent, such as dimethylformamide or dimethylsulfoxide affords the ester-amide (176). Other haloesters, such as ethyl
bromoacetate, propyl bromoacetate, butyl bromoacetate, and
20 the like can also be used to prepare the corresponding esters.

Saponification of compound (176), with sodium hydroxide in an inert solvent, such as methanol-water, affords (177). The intermediate and final products may
25 isolated and purified by conventional techniques such as chromatography or recrystallization. Regioisomeric products and intermediates can be separated by standard methods, such as, recrystallization or chromatography.

References:

- 30 10) L.-C. Chen et al., Synthesis 385 (1995)
11) S.-C. Yang et al., Heterocycles, 32, 2399 (1991)

The following examples further illustrate the preparation of the compounds of this invention. The
35 examples are illustrative only and are not intended to limit the scope of the invention in any way.

Example 1

5 Preparation of 9-benzyl-6-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A. Preparation of 9-benzyl-6-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide.

10 Compound (5) ($R^2=6\text{-MeO}$, $R^3(a)=H$, $R^4=\text{phenyl}$) was prepared using the method given in Julia, M. and Lenzi, J. Bull. Soc. Chim. France, 1962, 2262-2263. Equimolar quantities of N-benzyl-para-anisidine (3) and ethyl 3-bromo-2-cyclohexanonecarboxylate (Sheehan, J. and Mumaw, C.E., J. Am. Chem. Soc., 1950, 72, 2127-2129) were
15 dissolved in dimethylformamide and stirred in the presence of excess sodium bicarbonate for five days to give ethyl 3-N-benzyl-4-methoxyanilino-2-cyclohexanonecarboxylate (4) which was treated with zinc chloride in refluxing benzene to give (5) ($R^2=6\text{-MeO}$ $R^3=H$).

20 A solution of 0.5gm compound (5) and 2-3ml of hydrazine hydrate in 30ml of ethanol was refluxed for 66 hours, cooled, and filtered to give sub-titled compound, 405mg, 80%, mp 185-187°C.

Elemental Analyses for $C_{21}H_{23}N_3O_2$:

25 Calculated: C 72.18; H 6.63; N 12.02
Found: C 71.90; H 6.68; N 11.87.

B. Preparation of 9-benzyl-6-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

30 A mixture of 0.3gm of the compound of part A above, 2-3gm of Raney nickel catalyst, and 100ml of ethanol was refluxed for 2.5 hours, cooled, and the solution was decanted and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient
35 methylene chloride/1-3% methanol to give titled compound, 220mg, 80%, mp154-156°C/diethyl ether.

Elemental Analyses for $C_{21}H_{22}N_2O_2$:

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Calculated: C 75.42; H 6.63; N 8.38
Found: C 75.58; H 6.62; N 8.24.

Example 2

5

Preparation of 4-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]butyric acid

A solution of 280mg of compound (7) ($R^2=6\text{-MeO}$, $R^3=H$,
10 $R^4=\text{phenyl}$) in 25ml of dichloromethane was treated with 3ml
of 1M boron tribromide in dichloromethane for 2.75 hours,
washed with water, washed with brine, dried over sodium
sulfate, and evaporated *in vacuo* to give 290mg of crude
compound (7) ($R^2=6\text{-OH}$, $R^3=H$) which was dissolved in 10ml
15 of tetrahydrofuran and 50ml of dimethylsulfoxide and
treated with 40mg of sodium hydride (60% in mineral oil)
for 10 minutes and then with 0.15ml of ethyl 4-
bromobutyrate for 1.75 hours. The solution was diluted
with ethyl acetate and water and the organic phase washed
20 with water, washed with brine, dried over sodium sulfate,
and evaporated *in vacuo*. The residue was chromatographed
on silica gel eluting with a gradient methylene
chloride/0-2% methanol to give 340mg of compound (9) ($R^2=$
 $-\text{O}(\text{CH}_2)_4\text{CO}_2\text{Et}$, $R^3=H$) which was dissolved in 25ml of
25 ethanol containing 2-3ml of 2N sodium hydroxide and
stirred 4.25 hours, acidified with hydrochloric acid and
extracted with ethyl acetate. The organic phase was washed
with brine, dried over sodium sulfate, and concentrated *in*
vacuo to give title compound, 300mg, 90%, mp 199-200°C.
30 Elemental Analyses for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_4$:

Calculated: C 70.92; H 6.45; N 6.89
Found: C 70.63; H 6.49; N 6.87

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Example 3

Preparation of 3-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid dihydrate

5

A. Preparation of dimethyl-3-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid.

10

A solution of 840mg of compound (7) ($R^2(a)=OH$ $R^3=H$) (prepared as in example 2) in 20ml of tetrahydrofuran and 70ml of dimethylsulfoxide was treated with 120mg of sodium hydride (60% in mineral oil) for 10 minutes and then with 700mg of dimethyl 3-bromopropylphosphonate for 5 hours.

15

The solution was diluted with water and ethyl acetate. The organic phase was washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give sub-titled compound, 940mg, 75%, amorphous solid. Elemental Analyses for $C_{25}H_{31}N_2O_5P$:

20

Calculated: C 63.82; H 6.64; N 5.95

Found: C 63.94; H 6.58; N 6.15

25

B. A solution of 450mg of the compound of Part A and 1.5ml of trimethylsilyl bromide in 25ml of dichloromethane was stirred for 16 hours and then evaporated *in vacuo*. The residue was dissolved in 25ml of methanol, stirred for 2.5 hours, evaporated *in vacuo*, and crystallized from a mixture of ethyl acetate and methanol to give title compound, 325mg, 78%, mp 200-201°C.

30

Elemental Analyses for $C_{23}H_{27}N_2O_5P \cdot 2H_2O$:

Calculated: C 57.73; H 6.53; N 5.86

Found: C 57.51; H 5.94; N 6.00

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Example 4

Preparation of 2-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydro-carbazol-6-yl)oxy]methylbenzoic acid hydrate

5

A. Preparation of methyl 2-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]methylbenzoate.

A solution of 700mg of compound (7) ($R^2(a)=OH$, $R^3=H$, $R^4=phenyl$) (prepared as in example 2) in 20ml of tetrahydrofuran and 70ml of dimethylsulfoxide was treated with 100mg of sodium hydride (60% in mineral oil) for 10 minutes and then with 575mg of methyl 2-bromomethylbenzoate for 2.5 hours. The solution was diluted with water and ethyl acetate. The organic phase was washed with water, washed with brine, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/0-2% methanol to give sub-titled compound, 840mg, 90%, mp 119-120°C/Et₂O.

20 Elemental Analyses for C₂₉H₂₈N₂O₄:

Calculated: C 74.34; H 6.02; N 5.98

Found: C 74.22; H 6.03; N 5.70

B. Preparation of 2-[(9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]methylbenzoic acid hydrate.

A solution of 670mg of the compound of Part A and 5ml of 2N sodium hydroxide in 100ml of ethanol and 15ml of tetrahydrofuran was stirred for 16.5 hours, acidified with hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/2-4% methanol to give title compound, 230mg, 34%, amorphous solid.

35

Elemental Analyses for C₂₈H₂₆N₂O₄·H₂O:

Calculated: C 71.17; H 5.97; N 5.93

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Found: C 71.31; H 5.68; N 5.65

Example 5

5 Preparation of 9-benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide

A. Preparation of N-benzyl-3,5-dimethoxyaniline.

10 A solution of 25gm. (0.163 mol) of 3,5-dimethoxyaniline and 18.3ml. (0.18 mol) of benzaldehyde in 300ml. of methanol was cooled in ice-water and treated with 10.3gm. (0.18 mol) of sodium cyanoborohydride in portions. The solution was stirred and cooled for 3
15 hours, treated with 1-2gm. of sodium borohydride for 30 minutes, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient
20 hexane/15-70% ether to give 9-benzyl-3,5-dimethoxyaniline, 28.0gm., 71%, as an oil.

Elemental Analyses for C₁₅H₁₇NO₂:

Calculated: C 74.05; H 7.04; N 5.76

Found: C 74.30; H 7.12; N 5.70

25

B. Preparation of 9-benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide.

A solution of 9.72gm of the compound of part A and 4.98gm of 2-carbethoxy-6-bromocyclohexanone (J. Sheehan and
30 C.E. Mumaw, J. Am. Chem. Soc., 72, 2127-2129, (1950).) in 125ml of benzene was refluxed for 72 hours, cooled, filtered, and evaporated *in vacuo*. The residue (12gm) and 10gm of zinc chloride were refluxed in 250ml of benzene for 6 hours, cooled and evaporated *in vacuo*. The residue
35 was taken up in ethyl acetate, washed with 1N hydrochloric acid, washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on

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silica gel eluting with a gradient toluene/0-5% ethyl acetate to give compound (5) ($R^2=5\text{-MeO}$ $R^3=7\text{-MeO}$ $R^4=\text{phenyl}$), 1.88gm which was dissolved in 100ml of ethanol containing 10ml of hydrazine hydrate and refluxed for 5
5 days, cooled, the solution decanted, diluted with ethyl acetate, washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give title compound, 1.1gm, 60%, mp 189-190°C/ $\text{CH}_2\text{Cl}_2\text{-EtOH}$.

Elemental Analyses for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_3$:

10 Calculated: C 69.64; H 6.64; N 11.07
 Found: C 69.59; H 6.74; N 10.84

Example 6

15 Preparation of 9-benzyl-5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide

A mixture of 980mg of the compound of example 5, 2gm of Raney nickel catalyst, 1-2ml of hydrazine hydrate, and
20 125ml of ethanol was refluxed 1 hour, the solution decanted, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-3%
25 methanol to give title compound, 820mg, 84%, mp 190-192°C/ EtOH .

Elemental Analyses for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$:

 Calculated: C 72.51; H 6.64; N 7.69
 Found: C 71.88; H 6.89; N 7.81

30

Example 7

Preparation of [9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid sodium salt

35

A. Preparation of 9-benzyl-5-hydroxy-7-methoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

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A solution of 1.75gm. (4.8 mmol) of the compound of example 6 in 50ml. of dimethylformamide was mixed with a solution of sodium thioethoxide (13.5 mmol) in 75ml. of dimethylformamide and then heated at 100°C for 21 hours.

5 The mixture was cooled, diluted with water, acidified with hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient
10 methylene chloride/0-4% methanol to give the sub-titled product, 825mg., 50%, mp 225-7°C/ethanol.

Elemental Analyses for C₂₁H₂₂N₂O₃:

Calculated: C 71.98; H 6.33; N 7.99

Found: C 71.71; H 6.37; N 7.72

15

B. Preparation of [9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acidethyl ester.

A solution of 700mg. (2.0 mmol) of the product from Part A in 70ml. of dimethylformamide and 15ml. of tetrahydrofuran was treated with 100mg. of sodium hydride (60% in mineral oil; 2.5 mmol) for 10 minutes and then with 0.3ml. (2.7 mmol) of ethyl bromoacetate for 3 hours. The mixture was diluted with ethyl acetate, washed with
25 water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-2% methanol to give sub-titled product, 670mg., 77%, mp 167-169°C/ether.

30 Elemental Analyses for C₂₅H₂₈N₂O₅:

Calculated: C 68.79; H 6.47; N 6.42

Found: C 69.57; H 6.39; N 5.77

C. Preparation of [9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid.
35

A suspension of 650mg. of the product from Part B in 20ml. of tetrahydrofuran and 70ml. of ethanol was treated

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with 5ml. of 2N sodium hydroxide and the resulting solution was stirred for 15.5 hours. The solution was diluted with ethyl acetate and water and acidified with hydrochloric acid. The organic phase was washed with
5 brine, dried over sodium sulfate, concentrated *in vacuo*, and filtered to give title product, 540mg., 87%, mp 251-254°C.

Elemental Analyses for C₂₃H₂₄N₂O₅:

Calculated: C 67.63; H 5.92; N 6.86
10 Found: C 67.73; H 5.74; N 6.82

D. Preparation of [9-benzyl-4-carbamoyl-7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid sodium salt.

A suspension of 120mg. of the product from Part C in
15 20mL of ethanol was treated with 0.15mL of 2.0 N sodium hydroxide and warmed until dissolved. The resulting solution was concentrated *in vacuo*, diluted with ethyl acetate and again concentrated *in vacuo* and left to stand overnight. The precipitate was filtered and air dried to
20 give the title product as an amorphous solid, 80mg, 63%.

Elemental Analyses for C₂₃H₂₃NaN₂O₅·0.4H₂O:

Calculated: C 63.18; H 5.39; N 6.40
Found: C 63.31; H 5.48; N 6.25

25 Example 8

Preparation of 3-[(9-benzyl-4-carbamoyl-7-n-octyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid dihydrate

30

A. Preparation of ethyl 9-benzyl-6-methoxy-7-n-octyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate.

A mixture of 1.3gm of 9-benzyl-4-methoxy-5-n-octylaniline (3) (prepared by the procedures of Example 9,
35 Part A, utilizing n-heptyltriphenylphosphonium bromide),

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1.0gm of 2-carbethoxy-6-bromocyclohexanone, 675mg of sodium bicarbonate, and 40ml of dimethylformamide was stirred for 5 days, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue and 10gm of zinc chloride in 250ml of benzene was refluxed for 6 hours, cooled, diluted with ethyl acetate, washed with 1N hydrochloric acid, washed with brine dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/10-15% diethyl ether to give compound (5) ($R^2=6\text{-MeO}$ $R^{3a}=7\text{-n-octyl}$ $R^4=\text{phenyl}$), 930mg, which was dissolved in 30ml of benzene and treated with 15ml of an 0.67M solution of methyl chloroaluminum amide at 50°C for 16 hours, cooled, decomposed with ice and 1N hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give sub-titled compound, 795mg, 91%, mp 131-133°C/Et₂O.

Elemental Analyses for C₂₉H₃₈N₂O₂:

Calculated: C 77.97; H 8.58; N 6.27

Found: C 77.75; H 8.62; N 5.99

B. Preparation of 9-benzyl-6-hydroxy-7-n-octyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 770mg of the compound of Part A, in 75ml of dichloromethane was treated with 10ml of 1M boron tribromide in dichloromethane for 1.75 hours and then decomposed with ice and 1N hydrochloric acid. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-3% methanol to give sub-titled compound, 360mg, 47%, mp 223-225°C.

Elemental Analyses for C₂₈H₃₆N₂O₂:

Calculated: C 77.74; H 8.39; N 6.48

Found: C 77.97; H 8.45; N 6.40

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C. Preparation of 3-[(9-benzyl-4-carbamoyl-7-n-octyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid dihydrate.

5 A solution of 360mg of the compound of Part B in 10ml of tetrahydrofuran and 70ml of dimethylformamide was treated with 40mg of sodium hydride (60% in mineral oil) for 15 minutes and then with 230mg of dimethyl 3-bromopropylphosphonate for 4 hours, diluted with water,
10 and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-5% methanol to give compound (9) ($R^2=6-(\text{MeO})_2\text{P}=\text{O}(\text{CH}_2)_3$, $R^3=7-$
15 n-octyl, $R^4=\text{phenyl}$), 290mg, which was dissolved in 30ml of dichloromethane and 1ml of trimethylsilyl bromide, stirred for 20 hours, evaporated *in vacuo*, dissolved in 30ml of methanol, stirred 2.25 hours, evaporated *in vacuo*, and crystallized from a mixture of benzene-methanol-diethyl
20 ether, to give title compound, 185mg, 67%, mp 160-162°C. Elemental Analyses for $\text{C}_{31}\text{H}_{43}\text{N}_2\text{O}_5\text{P}\cdot 2\text{H}_2\text{O}$:

Calculated: C 63.03; H 8.02; N 4.74

Found: C 63.18; H 7.53; N 4.93

25 Example 9

Preparation of 4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocabazol-6-yl)oxy]butyric acid

30 A. Preparation of benzyl 9-benzyl-6-methoxy-7-ethyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate.

A suspension of 22gm (0.13mol) of 5-nitrosalicaldehyde, 10ml (0.16mol) of methyl iodide, 28gm (0.2mol) of potassium carbonate, 75ml of
35 dimethylsulfoxide, and 125ml of 2-butanone was refluxed for 20 hours, cooled, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate,

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and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/10-50% ether to give (1) ($R^2=4\text{-MeO}$ $R^3(a)=3\text{-CHO}$), 15gm, 67%.

A suspension of 19.6gm (0.055mol) of
5 methyltriphenylphosphonium bromide in 300ml of tetrahydrofuran was cooled at -5°C and treated slowly with 35ml of *n*-butyl lithium (1.6M in hexane, 0.055mol). The cooling bath was removed and the mixture allowed to warm to room temperature over 45 minutes. A solution of 9.1gm
10 (0.050mol) of the aldehyde prepared above was slowly added to this yellow solution and stirred 2 hours, diluted with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed
15 on silica gel eluting with a gradient hexane/15-50% ether to give (1) ($R^2=4\text{-MeO}$ $R^3(a)=3\text{-CH}_2\text{=CH}$), 7.7gm, 86%.

This product and 3gm of 10% Pd/C in 200ml of ethanol was stirred under 1 atmosphere of hydrogen for 6 hours, filtered, and evaporated *in vacuo* to give (2) ($R^2=4\text{-MeO}$
20 $R^3(a)=3\text{-CH}_3\text{CH}_2$). This crude product and 5ml of benzaldehyde in 150ml of methanol was stirred at $0\text{-}5^\circ\text{C}$, while adding in portions 2.5gm of sodium cyanoborohydride. After an additional 60 minutes at this temperature the mixture was diluted with water and extracted with ethyl
25 acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/5-15% ether to give 9-benzyl-4-methoxy-5-ethylaniline, 6.0gm, 60%.

30 A mixture of 3.3gm of 9-benzyl-4-methoxy-5-ethylaniline, 3.7gm of 2-carbethoxy-6-bromocyclohexanone, 1.3gm of sodium bicarbonate, and 100ml of dimethylformamide was stirred for 5 days, diluted with ethyl acetate, washed with water, washed with brine, dried
35 over sodium sulfate, and evaporated *in vacuo*. The residue and 10gm of zinc chloride in 250ml of benzene was refluxed for 1.75 hours, cooled, diluted with ethyl acetate, washed

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with 1N hydrochloric acid, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/10-20% diethyl ether to give sub-titled compound,
5 2.6gm, 50%, mp 85-86/EtOH.

Elemental Analyses for C₂₅H₂₉NO₃:

Calculated: C 76.70; H 7.47; N 3.58

Found: C 77.00; H 7.56; N 3.69

- 10 B. Preparation of 9-benzyl-6-methoxy-7-ethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 2.6gm of the compound of Part A in 75ml of benzene and 30ml of 0.67M methyl chloroaluminum amide in benzene/toluene was heated at 50°C for 24 hours,
15 cooled, decomposed with 1N hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give sub-titled compound, 2.2gm, 91%, mp 168-169°C/CH₂Cl₂-EtOH.

- 20 Elemental Analyses for C₂₃H₂₆N₂O₂:

Calculated: C 76.21; H 7.23; N 7.73

Found: C 76.55; H 7.74; N 6.84

- 25 C. Preparation of 4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]butyric acid.

A solution of 2.1gm of the compound of Part B in 150ml of dichloromethane and 15ml of 1M boron tribromide in dichloromethane was stirred for 2 hours, decomposed with ice and water, and the organic phase washed with
30 brine, dried over sodium sulfate, and evaporated *in vacuo* to give compound (7) (R^{2(a)}=6-HO, R³=7-ethyl, R⁴=phenyl), 1.6gm, 80%, mp 255°C dec./methylene chloride-ethanol. A solution of 750mg of this material in 20ml of tetrahydrofuran and 70 ml of dimethylformamide was treated
35 with 100mg of sodium hydride (60% in mineral oil) for 10 minutes and then with 0.33ml of ethyl 4-bromobutyrate for 4.5 hours, diluted with ethyl acetate, washed with water,

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washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-3% methanol to give compound (9) ($R^2=6\text{-EtO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{O}$, $R^3=7\text{-ethyl}$), 625mg, 64%, mp 134-136/ethylene chloride-ethanol, which was dissolved in 10ml of tetrahydrofuran and 40ml of ethanol containing 3ml of 2N sodium hydroxide and stirred for 22 hours. The solution was acidified with hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give title compound, 410mg, 73%, mp 208-210°C/ $\text{CH}_2\text{Cl}_2\text{-EtOH}$.

Elemental Analyses for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_4 \cdot 0.4\text{H}_2\text{O}$:

Calculated: C 64.05; H 7.15; N 5.54
Found: C 71.76; H 6.90; N 6.56

Example 10

Preparation of 3-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid

A. Preparation of dimethyl 3-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonate.

A solution of 750mg of the compound of example 8 in 20ml of tetrahydrofuran and 75ml of dimethylformamide was treated with 100mg of sodium hydride (60% in mineral oil) for 10 minutes and then with 510mg of dimethyl 3-bromopropylphosphonate for 5.25 hours, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient methylene chloride/1-5% methanol to give sub-titled, 655mg, 61%, amorphous solid.

Elemental Analyses for $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_5\text{P}$:

Calculated: C 64.12; H 7.15; N 5.54

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Found: C 64.27; H 7.00; N 5.92

5 B. Preparation of 3-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid.

A solution of the compound of Part A and 1ml of trimethylsilyl bromide in 30ml of dichloromethane was stirred 18 hours, evaporated *in vacuo*, dissolved in 25ml of methanol, stirred 3.75 hours, and concentrated *in vacuo* to give title compound, 475mg, 80%, mp 235-238°C dec. Elemental Analyses for C₂₅H₃₁N₂O₅P:

Calculated: C 63.82; H 6.64; N 5.95

Found: C 63.56; H 6.62; N 6.07

15 Example 11

Preparation of (S)-(+)-4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]butyric acid

20 A. Preparation of (S)-(-)-1-[(S)-(+)-9-benzyl-6-methoxy-7-ethyl-1,2,3,4-tetrahydrocarbazol-4-yl]carbonyl-4-benzyl-2-oxazolidinone.

A solution of 8.9gm. of the compound of example 8, Part A, in 25ml. of tetrahydrofuran, 150ml. of ethanol, and 25ml. of 5N sodium hydroxide was stirred for 21 hours, diluted with water, acidified with 5N hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated *in vacuo* to give the corresponding acid, 7.6gm., 92%, which was suspended in 200ml of dichloromethane containing 0.5ml. of dimethylformamide and treated with 2.2ml. of oxalyl chloride for 30 minutes and then evaporated *in vacuo*. The residue was dissolved in 100ml. of tetrahydrofuran and added slowly to a solution prepared by adding 25 mmole of n-butyl lithium to 25 mmole of (S)-(-)-4-benzyl-2-oxazolidinone in 150ml. of tetrahydrofuran at -75°C. After stirring for 2 hours at

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that temperature, the solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/15-60% ether to give first the (S,S)-diastereomer, 3.3gm., 28%, followed by 1.2gm., 11%, of mixture, and then 3.3gm., 28%, of the (R,S)-diastereomer.

Elemental Analyses for C₃₃H₃₄N₂O₄:

10 Calculated: C 75.84; H 6.56; N 5.36
 Found: C 76.09; H 6.44; N 5.42

B. Preparation of (S)-(+)-9-benzyl-6-methoxy-7-ethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

15 A solution of 3.2gm. (6 mmol) of the title compound of Part A in 50ml. of tetrahydrofuran was added to a solution prepared by adding 60 mmole of n-butyl lithium to 60 mmole of benzyl alcohol in 150ml. of tetrahydrofuran at -5°C. The resulting solution was stirred 20 minutes, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/10-15% ether to give the benzyl ester of the carbazole-4-carboxylic acid 2.6gm., 93%, which was treated with 4 equivalents of methylchloroaluminum amide in 100ml. of benzene at 50°C for 18 hours, cooled, decomposed with ice-hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the sub-titled product, 2.5gm., 100%, mp 184-186°C, rotation at 589 +39.7deg.

Elemental Analyses for C₂₃H₂₆N₂O₂:

35 Calculated: C 76.21; H 7.23; N 7.73
 Found: C 76.19; H 7.29; N 7.69

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C. Preparation of (S)-(+)-9-benzyl-6-hydroxy-7-ethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 2.4gm. of the above 6-methoxy derivative in 200ml. of dichloromethane was treated with 20ml. of 1M boron tribromide in dichloromethane for 2.5 hours, decomposed with ice-water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the 6-hydroxytetrahydrocarbazole, 2.2gm., 100%, mp 240-242°C/EtOH-CH₂Cl₂.

10 Elemental Analyses for C₂₂H₂₄N₂O₂:

Calculated: C 75.84; H 6.94; N 8.04

Found: C 76.01; H 7.18; N 8.13

D. Preparation of (S)-(+)-ethyl 4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]butyrate.

A solution of 2.1gm. (6 mmol) of the above 6-hydroxycarbazole in 25ml. of tetrahydrofuran and 125ml. of dimethylformamide was treated with 280mg. of sodium hydride (60% in mineral oil; 7 mmol) for 5 minutes and then with 1.0ml. (7 mmol) of ethyl 4-bromobutyrate for 1.5 hours, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient dichloromethane/0-5% methanol to give sub-titled product, 760mg., 29%, mp 188-190°C/MeOH, rotation at 589 +32.2deg.

25 Elemental Analyses for C₂₈H₃₄N₂O₄:

Calculated: C 72.70; H 7.41; N 6.06

30 Found: C 72.94; H 7.34; N 6.20

E. Preparation of (S)-(+)-4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]butyric acid.

35 A solution of 635mg. of the above ester and 250mg. of lithium hydroxide in 15ml. of water and 50ml. of tetrahydrofuran was stirred 5 hours, washed with ether,

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acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give title product, 260mg., 44%, mp 188-190°C, rotation at 589
5 +22.8deg.

Elemental Analyses for C₂₆H₃₀N₂O₄:

Calculated: C 71.87; H 6.96; N 6.45

Found: C 72.08; H 7.11; N 6.32

10

Example 12

Preparation of 4-[9-benzyl-4-carbamoyl-7-(2-cyanoethyl)-
1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid

15 A. Preparation of methyl 2-methoxy-5-nitrocinnamate.

A solution of 11.0gm. (0.06 mol) of 2-methoxy-5-nitrobenzaldehyde and 23.1gm. (0.07 mol) of methyl triphenylphosphoranylidene acetate in 250ml. of tetrahydrofuran was refluxed for 1.5 hours, cooled,
20 diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with dichloromethane to give sub-titled product, 14.0gm., 97%, mp 156-158°C.

25 Elemental Analyses for C₁₁H₁₁NO₅:

Calculated: C 55.70; H 4.67; N 5.90

Found: C 55.92; H 4.64; N 6.01

30 B. Preparation of ethyl 9-benzyl-6-methoxy-7-(3-amino-3-oxopropyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate.

A mixture of 14gm. of the above cinnamate, 5gm. of 10% Pd/C, 100ml. of tetrahydrofuran, and 150ml. of ethanol was stirred under 1 atmosphere of hydrogen for 14 hours, filtered and evaporated *in vacuo* to give methyl 3-(2-
35 methoxy-5-aminophenyl)propionate, (2), 11.5gm., 94%, which was dissolved in 200ml. of methanol containing 7ml. of benzaldehyde and cooled to 0-5°C. After portionwise

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addition of 5gm. of sodium cyanoborohydride, the solution was stirred for 3 hours at that temperature, decomposed with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a gradient hexane/10-25% ether to give methyl 3-(9-benzyl-2-methoxy-5-aminophenyl)propionate, 11.4gm., 70%. A mixture of 4.5gm. (15 mmol) of this material, 5gm. (20 mmol) of 2-bromo-6-ethoxycarbonylcyclohexanone, 2.5gm. (30 mmol) of sodium bicarbonate, and 75ml. of dimethylformamide was stirred for four days, diluted with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue and 15gm. of zinc chloride in 300ml. of benzene was refluxed with a water separator for 6 hours, cooled, diluted with ethyl acetate, and stirred well with 1N hydrochloric acid. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/0-25% ether to give ethyl 9-benzyl-6-methoxy-7-(2-methoxycarbonyl)ethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate, 3.0gm., 40%, which was dissolved in 90ml. of benzene and treated with 4 equivalents of methylchloroaluminum amide at 50°C for 3 hours, cooled, decomposed with ice-hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give ethyl 9-benzyl-6-methoxy-7-(3-amino-3-oxopropyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate, 1.97gm., 73%, mp 125-130°C.

Elemental Analyses for C₂₄H₂₇N₃O₃:

Calculated: C 71.87; H 6.96; N 6.45

Found: C 71.62; H 7.02; N 6.51

35

C. Preparation of 9-benzyl-6-methoxy-7-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide and 9-

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benzyl-6-methoxy-7-(3-amino-3-oxopropyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A suspension of 2.0gm. of the above ester in 100ml. of benzene was heated at 50°C with 4 equivalents of methylchloroaluminum amide for 66 hours, cooled, decomposed with ice-hydrochloric acid, shaken with ethyl acetate, and filtered to give 9-benzyl-6-methoxy(3-amino-3-oxopropyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide, 380mg., 21%, mp 253-255°C.

10 Elemental Analyses for C₂₄H₂₇N₃O₃:

Calculated: C 71.09; H 6.71; N 10.36

Found: C 70.85; H 6.83; N 10.20

The filtrate was extracted with ethyl acetate and the organic phase washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient dichloromethane/2-7% methanol to give the bis amide above, 395mg., 22%, and subtitled product, 560mg., 33%, mp 177-180°C/ether.

20 Elemental Analyses for C₂₄H₂₅N₃O₂:

Calculated: C 74.39; H 6.50; N 10.85

Found: C 72.55; H 6.50; N 10.09

25 D. Preparation of 9-benzyl-6-hydroxy-7-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 500mg. of the product from Part C and 10ml. of 1M boron tribromide in dichloromethane and 75ml. of dichloromethane was stirred for 45 hours, decomposed with ice-water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient dichloromethane/2-5% methanol to give sub-titled product, 225mg., 47%, mp 238-240°C.

35 Elemental Analyses for C₂₃H₂₃N₃O₂:

Calculated: C 73.97; H 6.21; N 11.25

Found: C 73.74; H 6.29; N 11.48

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E. Preparation of ethyl 4-[9-benzyl-4-carboxamido-7-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyrate.

5 A solution of 210mg. (0.6 mmol) of the above 6-hydroxytetrahydrocarbazole in 5ml. of tetrahydrofuran and 20ml. of dimethylformamide was treated with 40mg. of sodium hydride (60% in mineral oil; 0.8 mmol) for 5 minutes and then with 0.1ml. (0.9 mmol) of ethyl 4-
10 bromobutyrate for 2 hours, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient dichloromethane/ 1-3%
15 methanol to give sub-titled product, 190mg., 70%, mp 122-124°C/ether.

Elemental Analyses for C₂₉H₃₃N₃O₄:

Calculated: C 71.44; H 6.82; N 8.62

Found: C 71.51; H 6.77; N 8.38

20

F. Preparation of [9-benzyl-4-carboxamido-7-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid.

A solution of 175mg. of the above ester and 2ml. of
25 2N sodium hydroxide in 20ml. of ethanol was stirred for 15 hours, diluted with 1N hydrochloric acid, and extracted in ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give title product, 125mg., 76%, mp 184-192°C.

30 Elemental Analyses for C₂₇H₂₉N₃O₄:

Calculated: C 70.57; H 6.36; N 9.14

Found: C 70.78; H 6.52; N 9.38

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Example 13

Preparation of 4-[9-benzyl-4-carboxamido-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid

5

A. Preparation of 3-(2-phenylethenyl)-4-methoxy nitrobenzene.

A suspension of 14.3gm. (33 mmol) of benzyltriphenylphosphonium bromide in 200ml. of tetrahydrofuran was cooled to -5°C and treated slowly with 21ml. of n-butyl lithium (1.6M in hexane; 34 mmol). The cooling bath was removed and the mixture stirred and allowed to warm to room temperature over 60 minutes. A solution of 5.4gm. (30 mmol) of 2-methoxy-5-nitrosalicylaldehyde in 50ml. of tetrahydrofuran was added rapidly dropwise and then stirred for 2 hours, diluted with water, acidified with hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a gradient hexane/15-25% ether to give sub-titled product, 7.8gm., 93%, mp 109-111°C/ether-hexane.

Elemental Analyses for C₁₅H₁₃NO₃:

Calculated: C 70.58; H 5.13; N 5.49

Found: C 70.82; H 5.17; N 5.60

B. Preparation of N-benzyl-3-(2-phenylethyl)-4-methoxyaniline.

A mixture of 7.8gm. of the product from Part A, 4gm. of 10% Pd/C, 25ml. of tetrahydrofuran, and 175ml. of ethanol was stirred under 1 atmosphere of hydrogen for 6.5 hours, filtered, and evaporated in vacuo. The residue was dissolved in 200ml. of methanol containing 3ml. of benzaldehyde and cooled to -5°C. Sodium cyanoborohydride (6gm.) was added in portions and the solution was stirred

35

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and cooled for 3 hours, diluted with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient hexane/5-10% ether to give sub-titled product,
5 4.8gm., 50% (two steps), as an oil.

Elemental Analyses for C₂₂H₂₃NO:

Calculated: C 83.24; H 7.30; N 4.41

Found: C 83.53; H 7.30; N 4.69

10

C. Preparation of N-benzyl-6-methoxy-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A mixture of 1.6gm. (5.0 mmol) of the product from Part B, 1.5gm. (6 mmol) of ethyl 3-bromo-2-cyclohexanone
15 carboxylate, 1.0gm. (12 mmol) of sodium bicarbonate, and 40ml. of dimethylformamide was stirred for 6 days, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue and 3.5gm. (30 mmol) of zinc chloride in 250ml. of
20 benzene was refluxed with a water trap for 6 hours, cooled, diluted with ethyl acetate, and stirred well with 1N hydrochloric acid. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with
25 a gradient hexane/10-20% ether to give ethyl 9-benzyl-6-methoxy-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate as an oil, 910mg., 39%, which was dissolved in 60ml. of benzene, mixed with 10-15ml. of an 0.67M solution of methylchloroaluminum amide in 2:1 benzene:toluene and
30 heated at 50°C for 16 hours. The mixture was cooled, decomposed with ice-water, and extracted with 3:1 dichloromethane:isopropanol. The organic phase was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel
35 eluting with a gradient dichloromethane/1-2% methanol to give sub-titled product, 630mg., 76%, mp 165-166°C/ethanol.

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Elemental Analyses for C₂₉H₃₀N₂O₂:

Calculated: C 79.42; H 6.90; N 6.39

Found: C 79.64; H 6.90; N 6.32

- 5 D. Preparation of 9-benzyl-6-hydroxy-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 610mg. of the product from Part C in 100ml. of dichloromethane was treated with 5ml. of 1M boron tribromide in dichloromethane for 4hr., decomposed
10 with ice-water, and extracted with 3:1 dichloromethane:isopropanol. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo to give sub-titled product, 580mg., 100%, mp 209-211°C/ethanol.

- 15 Elemental Analyses for C₂₈H₂₈N₂O₂:

Calculated: C 78.84; H 7.09; N 6.57

Found: C 78.54; H 6.79; N 6.33

- 20 E. Preparation of ethyl 4-[9-benzyl-4-carboxamido-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid.

A solution of 560mg. (1.3 mmol) of the product of Part D in 50ml. of dimethylformamide and 10ml. of tetrahydrofuran was stirred with 60mg. of sodium hydride
25 (60% in mineral oil; 1.5 mmol) for 5 minutes and then with 0.2ml. (1.4 mmol) of ethyl 4-bromobutyrate for 3 hours, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with
30 a gradient dichloromethane/1-2% methanol to give sub-titled product, 535mg., 75%, mp 144-146°C/ethanol.

Elemental Analyses for C₃₄H₃₈N₂O₄:

Calculated: C 75.81; H 7.11; N 5.20

Found: C 75.71; H 7.10; N 5.12

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F. Preparation of 4-[9-benzyl-4-carboxamido-7-(2-phenylethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid.

A solution of 520mg. of the product from Part E and
5 4ml. of 2N sodium hydroxide in 25ml. of tetrahydrofuran
and 25ml. of ethanol was stirred for 16 hours, diluted
with ethyl acetate, acidified with hydrochloric acid,
washed with brine, dried over sodium sulfate, and
concentrated *in vacuo*, and filtered to give title product,
10 230mg., 44%, mp 202-205°C.

Elemental Analyses for C₃₂H₃₄N₂O₄:

Calculated: C 75.27; H 6.71; N 5.49

Found: C 75.04; H 6.69; N 5.41

15

Example 14

Preparation of 4-[9-benzyl-4-carboxamidocarbazol-6-yl]oxybutyric acid

20

A. Preparation of 9-benzyl-6-methoxycarbazole-4-carboxamide.

A mixture of 2.5gm. of of the tetrahydrocarbazole
from Example 1, Part A, and 5gm. of 5% Pd/C in 130ml. of
25 carbitol was refluxed for 7 hours, cooled, and evaporated
in vacuo. The residue was crystallized from
dichloromethane-ethanol to give sub-titled product,
1.1gm., 44%, mp 226-226°C.

Elemental Analyses for C₂₁H₁₈N₂O₂:

30 Calculated: C 76.34; H 5.49; N 8.48

Found: C 76.61; H 5.75; N 8.41

B. Preparation of 9-benzyl-6-hydroxycarbazole-4-carboxamide.

35 A suspension of 1.0gm. of the 6-methoxycarbazole from
Part A, above, and 10ml. of 1M boron tribromide in 250ml.
of dichloromethane was stirred for 2 hours, decomposed

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with ice-water, and extracted with 3:1 dichloromethane:isopropanol. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo to give sub-titled product, 1.0gm., 100%, mp 246-
5 248°C.

Elemental Analyses for $C_{20}H_{16}N_2O_2 \cdot 0.3H_2O$:

Calculated: C 74.66; H 5.20; N 8.71

Found: C 74.46; H 5.19; N 8.45

10 C. Preparation of 4-[9-benzyl-4-carboxamidocarbazol-6-yl]oxybutyric acid.

A solution of 700mg. (2.2mmol) of the above 6-hydroxycarbazole in 25ml. of tetrahydrofuran and 75ml. of dimethylformamide was treated with 100mg. of sodium
15 hydride (60% in mineral oil, 2.5mmol) for 5 minutes and then 0.35ml. (2.5mmol) of ethyl 4-bromobutyrate for 3 hours, diluted with water, and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue
20 was chromatographed on silica gel eluting with a gradient dichloromethane/0-3% methanol to give the O-alkylated derivative, 700mg., 74%, mp 150-152°C, which was dissolved in 75ml. of ethanol and 5ml. of 2N sodium hydroxide, stirred 16 hours, acidified with 1N hydrochloric acid, and
25 extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and evaporated in vacuo to give title product, 475mg., 72%, mp 252-254°C.

Elemental Analyses for $C_{24}H_{22}N_2O_4$:

30 Calculated: C 71.63; H 5.51; N 6.96

Found: C 71.39; H 5.66; N 6.72

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Example 15

Preparation of [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid.

5

A mixture of 430mg. of the product from Example 7 Part D, 2.0gm. of 5% Pd/C, and 20mL of carbitol was heated to reflux and refluxed for 21 hours, cooled, and filtered. The filtrate was diluted with water, acidified with hydrochloric acid, and extracted well with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and evaporated *in vacuo*. The residue was triturated with dichloromethane and filtered to remove solid tetrahydrocarbazole. The filtrate was evaporated *in vacuo* to give the title product, 125mg, 31%.

10

Elemental Analyses for $C_{23}H_{20}N_2O_5 \cdot 0.4H_2O$:

Calculated: C 67.11; H 5.09; N 6.81

Found: C 67.25; H 5.19; N 6.75

20

Example 16

Preparation of methyl [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid

25 A. Preparation of 9-benzyl-4-carbamoyl-5,7-dimethoxycarbazole

A mixture of 2.0gm. of the product from Example 6, 2gm. of 5% Pd/C, and 100mL of carbitol was refluxed for 17 hours, filtered while still hot, and the solid washed well with ethyl acetate. The combined filtrates were washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give subtitled product, 1.4gm., 70%, mp 240-243°C.

30

Elemental Analyses for $C_{22}H_{20}N_2O_3$:

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Calculated: C 73.32; H 5.59; N 7.77

Found: C 74.26; H 5.73; N 8.04

5 B. Preparation of 9-benzyl-4-carbamoyl-5-hydroxy-7-methoxycarbazole.

A solution of 1.2gm. (3.3 mmol) of the product from Part A and 10 mmol of sodium ethanethiolate in 100mL of dimethylformamide was heated at 100°C for 42 hours, cooled, diluted with water, and the pH adjusted to 5-6 with
10 hydrochloric acid. The mixture was extracted with ethyl acetate, the organic phase was washed with water, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate to give product, 550mg., 48%, mp 234-
15 236°C dec.

Elemental Analyses for $C_{21}H_{18}N_2O_3$:

Calculated: C 72.82; H 5.24; N 8.09

Found: C 72.54; H 5.19; N 8.04

20 C. Preparation of methyl [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid.

A solution of 430mg. (1.2 mmol) of the product from Part B in 40mL of dimethylformamide and a few mLs of tetrahydrofuran was treated with 60mg. of sodium hydride
25 (60% in mineral oil; 1.5 mmol) for 15 minutes and then with 0.13mL (1.4 mmol) of methylbromoacetate for 16 hours, diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a
30 gradient dichloromethane/ 1-3% methanol to give title compound, 320mg., 62%, mp 170-172°C.

Elemental Analyses for $C_{24}H_{22}N_2O_5$:

Calculated: C 68.89; H 5.30; N 6.69

Found: C 68.64; H 5.41; N 6.57

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D. Preparation of [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid sodium salt

To a suspension of 60mg (0.15mmol) of the product from part C in 30mL of ethanol was added 0.075mL of 2.0 N sodium hydroxide. The mixture was heated until solution, cooled, concentrated *in vacuo*, diluted with ethyl acetate, concentrated *in vacuo*, cooled, and filtered to give product, amorphous solid, 50mg., 80%.

MS (FAB+) 427.2 : MS (ion spray) +Q1 405.5, -Q1 403.5

10

Example 17

Preparation of 9-benzyl-7-methoxy-5-cyanomethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

A solution of 1.47gram (4.19 mmol) of the product from Example 7, Part A in 146ml. of dimethylformamide and 31ml. tetrahydrofuran was treated with 210mg. of sodium hydride (60% in mineral oil; 5.24mmol) for 10 minutes and then with 0.39ml. (0.66 mmol) of bromoacetonitrile for 3.5 hours. The mixture was diluted with ethyl acetate, washed with water, washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient of 0 to 4% methanol in methylene chloride to give the titled product, 1.34gram, 82%.

20
25

Elemental analysis for $C_{23}H_{23}N_3O_3$:

Calculated: C 70.93; H 5.95; N 10.79

Theory: C 70.67; H 6.06; N 10.83

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Example 18

Preparation of 9-benzyl-7-methoxy-5-(1H-tetrazol-5-yl-methyl)oxy)-1,2,3,4-tetrahydrocarbazole-4-carboxamide.

5

A portion of the compound of Example 17, 0.45gram (1.16mmol) was heated with 5ml. tri-n-butyl in hydride at 95°C for 1 hour. The reaction was then added to a mixture of 125 ml. acetonitrile, 25ml. tetrahydrofuran, and 50ml. acetic acid and stirred for 2 hours. The mixture was extracted 4 times with hexane and the residue evaporated *in vacuo*. Crystallization from acetone and hexane afforded the titled compound, 0.30gram, 60%.

10

Elemental analysis for $C_{23}H_{24}N_6O_3$:

15

Calculated: C 63.88; H 5.59; N 19.43

Theory: C 64.06; H 5.64; N 19.28

Example 19

Preparation of 2-[(2,9 bis-benzyl-4-carbamoyl-1,2,3,4-tetrahydro-beta-carbol-5-yl)oxy]acetic acid

20

A. Preparation of 4-(tert-butyldimethylsilyl)oxyindole.

Imidazole (15.3 g, 225 mmol) was added to a solution of 4-hydroxyindole (20 g, 150 mmol) in 300 mL of anhydrous CH_2Cl_2 at ambient temperature. The resulting mixture was treated with tert-butyldimethylsilyl chloride (25 g, 165 mmol). After stirring overnight at ambient temperature, the reaction mixture was poured into 300 mL of water. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 X 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to a black oil. The crude residue was purified on the Prep 500 (silica gel; 0% to 5% ethyl acetate/hexanes) to

30

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give the title compound as a light purple waxy solid in quantitative yield.

MS (ion spray, NH₄OAc) m/e [M+1]⁺ 248, [M-1]⁻ 246.

Elemental Analysis for C₁₄H₂₁NOSi:

5 Calculated: C 67.96; H 8.55; N 5.66
 Found: C 69.10; H 8.79; N 5.70

B. Preparation of Ethyl [4-(tert-butyl-
 butyldimethylsilyl)oxyindole]-3-acetic acid

10

A solution of indole (78) (247 mg, 1.00 mmol) in dry tetrahydrofuran (2 mL) under a nitrogen atmosphere was cooled to -10°C then n-butyllithium (0.625 mL, 1.00 mmol), 1.6 M in hexanes, was added dropwise over 30 sec by syringe. The resultant solution was stirred 15 minutes the zinc chloride (1.0 mL, 1.0 mmol), 1 M in ether, was added all at once. The solution was stirred 2 hours while warming to ambient temperature. To this solution was added ethyl iodoacetate (0.118 mL, 1.00 mmol) all at once. The reaction mixture darkened but remained clear. The mixture was stirred 3 hours at ambient temperature the concentrated in vacuo. The residue was purified directly on silica gel (30 X 35 mm column) eluting with methylene chloride.

15 Concentration of appropriate fractions yielded 192 mg
20 (57.8%) of the titled product as a white solid.

MS (ion spray, NH₄OAc) m/e [M+1]⁺ 334, [M-1]⁻ 332.

Elemental Analyses for C₁₈H₂₇NO₃Si:

 Calculated: C 64.86; H 8.11; N 4.20
 Found: C 65.11; H 8.02; N 4.24

30

C. Preparation of Ethyl [2,9-bis-benzyl-5-(tert-butyl-
 butyldimethylsilyl)oxy-1,2,3,4-tetrahydro-beta-carboline]-4-acetic acid

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A solution of the ester (79) (5.08 g, 15.2 mmol) in dry tetrahydrofuran (100 mL) was cooled to -78°C then treated dropwise with 0.5 M potassium bis(trimethylsilyl)amide in 5 toluene (32 mL, 16 mmol). The resultant solution was stirred 10 min then benzyl iodide (3.32g, 15.2 mmol) was added all at once. The cooling bath was removed, the mixture warmed quickly to 0°C, then slowly to ambient temperature. After stirring 75 minutes at ambient 10 temperature the mixture was concentrated in vacuo. The residue was taken up in ether and washed successively with 10% aqueous citric acid, water and saturated sodium bicarbonate solution. The ethereal solution was dried over magnesium sulfate and concentrated in vacuo. The residue 15 was purified on silica gel (70 X 130 mm column) eluting with 500 mL 1:1 methylene chloride/hexanes then 500 mL methylene chloride. The appropriate fractions were combined and concentrated in vacuo to yield 5.90 g (91%) of ethyl [1-benzyl-4-(tert-butyl dimethylsilyl)oxyindole]-3-acetic acid 20 as a brown oil.

Benzyl amine (2.14 g, 20.0 mmol) and paraformaldehyde (1.80 g, 120 mmol) were combined and warmed to reflux in anhydrous methanol (10 mL) for 2 hours. The mixture was concentrated in vacuo and dried under vacuum for 30 minutes 25 to yield crude benzyl bis(methoxymethyl)amine as a water white oil. This material was used immediately without purification.

To a cooled solution of ethyl [1-benzyl-4-(tert-butyl dimethylsilyl)oxyindole]-3-acetic acid (190 mg, 0.45 30 mmol) in dry tetrahydrofuran (2 mL) was added potassium bis(trimethylsilyl)amide (0.98 mL, 0.49 mmol), 0.5 M in toluene, dropwise by syringe. After stirring the mixture 10 minutes, trimethylsilylchloride (0.057 mL, 0.45 mmol) was added all at once. The mixture was allowed to warm to

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ambient temperature then concentrated in vacuo. The residue was dried 30 minutes under vacuum to yield the trimethylsilylketene acetal (81). The residual ketene acetal (81) was immediately dissolved in methylene chloride (30 mL) to which was added freshly prepared benzyl bis(methoxymethyl)amine (175 mg, 0.90 mmol). The mixture was cooled to -78°C and treated with 1 M zinc chloride in ether (0.9 mL, 0.9 mmol). The mixture was allowed to warm to ambient temperature and stirred for an additional 45 minutes. The mixture was washed with saturated sodium bicarbonate solution then passed through a silica gel plug eluting with 1:4 ethyl acetate/hexane. The desired fractions were combined and concentrated in vacuo then further purified on an SCX cartridge (1g, Varian) with methanol and ammonia. Desired fractions were combined, concentrated and finally purified on silica gel eluting with methylene chloride to yield 34 mg (14%) of the titled tricyclic indole.

MS (ion spray, NH₄OAc) m/e [M+1]⁺ 555.

Elemental Analyses for C₃₄H₄₂N₂O₃Si:

Calculated: C 73.64; H 7.58; N 5.05

Found: C 73.42; H 7.61; N 5.15

D. Preparation of ethyl 2-[(2,9-bis-benzyl-4-carbamoyl-1,2,3,4-tetrahydro-beta-carbol-5-yl)oxy]acetic acid

A solution of 565 mg (1.02 mmol) of the compound of Part C in 10 mL 1:1 methanol/tetrahydrofuran was treated with 5 mL (5 mmol) 1 N lithium hydroxide under an atmosphere of nitrogen. The mixture was warmed briefly, allowed to stir at ambient temperature for 2 hours then concentrated in vacuo to about 5 mL. The pH of the solution was adjusted to ~5 to 6 with 1 N hydrochloric acid. The resultant

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precipitate was collected and dried to yield 430 mg (102%) of hydroxy acid.

This product was suspended with hydroxybenzotriazole (160 mg, 1.19mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (940 mg, 2.30 mmol) in 30 mL of 1:1 tetrahydrofuran/methylene chloride. The mixture was stirred vigorously for 10 minutes, saturated with ammonia gas, stirred vigorously for 1 hour, then concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was passed through a plug of silica gel with ethyl acetate. The eluant was evaporated to yield 175 mg (43%) of the carboxamide.

This compound was dissolved in 3 mL dry tetrahydrofuran, cooled to -70°C and treated with 0.5 M potassium bis(trimethylsilyl)amide in toluene (0.85 mL, 0.425 mmol). The solution was stirred 10 min then ethyl bromoacetate was added all at once. The reaction was stirred 6 hours while warming to ambient temperature. The mixture was concentrated in vacuo and the residue purified on silica gel eluting with ethyl acetate to yield 86 mg (41%) of the title compound.

MS (ion spray, NH_4OAc) m/e $[\text{M}+1]^+$ 498.

Elemental Analyses for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_4$:

Calculated:	C	72.43;	H	6.24;	N	8.45
Found:	C	72.54;	H	6.36;	N	8.64

E. Preparation of 2-[(2,9-bis-benzyl-4-carbamoyl-1,2,3,4-tetrahydro-beta-carbol-5-yl)oxy]acetic acid

A solution of the compound from Part D (78 mg, 0.16 mmol) in 2 mL 1:1 tetrahydrofuran/methanol was stirred with 1 M lithium hydroxide (0.63 mL, 0.63 mmol) for 3 hours. The

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mixture was concentrated in vacuo to give a white solid. The solid was suspended in 2 mL water and the pH adjusted to ~ 5 to 6 with 1 N hydrochloric acid forming a somewhat different white solid. The new solid was collected by
5 filtration and dried under vacuum to yield 68 mg (93%) of the title compound.

MS (ion spray, NH₄OAc) m/e [M+1]⁺ 470.

Elemental Analyses for C₂₈H₂₇N₃O₄ · 0.8 H₂O:

	Calculated:	C	69.49;	H	5.96;	N	8.68
10	Found:	C	69.50;	H	5.64;	N	8.54

Therapeutic Use of Tricyclic Compounds

15 The compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of human sPLA₂, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade,
20 such as 5-lipoxygenases, cyclooxygenases, etc.

The method of the invention for inhibiting sPLA₂ mediated release of fatty acids comprises contacting sPLA₂ with an therapeutically effective amount of the compound of Formula (III) or its salt.

25 The compounds of the invention may be used in a method of treating a mammal (e.g., a human) to alleviate the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, and rheumatoid
30 arthritis; wherein the method comprises administering to the mammal a compound of formula (III) in a therapeutically effective amount. A "therapeutically effective" amount is an amount sufficient to inhibit sPLA₂ mediated release of fatty acid and to thereby inhibit or
35 prevent the arachidonic acid cascade and its deleterious

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products. The therapeutic amount of compound of the invention needed to inhibit sPLA₂ may be readily determined by taking a sample of body fluid and assaying it for sPLA₂ content by conventional methods.

5

Pharmaceutical Formulations of the Invention

As previously noted the compounds of this invention are useful for inhibiting sPLA₂ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of sPLA₂ initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In general, the compounds of the invention are most desirably administered at a dose that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the route of administration, the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms. Typical daily doses will contain a non-toxic dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably the pharmaceutical formulation is in unit dosage form. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of

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these. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be
5 necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

A "chronic" condition means a deteriorating condition of slow progress and long continuance. As such,
10 it is treated when it is diagnosed and continued throughout the course of the disease. An "acute" condition is an exacerbation of short course followed by a period of remission. In an acute event, compound is administered at the onset of symptoms and discontinued
15 when the symptoms disappear.

Pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis may occur as an acute event or a chronic event. Thus, the treatment of these conditions contemplates both acute and
20 chronic forms. Septic shock and adult respiratory distress, on the other hand, are acute conditions treated when diagnosed.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal,
25 subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compounds of the invention together with a pharmaceutically acceptable carrier or
30 diluent therefor. The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the active ingredient will usually be admixed
35 with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves

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as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

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Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (III) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity <u>(mg/capsule)</u>
5-hydroxy-7-(5-cyanopentyl)-9-methyl- 1,2,3,4-tetrahydrocarbazole-4- carboxamide	250
Starch, dried	200
Magnesium stearate	<u>10</u>
Total	460 mg

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Formulation 2

A tablet is prepared using the ingredients below:

	<u>Quantity</u> <u>(mg/tablet)</u>
6-(3-(4-carboxyphenyl)prop-1-yl)oxy- 8-heptyl-9-(5-ethylphenyl)phenyl methylcarbazole-4-carboxamide	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	665 mg

- 5 The components are blended and compressed to form tablets
each weighing 665 mg

Formulation 3

- 10 An aerosol solution is prepared containing the
following components:

	<u>Weight</u>
5-(di-t-butoxyphosphonyl)methoxy-7- decyl-9-(5-propylthiophenyl)methyl- 1,2,3,4-tetrahydrocarbazole-4- carboxylic acid hydrazide	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	<u>74.00</u>
Total	100.00

- 15 The active compound is mixed with ethanol and
the mixture added to a portion of the propellant 22,
cooled to -30°C and transferred to a filling device. The
required amount is then fed to a stainless steel container
and diluted with the remainder of the propellant. The
valve units are then fitted to the container.

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Formulation 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

5

5-(di-t-butoxyphosphonyl)methoxy-7-decyl-9-(5-propylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide 60 mg

Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	<u>1 mg</u>
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

20

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Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

5-ethoxycarbonylmethoxy-8-(5-carbamoylpent-1-yl)-9-(3,5-dipropylphenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	<u>2 mg</u>
Total	200 mg

5

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

10

Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

15

6-hydroxy-8-(4-(N,N-diethylamino)but-1-yl)-9-(5-fluorophenyl)methyl-4-carboxamide	225 mg
Saturated fatty acid glycerides	<u>2,000 mg</u>
Total	2,225 mg

20

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

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Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

5-(propoxycarbonyl)methoxy-9-cyclopentylmethyl-1,2,3,4-tetrahydrocarbazole-4-carboxamide	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

5

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

10

Formulation 8

An intravenous formulation may be prepared as follows:

15

5-(di-t-butoxyphosphonyl)methoxy-7-decyl-9-(5-propylthiophenyl)methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid hydrazide	100 mg
Isotonic saline	1,000 ml

20

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

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Assay ExperimentsAssay Example 1

The following chromogenic assay procedure was
5 used to identify and evaluate inhibitors of recombinant
human secreted phospholipase A₂. The assay described
herein has been adapted for high volume screening using 96
well microtiter plates. A general description of this
10 assay method is found in the article, "Analysis of Human
Synovial Fluid Phospholipase A₂ on Short Chain
Phosphatidylcholine-Mixed Micelles: Development of a
Spectrophotometric Assay Suitable for a Microtiterplate
Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward
A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992
15 (the disclosure of which is incorporated herein by
reference):

Reagents:

REACTION BUFFER -
CaCl₂.2H₂O (1.47 g/L)
20 KCl (7.455 g/L)
Bovine Serum Albumin (fatty acid free) (1 g/L)
(Sigma A-7030, product of Sigma Chemical
Co. St. Louis MO, USA)
TRIS HCl (3.94 g/L)
25 pH 7.5 (adjust with NaOH)
ENZYME BUFFER -
0.05 NaOAc.3H₂O, pH 4.5
0.2 NaCl
Adjust pH to 4.5 with acetic acid
30 DTNB - 5,5'-dithiobis-2-nitrobenzoic acid
RACEMIC DIHEPTANOYL THIO - PC
racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-sn-
glycero-3-phosphorylcholine
TRITON X-100TM prepare at 6.249 mg/ml in
35 reaction buffer to equal 10uM
TRITON X-100TM is a polyoxy ethylene non-ionic
detergent supplied by

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Pierce Chemical Company,
3747 N. Meridian Road, Rockford, Illinois
61101.

REACTION MIXTURE -

5 A measured volume of racemic dipheptanoyl thio
PC supplied in chloroform at a concentration of 100 mg/ml
is taken to dryness and redissolved in 10 millimolar
TRITON X-100TM nonionic detergent aqueous solution.
Reaction Buffer is added to the solution, then DTNB to
10 give the Reaction Mixture.

 The reaction mixture thus obtained contains 1mM
diheptanoly thio-PC substrate, 0.29 mM Triton X-100TM
detergent, and 0.12 mM DTMB in a buffered aqueous solution
at pH 7.5.

15

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to
appropriate wells, mix 20 seconds;
- 20 3. Add 50 nanograms of sPLA₂ (10 microliters) to
appropriate wells;
4. Incubate plate at 40°C for 30 minutes;
5. Read absorbance of wells at 405 nanometers with an
automatic plate reader.

25

 All compounds were tested in triplicate.
Typically, compounds were tested at a final concentration
of 5 ug/ml. Compounds were considered active when they
exhibited 40% inhibition or greater compared to
uninhibited control reactions when measured at 405
30 nanometers. Lack of color development at 405 nanometers
evidenced inhibition. Compounds initially found to be
active were reassayed to confirm their activity and, if
sufficiently active, IC₅₀ values were determined.
Typically, the IC₅₀ values (see, Table I, below) were
35 determined by diluting test compound serially two-fold
such that the final concentration in the reaction ranged
from 45 ug/mL to 0.35 ug/ml. More potent inhibitors

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required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC₅₀ values. IC₅₀ were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

Compounds of the instant invention (Examples 1-19) were tested in Assay Example 1 and were found to be effective at concentrations of less than 100µM.

Assay Example 2

Method:

Male Hartley strain guinea pigs (500-700g) were killed by cervical dislocation and their heart and lungs removed intact and placed in aerated (95% O₂:5% CO₂) Krebs buffer. Dorsal pleural strips (4x1x25mm) were dissected from intact parenchymal segments (8x4x25mm) cut parallel to the outer edge of the lower lung lobes. Two adjacent pleural strips, obtained from a single lobe and representing a single tissue sample, were tied at either end and independently attached to a metal support rod. One rod was attached to a Grass force-displacement transducer Model FTO3C, product of Grass Medical Instruments Co., Quincy, MA, USA). Changes in isometric tension were displayed on a monitor and thermal recorder (product of Modular Instruments, Malvern, PA). All tissues were placed in 10 ml jacketed tissue baths maintained at 37°C. The tissue baths were continuously aerated and contained a modified Krebs solution of the following composition (millimolar) NaCl, 118.2; KCl, 4.6; CaCl₂·2H₂O, 2.5; MgSO₄·7H₂O, 1.2; NaHCO₃, 24.8; KH₂PO₄, 1.0; and dextrose, 10.0. Pleural strips from the opposite lobes of the lung were used for paired experiments. Preliminary data generated from tension/response curves demonstrated that resting tension of 800mg was optimal.

The tissues were allowed to equilibrate for 45 min. as the bath fluid was changed periodically.

Cumulative concentration-response curves:

5 Initially tissues were challenged 3 times with
KCl (40 mM) to test tissue viability and to obtain a
consistent response. After recording the maximal response
to KCl, the tissues were washed and allowed to return to
baseline before the next challenge. Cumulative
10 concentration-response curves were obtained from pleural
strips by increasing the agonist concentration (sPLA₂) in
the tissue bath by half-log₁₀ increments while the
previous concentration remained in contact with the
tissues (Ref.1, supra.). Agonist concentration was
15 increased after reaching the plateau of the contraction
elicited by the preceding concentration. One
concentration-response curve was obtained from each
tissue. To minimize variability between tissues obtained
from different animals, contractile responses were
20 expressed as a percentage of the maximal response obtained
with the final KCl challenge. When studying the effects
of various drugs on the contractile effects of sPLA₂, the
compounds and their respective vehicles were added to the
tissues 30 minutes prior to starting the sPLA₂
25 concentration-response curves.

Statistical analysis:

 Data from different experiments were pooled and
presented as a percentage of the maximal KCl responses
30 (mean ± S.E.). To estimate the drug induced rightward
shifts in the concentration response curves, the curves
were analyzed simultaneously using statistical nonlinear
modeling methods similar to those described by Waud
(1976), Equation 26, p. 163, (Ref.2). The model includes
35 four parameters: the maximum tissue response which was
assumed the same for each curve, the ED₅₀ for the control
curve, the steepness of the curves, and the pA₂, the

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concentration of antagonist that requires a two-fold increase in agonist to achieve an equivalent response. The Schild slope was determined to be 1, using statistical nonlinear modeling methods similar to those described by Waud (1976), Equation 27, p. 164 (Ref. 2). The Schild slope equal to 1 indicates the model is consistent with the assumptions of a competitive antagonist; therefore, the pA_2 may be interpreted as the apparent K_B , the dissociation constant of the inhibitor.

To estimate the drug-induced suppression of the maximal responses, sPLA₂ responses (10 ug/ml) were determined in the absence and presence of drug, and percent suppression was calculated for each pair of tissues. Representative examples of inhibitory activities are presented in Table 2, below.

Ref. 1 - Van, J.M.: Cumulative dose-response curves. II. Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters. Arch. Int. Pharmacodyn. Ther., 143: 299-330, 1963.

Ref. 2 - Waud, D.: Analysis of dose-response relationships. in Advances in General and Cellular Pharmacology eds Narahashi, Bianchi 1:145-178, 1976.

Compounds of the instant invention (Examples 1-19) were tested in Assay Example 2 and were found to be effective at concentrations below 20 μ M.

Assay Example 3

sPLA₂ Transgenic Mice Assay

Materials & Methods

The mice utilized in these studies were mature, 6-8 month old, ZnSO₄-stimulated, hemizygous line 2608^a transgenic mice (Fox et. al. 1996). Transgenic mice from this line express human sPLA₂ in the liver and other

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tissues and typically achieve levels of human sPLA₂ in their circulation of approximately 173 ± 10 ng/ml when maximally stimulated with ZnSO₄ (Fox, et al. 1996). The mice were housed under constant humidity and temperature and received food and water ad libitum. Animal room lighting was maintained on a 12-hour light/dark cycle and all experiments were performed at the same time of the day during the early morning light period.

For intravenous testing, compounds or vehicle were administered as an IV bolus via the tail vein in a volume of 0.15 ml. Vehicle consisted of 1-5% dimethylsulfoxide, 1-5% ethanol and 10-30% polyethylene glycol 300 in H₂O; the concentrations of these ingredients were adjusted according to the solubility of the compound. Mice were bled retro-orbitally prior to drug or vehicle administration and 30 minutes, 2 and 4 hours thereafter. Three to six mice were used for each dose. PLA₂ catalytic activity in the serum was assayed with a modified phosphatidylcholine/deoxycholine mixed micelle assay (Fox, et al. 1996, Schadlich, et al., 1987) utilizing 3 mM sodium deoxycholate and 1 mM 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.

For oral testing, compounds were dissolved in 1-5% ethanol/10-30% polyethylene glycol 300 in H₂O or were suspended in 5% dextrose in H₂O and administered by oral gavage. Serum was prepared from retro-orbital blood and assayed for PLA₂ catalytic activity as above.

References

- Fox, N., M. Song, J. Schrementi, J. D. Sharp, D. L. White, D. W. Snyder, L. W. Hartley, D. G. Carlson, N. J. Bach, R. D. Dillard, S. E. Draheim, J. L. Bobbitt, L. Fisher and E. D. Mihelich. 1996.
Eur. J. Pharmacol. 308: 195.

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Schadlich, H.R., M. Buchler, and H. G. Beger, 1987, J.
Clin. Chem. Clin.

Biochem. 25, 505.

5 Compounds of the instant invention were tested
in Assay Example 3 and were found to be effective.

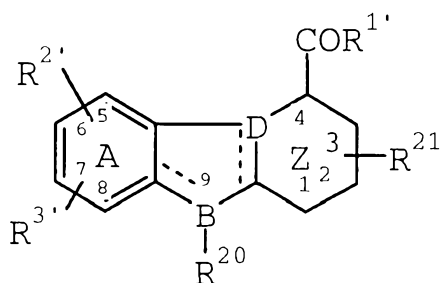
 While the present invention has been illustrated
above by certain specific embodiments, it is not intended
that these specific examples should limit the scope of the
10 invention as described in the appended claims.

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5

Claims

1. A compound of the formula (III)



(III)

10

wherein ;

A is phenyl or pyridyl wherein the nitrogen is at the 5-, 6-, 7- or 8-position;

one of B or D is nitrogen and the other is carbon;

15

Z is cyclohexenyl, phenyl, pyridyl, wherein the nitrogen is at the 1-, 2- or 3-position, or a 6-membered heterocyclic ring having one heteroatom selected from the group consisting of sulfur or oxygen at the 1-, 2- or 3-position, and nitrogen at the 1-, 2-, 3- or 4-position;

20

--- is a double or single bond;

R^{20} is selected from groups (a), (b) and (c) where;

(a) is $-(C_5-C_{20})$ alkyl, $-(C_5-C_{20})$ alkenyl, $-(C_5-C_{20})$ alkynyl, carbocyclic radicals, or heterocyclic radicals, or

25

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

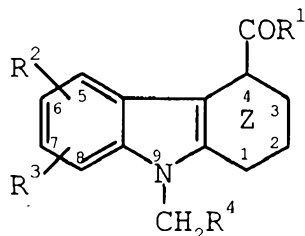
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(c) is the group $-(L)-R^{80}$; where, $-(L)-$ is a divalent linking group of 1 to 12 atoms selected from carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein the combination of atoms in $-(L)-$ are selected from the group consisting of (i) carbon and hydrogen only, (ii) one sulfur only, (iii) one oxygen only, (iv) one or two nitrogen and hydrogen only, (v) carbon, hydrogen, and one

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- 5 sulfur only, and (vi) and carbon, hydrogen, and oxygen only; and where R^{80} is a group selected from (a) or (b);
 R^{21} is a non-interfering substituent;
 $R^{1'}$ is $-NHNH_2$ or $-NH_2$;
 $R^{2'}$ is selected from the group $-OH$, $-O(CH_2)_tR^5$ where
 10 R^5 is CN or phenyl, or $-(L_a)-(acidic\ group)$; wherein $-(L_a)-$ is an acid linker having an acid linker length of 1 to 7 and t is 1-5;
 $R^{3'}$ is selected from non-interfering substituent, carbocyclic radicals, carbocyclic radicals substituted
 15 with non-interfering substituents, heterocyclic radicals, and heterocyclic radicals substituted with non-interfering substituents;
 or a pharmaceutically acceptable salt, racemate, solvate, tautomer, optical isomer or prodrug derivative
 20 thereof;
 provided that when $R^{3'}$ is H, R^{20} is benzyl and m is 1 or 2, $R^{2'}$ cannot be $-O(CH_2)_mH$;
 and when D is nitrogen, the heteroatom of Z is selected from the group consisting of sulfur or oxygen at
 25 the 1-, 2- or 3-position and nitrogen at the 1-, 2-, 3- or 4-position.

2. A compound of the formula (I)



(I)

30

wherein:

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is $-OH$, or $-O(CH_2)_mR^5$ where

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5 R^5 is H, $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$,

$\begin{array}{c} O \\ || \\ -P \end{array} (R^6R^7)$, phenyl, or phenyl substituted with
 $-CO_2H$ or $-CO_2(C_1-C_4 \text{ alkyl})$ where R^6 and R^7 are
 each independently $-OH$ or $-O(C_1-C_4 \text{ alkyl})$ and m
 is 1-3;

10 R^3 is H, $-O(C_1-C_4 \text{ alkyl})$, or $-(CH_2)_nR^8$ where

$\begin{array}{c} O \\ || \\ -C \end{array} NH_2$, $-CN$, or phenyl where
 R^8 is H, $-NR^9R^{10}$, $-C$
 R^9 and R^{10} are independently $-(C_1-C_4)alkyl$, or
 phenyl(C_1-C_4)alkyl and n is 1-8;

R^4 is H, $-(C_5-C_{14})alkyl$, $-(C_3-C_{14})cycloalkyl$, phenyl,

15 or phenyl substituted with 1 or 2 substituents
 selected from the group consisting of
 $-(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$,
 phenyl(C_1-C_4)alkyl, $(C_1-C_4)alkylthio$, halo or
 phenyl; and

20 Z is cyclohexenyl or phenyl;

or a pharmaceutically acceptable salt, racemate,
 optical isomer, solvate, tautomer or prodrug
 derivative thereof;

provided that when R^3 is H, R^4 is phenyl, m is 1 or 2

25 and R^2 is substituted at the 6 position, R^5
 cannot be H; and

when R^1 is $NHNH_2$, R^8 cannot be $\begin{array}{c} O \\ || \\ -C \end{array} NH_2$.

3. A compound of formula I as claimed in Claim

30 2 wherein

R^1 is $-NHNH_2$ or $-NH_2$;

R^2 is $-O(CH_2)_mR^5$ where R^5 is $-CO_2H$ or $\begin{array}{c} O \\ || \\ -P \end{array} (R^6R^7)$ where
 R^6 and R^7 are $-OH$;

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- 5 R³ is H, -O(C₁-C₄ alkyl) or -(CH₂)_nR⁸ where R⁸ is H
 or phenyl;
 R⁴ is phenyl; and
 Z is cyclohexene.

- 10 4. A compound of Claim 3 which is 4-[(9-
benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-
yl)oxy]butyric acid; 3-[(9-benzyl-4-carbamoyl-1,2,3,4-
tetrahydrocarbazol-6-yl)oxy]propylphosphonic acid; 2-[(9-
benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-6-
15 yl)oxy]methylbenzoic acid; 3-[(9-benzyl-4-carbamoyl-7-n-
octyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic
acid; 4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-
tetrahydrocarbazol-6-yl)oxy]butyric acid; 3-[(9-benzyl-4-
carbamoyl-7-ethyl-1,2,3,4-tetrahydrocarbazol-6-
20 yl)oxy]propylphosphonic acid; 3-[(9-benzyl-4-carbamoyl-7-
ethyl-1,2,3,4-tetrahydrocarbazol-6-yl)oxy]propylphosphonic
acid; (S)-(+)-4-[(9-benzyl-4-carbamoyl-7-ethyl-1,2,3,4-
tetrahydrocarbazol-6-yl)oxy]butyric acid; 4-[9-benzyl-4-
carbamoyl-6-(2-cyanoethyl)-1,2,3,4-tetrahydrocarbazol-6-
25 yl]oxybutyric acid; 4-[9-benzyl-4-carboxamido-7-(2-
phenylethyl)-1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric
acid; 4-[9-benzyl-4-carboxamidocarbazol-6-yl]oxybutyric
acid; methyl 2-[(9-benzyl-4-carbamoyl-1,2,3,4-
tetrahydrocarbazol-6-yl)oxy]methylbenzoate; 9-benzyl-5,7-
30 dimethoxy-1,2,3,4-tetrahydrocarbazole-4-carboxylic acid
hydrazide; 9-benzyl-5,7-dimethoxy-1,2,3,4-
tetrahydrocarbazole-4-carboxamide; [9-benzyl-4-carbamoyl-
7-methoxy-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid
sodium salt; 4-[9-benzyl-4-carbamoyl-7-(2-cyanoethyl)-
35 1,2,3,4-tetrahydrocarbazol-6-yl]oxybutyric acid; [9-
benzyl-4-carbamoyl-7-methoxycarbazol-5-yl]oxyacetic acid;
methyl [9-benzyl-4-carbamoyl-7-methoxycarbazol-5-
yl]oxyacetic acid; 9-benzyl-7-methoxy-5-cyanomethoxy-
1,2,3,4-tetrahydrocarbazole-4-carboxamide; 9-benzyl-7-
40 methoxy-5-(1H-tetrazol-5-yl-methyl)oxy)-1,2,3,4-

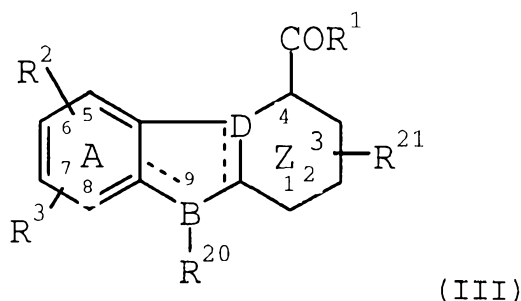
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5 tetrahydrocarbazole-4-carboxamide; [9-benzyl-4-carbamoyl-8-methyl-1,2,3,4-tetrahydrocarbazole-5-yl]oxyacetic acid; [9-benzyl-4-carbamoyl-8-methyl-carbazole-5-yl]oxyacetic acid; [9-benzyl-4-carbamoyl-1,2,3,4-tetrahydrocarbazol-5-yl]oxyacetic acid; and [9-benzyl-4-carbamoyl-carbazole-5-yl]oxyacetic acid or a pharmaceutically acceptable salt,
 10 racemate, solvate, tautomer, optical isomer or prodrug derivative thereof.

5. A pharmaceutical formulation comprising a
 15 compound of formula III as claimed in Claim 1 together with a pharmaceutically acceptable carrier or diluent therefor.

6. A pharmaceutical formulation comprising a
 20 compound of formula I as claimed in Claim 2 together with a pharmaceutically acceptable carrier or diluent therefor.

7. A method of selectively inhibiting sPLA₂ in a mammal in need of such treatment comprising
 25 administering to said mammal a pharmaceutically effective amount of a compound of formula (III)



wherein ;

30 A is phenyl or pyridyl;
 B and D are each independently nitrogen or carbon;
 Z is cyclohexenyl, phenyl, pyridyl, wherein the nitrogen is at the 1-, 2- or 3-position or a 6-membered heterocyclic ring having one to three heteroatoms which
 35 are the same or different and which are selected from the

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5 group consisting of sulfur or oxygen at the 1-, 2- or 3-
position, and nitrogen at the 1-, 2-, 3- or 4-position;

 is a double or single bond;

R²⁰ is selected from groups (a), (b) and (c) where;

10 (a) is C₅-C₂₀ alkyl, C₅-C₂₀ alkenyl, C₅-C₂₀
alkynyl, carbocyclic radicals, or heterocyclic radicals,
or

(b) is a member of (a) substituted with one or
more independently selected non-interfering substituents;
or

15 (c) is the group -(L)-R⁸⁰; where, -(L)- is a
divalent linking group of 1 to 12 atoms selected from
carbon, hydrogen, oxygen, nitrogen, and sulfur; wherein
the combination of atoms in -(L)- are selected from the
group consisting of (i) carbon and hydrogen only, (ii) one
20 sulfur only, (iii) one oxygen only, (iv) one or two
nitrogen and hydrogen only, (v) carbon, hydrogen, and one
sulfur only, and (vi) and carbon, hydrogen, and oxygen
only; and where R⁸⁰ is a group selected from (a) or (b);

R²¹ is a non-interfering substituent;

25 R^{1'} is -NHNH₂ or -NH₂;

R^{2'} is selected from the group -OH, -O(CH₂)_tR⁵ where
R⁵ is CN or phenyl, or -(L_a)-(acidic group); wherein
-(L_a)- is an acid linker having an acid linker length of 1
to 7 and t is 1-5;

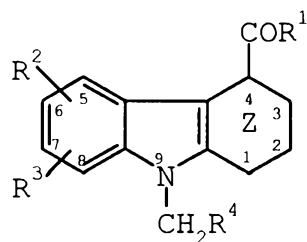
30 R^{3'} is selected from non-interfering substituent,
carbocyclic radicals, carbocyclic radicals substituted
with non-interfering substituents, heterocyclic radicals,
and heterocyclic radicals substituted with non-interfering
substituents;

35 or a pharmaceutically acceptable salt, racemate,
solvate, tautomer, optical isomer or prodrug derivative
thereof.

8. A method of selectively inhibiting sPLA₂ in
40 a mammal in need of such treatment comprising

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5 administering to said mammal a pharmaceutically effective amount of a compound of formula (II)



(II)

10 wherein:

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is $-OH$, or $-O(CH_2)_mR^5$ where

R^5 is H , $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$,

$\begin{matrix} O \\ || \\ -P(R^6R^7) \end{matrix}$, $-NHSO_2(C_1-C_6)alkyl$, $-CONHSO_2(C_1-$

15 $C_6)alkyl$, $-CN$, tetrazolyl, phenyl, or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4 \text{ alkyl})$ where R^6 and R^7 are each independently $-OH$ or $-O(C_1-C_4 \text{ alkyl})$ and m is 1-3;

R^3 is H , $-O(C_1-C_4 \text{ alkyl})$, or $-(CH_2)_nR^8$ where

20 R^8 is H , $-NR^9R^{10}$, $\begin{matrix} O \\ || \\ -C \\ | \\ NH_2 \end{matrix}$, $-CN$, or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)alkyl$, or $-phenyl(C_1-C_4)alkyl$ and n is 1-8;

R^4 is H , $-(C_5-C_{14})alkyl$, $-(C_3-C_{14})cycloalkyl$, phenyl, or phenyl substituted with 1 or 2 substituents
25 selected from the group consisting of $-(C_1-C_4)alkyl$, $-(C_1-C_4)alkoxy$, $-phenyl(C_1-C_4)alkyl$, $-(C_1-C_4)alkylthio$, halo or phenyl; and

Z is cyclohexenyl, phenyl, pyridyl wherein the
30 nitrogen is at the 1-, 2-, 3- or 4-position or a 6-membered heterocyclic ring having one heteroatom selected from the group consisting of

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5 sulfur or oxygen at the 1-, 2- or 3-position and
nitrogen at the 1-, 2-, 3- or 4-position, or
wherein one carbon on the heterocyclic ring is
optionally substituted with =O;

A is phenyl or pyridyl wherein the nitrogen is at the
10 5-, 6-, 7- or 8-position;

or a pharmaceutically acceptable salt, racemate,
optical isomer, tautomer, solvate or prodrug
derivative thereof;

provided that when R³ is H, R⁴ is phenyl, m is 1 or 2
15 and R² is substituted at the 6 position, R⁵
cannot be H; and

when R¹ is NHNH₂, R⁸ cannot be $\overset{\text{O}}{\parallel}\text{-C-NH}_2$.

9. A method of Claim 6 wherein the mammal is a
20 human.

10. A method of Claim 7 wherein the mammal is a
human.

25 11. A method of Claim 6 of alleviating the
pathological effects of septic shock, adult respiratory
distress syndrome, pancreatitis, trauma-induced shock,
bronchial asthma, allergic rhinitis, rheumatoid arthritis,
cystic fibrosis, stroke, acute bronchitis, chronic
30 bronchitis, acute bronchiolitis, chronic bronchiolitis,
osteoarthritis, gout, spondylarthropathris, ankylosing
spondylitis, Reiter's syndrome, psoriatic arthropathy,
enteropathic spondylitis, Juvenile arthropathy or juvenile
ankylosing spondylitis, Reactive arthropathy, infectious or
35 post-infectious arthritis, gonococcal arthritis, Tuberculous
arthritis, viral arthritis, fungal arthritis, syphilitic
arthritis, Lyme disease, arthritis associated with

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5 "vasculitic syndromes", polyarteritis nodosa,
hypersensitivity vasculitis, Luegenec's granulomatosis,
polymyalgin rheumatica, joint cell arteritis, calcium
crystal deposition arthropathris, pseudo gout, non-articular
rheumatism, bursitis, tenosynomitis, epicondylitis (tennis
10 elbow), carpal tunnel syndrome, repetitive use injury
(typing), miscellaneous forms of arthritis, neuropathic
joint disease (charco and joint), hemarthrosis
(hemarthrosic), Henoch-Schonlein Purpura, hypertrophic
osteoarthropathy, multicentric reticulohistiocytosis,
15 arthritis associated with certain diseases, surcoilosis,
hemochromatosis, sickle cell disease and other
hemoglobinopathries, hyperlipoproteineimia,
hypogammaglobulinemia, hyperparathyroidism, acromegaly,
familial Mediterranean fever, Behat's Disease, systemic
20 lupus erythrematosis, or relapsing polychondritis;
and related diseases which comprises administering to a
mammal in need of such treatment a compound of formula III
in an amount sufficient to inhibit sPLA₂ mediated release
of fatty acid and to thereby inhibit or prevent the
25 arachidonic acid cascade and its deleterious products.

12. A method of Claim 7 of alleviating the
pathological effects of septic shock, adult respiratory
distress syndrome, pancreatitis, trauma-induced shock,
30 bronchial asthma, allergic rhinitis, rheumatoid arthritis,
cystic fibrosis, stroke, acute bronchitis, chronic
bronchitis, acute bronchiolitis, chronic bronchiolitis,
osteoarthritis, gout, spondylarthropathris, ankylosing
spondylitis, Reiter's syndrome, psoriatic arthropathy,
35 enterapathric spondylitis, Juvenile arthropathy or juvenile
ankylosing spondylitis, Reactive arthropathy, infectious or

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5 post-infectious arthritis, gonococcal arthritis, Tuberculous
arthritis, viral arthritis, fungal arthritis, syphilitic
arthritis, Lyme disease, arthritis associated with
"vasculitic syndromes", polyarteritis nodosa,
hypersensitivity vasculitis, Luegenec's granulomatosis,
10 polymyalgin rheumatica, joint cell arteritis, calcium
crystal deposition arthropathris, pseudo gout, non-articular
rheumatism, bursitis, tenosynovitis, epicondylitis (tennis
elbow), carpal tunnel syndrome, repetitive use injury
(typing), miscellaneous forms of arthritis, neuropathic
15 joint disease (charco and joint), hemarthrosis
(hemarthrosic), Henoch-Schonlein Purpura, hypertrophic
osteoarthropathy, multicentric reticulohistiocytosis,
arthritis associated with certain diseases, surcoilosis,
hemochromatosis, sickle cell disease and other
20 hemoglobinopathries, hyperlipoproteineimia,
hypogammaglobulinemia, hyperparathyroidism, acromegaly,
familial Mediterranean fever, Behat's Disease, systemic
lupus erythrematosis, or relapsing polychondritis;
and related diseases which comprises administering to a
25 mammal in need of such treatment a compound of formula II
in an amount sufficient to inhibit sPLA₂ mediated release
of fatty acid and to thereby inhibit or prevent the
arachidonic acid cascade and its deleterious products.

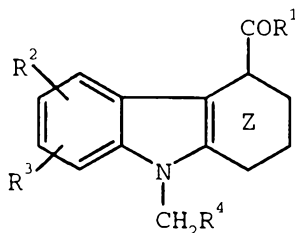
30 13. A method of Claim 10 wherein the mammal is
a human.

14. A method of Claim 11 wherein the mammal is
a human.

35

15. A process of preparing compounds of formula

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5

wherein

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is $-OH$, or $-O(CH_2)_mR^5$ where

R^5 is H , $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$,

10 $\overset{O}{\parallel}$
 $-P(R^6R^7)$, phenyl, or phenyl substituted with
 $-CO_2H$ or $-CO_2(C_1-C_4 \text{ alkyl})$ where R^6 and R^7 are
each independently $-OH$ or $-O(C_1-C_4 \text{ alkyl})$ and m
is 1-3;

R^3 is H , $-O(C_1-C_4 \text{ alkyl})$, or $-(CH_2)_nR^8$ where

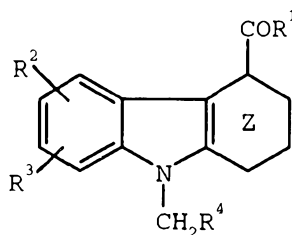
15 $\overset{O}{\parallel}$
 R^8 is H , $-NR^9R^{10}$, $-C^{\overset{O}{\parallel}}NH_2$, $-CN$, or phenyl where
 R^9 and R^{10} are independently $-(C_1-C_4)alkyl$, or
 $-phenyl(C_1-C_4)alkyl$ and n is 1-8;

R^4 is H , $-(C_5-C_{14})alkyl$, $-(C_3-C_{14})cycloalkyl$, phenyl,

20 or phenyl substituted with 1 or 2 substituents
selected from the group consisting of
 $-(C_1-C_4)alkyl$, $-(C_1-C_4)alkoxy$,
 $-phenyl(C_1-C_4)alkyl$, $-(C_1-C_4)alkylthio$, halo or
phenyl; and

25 Z is phenyl comprising dehydrogenating a compound of
the formula .

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5

wherein

R^1 is $-NHNH_2$, or $-NH_2$;

R^2 is $-OH$, or $-O(CH_2)_mR^5$ where

R^5 is H , $-CO_2H$, $-CO_2(C_1-C_4 \text{ alkyl})$,

10 $\begin{array}{c} O \\ || \\ -P(R^6R^7) \end{array}$, phenyl, or phenyl substituted with $-CO_2H$ or $-CO_2(C_1-C_4 \text{ alkyl})$ where R^6 and R^7 are each independently $-OH$ or $-O(C_1-C_4 \text{ alkyl})$ and m is 1-3;

R^3 is H , $-O(C_1-C_4 \text{ alkyl})$, or $-(CH_2)_nR^8$ where

15 R^8 is H , $-NR^9R^{10}$, $\begin{array}{c} O \\ || \\ -C \\ | \\ NH_2 \end{array}$, $-CN$, or phenyl where R^9 and R^{10} are independently $-(C_1-C_4)\text{alkyl}$, or $-phenyl(C_1-C_4)\text{alkyl}$ and n is 1-8;

R^4 is H , $-(C_5-C_{14})\text{alkyl}$, $-(C_3-C_{14})\text{cycloalkyl}$, phenyl, or phenyl substituted with 1 or 2 substituents
20 selected from the group consisting of $-(C_1-C_4)\text{alkyl}$, $-(C_1-C_4)\text{alkoxy}$, $-phenyl(C_1-C_4)\text{alkyl}$, $-(C_1-C_4)\text{alkylthio}$, halo or phenyl; and

Z is cyclohexenyl.

25

16. A compound of Formula III as claimed in Claim 1 substantially as herein before described with reference to any one of the foregoing Examples.

30

17. A compound of Formula I as claimed in any one of Claims 2 to 4 substantially as herein before

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5 described with reference to any one of the foregoing
Examples.

18. A compound of Formula III as claimed in Claim
1 for treating pathological effects of septic shock, adult
10 respiratory distress syndrome, pancreatitis, trauma-induced
shock, bronchial asthma, allergic rhinitis, rheumatoid
arthritis, cystic fibrosis, stroke, acute bronchitis,
chronic bronchitis, acute bronchiolitis, chronic
bronchiolitis, osteoarthritis, gout, spondylarthropathris,
15 ankylosing spondylitis, Reiter's syndrome, psoriatic
arthropathy, enteropathic spondylitis, Juvenile arthropathy
or juvenile ankylosing spondylitis, Reactive arthropathy,
infectious or post-infectious arthritis, gonococcal
arthritis, Tuberculous arthritis, viral arthritis, fungal
20 arthritis, syphilitic arthritis, Lyme disease, arthritis
associated with "vasculitic syndromes", polyarteritis
nodosa, hypersensitivity vasculitis, Luegenec's
granulomatosis, polymyalgin rheumatica, joint cell
arteritis, calcium crystal deposition arthropathris, pseudo
25 gout, non-articular rheumatism, bursitis, tenosynovitis,
epicondylitis (tennis elbow), carpal tunnel syndrome,
repetitive use injury (typing), miscellaneous forms of
arthritis, neuropathic joint disease (charco and joint),
hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura,
30 hypertrophic osteoarthropathy, multicentric
reticulohistiocytosis, arthritis associated with certain
diseases, surcoilosis, hemochromatosis, sickle cell disease
and other hemoglobinopathries, hyperlipoproteineimia,
hypogammaglobulinemia, hyperparathyroidism, acromegaly,
35 familial Mediterranean fever, Behat's Disease, systemic
lupus erythrematosis, or relapsing polychondritis;

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5 and related diseases.

19. A compound of Formula I as claimed in any one of Claims 2 to 4 for treating pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis; and related diseases.

5

20. The use of a compound of Formula III as claimed in Claim 1 for the manufacture of a medicament for treating pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis;

35

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5 and related diseases.

21. The use of a compound of Formula III as claimed in any one of Claims 2 to 4 pathological effects of septic shock, adult respiratory distress syndrome,
10 pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's
15 syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis,
20 Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism,
25 bursitis, tenosynovitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy,
30 multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean
35 fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis;

5 and related diseases.

22. A pharmaceutical formulation adapted for the treatment of pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced
10 shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic
15 arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis
20 associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynovitis,
25 epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric
30 reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic
35 lupus erythrematosis, or relapsing polychondritis;

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5 and related diseases containing a compound of Formula III
as claimed in Claim 1.

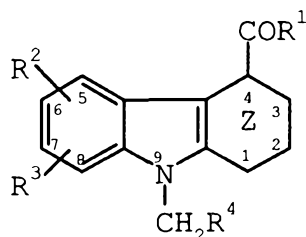
23. A method as in any one of Claims 7 to 10 of
alleviating the pathological effects of pathological effects
10 of septic shock, adult respiratory distress syndrome,
pancreatitis, trauma-induced shock, bronchial asthma,
allergic rhinitis, rheumatoid arthritis, cystic fibrosis,
stroke, acute bronchitis, chronic bronchitis, acute
bronchiolitis, chronic bronchiolitis, osteoarthritis, gout,
15 spondylarthropathris, ankylosing spondylitis, Reiter's
syndrome, psoriatic arthropathy, enteropathic spondylitis,
Juvenile arthropathy or juvenile ankylosing spondylitis,
Reactive arthropathy, infectious or post-infectious
arthritis, gonococcal arthritis, Tuberculous arthritis,
20 viral arthritis, fungal arthritis, syphilitic arthritis,
Lyme disease, arthritis associated with "vasculitic
syndromes", polyarteritis nodosa, hypersensitivity
vasculitis, Luegenec's granulomatosis, polymyalgin
rheumatica, joint cell arteritis, calcium crystal deposition
25 arthropathris, pseudo gout, non-articular rheumatism,
bursitis, tenosynovitis, epicondylitis (tennis elbow),
carpal tunnel syndrome, repetitive use injury (typing),
miscellaneous forms of arthritis, neuropathic joint disease
(charco and joint), hemarthrosis (hemarthrosic), Henoch-
30 Schonlein Purpura, hypertrophic osteoarthropathy,
multicentric reticulohistiocytosis, arthritis associated
with certain diseases, surcoilosis, hemochromatosis, sickle
cell disease and other hemoglobinopathries,
hyperlipoproteineimia, hypogammaglobulinemia,
35 hyperparathyroidism, acromegaly, familial Mediterranean

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5 fever, Behat's Disease, systemic lupus erythrematosis, or
relapsing polychondritis;
and related diseases.

24. A process for preparing a compound of
10 Formula III as claimed in Claim 1 substantially as
described in any one of the foregoing Examples.

25. A process of the formula (I)



(I)

15

wherein:

R¹ is -NHNH₂, or -NH₂;

R² is -OH, or -O(CH₂)_mR⁵ where

20 R⁵ is H, -CO₂H, -CO₂(C₁-C₄ alkyl),

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{P} \end{array}$ (R⁶R⁷), phenyl, or phenyl substituted with
-CO₂H or -CO₂(C₁-C₄ alkyl) where R⁶ and R⁷ are
each independently -OH or -O(C₁-C₄ alkyl) and m
is 1-3;

25 R³ is H, -O(C₁-C₄ alkyl), or -(CH₂)_nR⁸ where

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C} \end{array}$ NH₂, -CN, or phenyl where
R⁸ is H, -NR⁹R¹⁰, -C NH₂, -CN, or phenyl where
R⁹ and R¹⁰ are independently -(C₁-C₄)alkyl, or
phenyl(C₁-C₄)alkyl and n is 1-8;

R⁴ is H, -(C₅-C₁₄)alkyl, -(C₃-C₁₄)cycloalkyl, phenyl,
30 or phenyl substituted with 1 or 2 substituents

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5 selected from the group consisting of
-(C₁-C₄)alkyl, (C₁-C₄)alkoxy,
phenyl(C₁-C₄)alkyl, (C₁-C₄)alkylthio, halo or
phenyl; and

Z is cyclohexenyl or phenyl;

10 or a pharmaceutically acceptable salt, racemate,
optical isomer, solvate, tautomer or prodrug
derivative thereof;

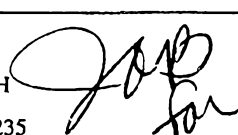
provided that when R³ is H, R⁴ is phenyl, m is 1 or 2
and R² is substituted at the 6 position, R⁵

15 cannot be H; and

when R¹ is NHNH₂, R⁸ cannot be $\overset{\text{O}}{\parallel}{\text{C}}\text{NH}_2$.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19183

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(6) :A61K 31/38, 31/405, 31/445; C07D 209/90, 471/02, 495/16, 513/16 US CL :514/292,411; 546/85, 86, 87; 548/430, 441 According to International Patent Classification (IPC) or to both national classification and IPC</p>														
<p>B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/292,411; 546/85, 86, 87; 548/430, 441 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 ONLINE, REGISTRY, MARPAT, BEILSTEIN</p>														
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 3,979,391 A (ALEXANDER et al.) 07 September 1976, see claims 1-16.</td> <td>1-2, 5-6, 16-20, 22, 24</td> </tr> <tr> <td>X</td> <td>US 3,939,177 A (ALEXANDER et al.) 17 February 1976, claims 1-6.</td> <td>1-2, 5-6, 16-20, 22 24</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 3,979,391 A (ALEXANDER et al.) 07 September 1976, see claims 1-16.	1-2, 5-6, 16-20, 22, 24	X	US 3,939,177 A (ALEXANDER et al.) 17 February 1976, claims 1-6.	1-2, 5-6, 16-20, 22 24			
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X	US 3,939,177 A (ALEXANDER et al.) 17 February 1976, claims 1-6.	1-2, 5-6, 16-20, 22 24												
<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>														
<table border="0"> <tr> <td>* Special categories of cited documents:</td> <td>*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</td> </tr> <tr> <td>*A* document defining the general state of the art which is not considered to be of particular relevance</td> <td>*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</td> </tr> <tr> <td>*E* earlier document published on or after the international filing date</td> <td>*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</td> </tr> <tr> <td>*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)</td> <td>*&* document member of the same patent family</td> </tr> <tr> <td>*O* document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>*P* document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			* 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	
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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														
<p>Date of the actual completion of the international search 04 FEBRUARY 1998</p>		<p>Date of mailing of the international search report 06 MAR 1998</p>												
<p>Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230</p>		<p>Authorized officer D. MARGARET M. MACH  Telephone No. (703) 308-1235</p>												

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19183**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.: 21 and 25
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:

claim 21 is missing a phrase between "claims 2 to 4" and "pathological effects" that would give the claim meaning and claim 25 is drawn to a method for making compounds but the claim lacks any process steps.

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

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

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

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

2. As all searchable claims could be 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.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.