

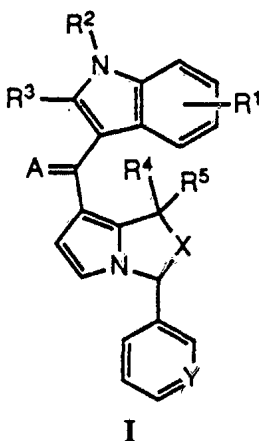


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PLATELET ACTIVATING FACTOR ANTAGONISTS
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- (57) Claim

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof wherein

R¹ is one or more groups independently selected from the group consisting of
hydrogen,
halogen,
alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms,
alkoyl of from one to seven carbon atoms,
phenyl, optionally substituted by

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms, or
halogen,
NR⁷R⁸ where R⁷ and R⁸ are independently selected from,
hydrogen,
alkyl of from one to six carbon atoms,
or taken together with the nitrogen atom to which they
are attached form a saturated 5- or 6-membered
nitrogen-containing ring,
-COOR⁹ where R⁹ is independently selected from,
hydrogen, and alkyl of from one to six carbon atoms,
-CONR⁷R⁸ where R⁷ and R⁸ are as defined above, and
-SO₂NR⁷R⁸ where R⁷ and R⁸ are as defined above,

2- or 3-furyl,

2- or 3-thienyl,

2-, 4-, or 5-thiazolyl,

2-, 3-, or 4-pyridyl,

2-, or 4-pyrimidyl,

benzoyl, wherein the phenyl moiety is optionally substituted by
halogen,

alkyl of from one to six carbon atoms, or

alkoxy of from one to six carbon atoms,

phenoxy optionally substituted by

halogen,

alkyl of from one to six carbon atoms, or

alkoxy of from one to six carbon atoms,

phenylalkyloxy in which the alkyl portion contains from one to six
carbon atoms and the phenyl is optionally substituted with
halogen,

alkyl of from one to six carbon atoms, or

alkoxy of from one to six carbon atoms, or

phenylalkoyl in which the alkoyl portion contains from one to seven
carbon atoms and the phenyl moiety is optionally substituted by;
halogen,

alkyl of from one to six carbon atoms, or

alkoxy of from one to six carbon atoms;

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R² is selected from the group consisting of

- hydrogen,
- alkyl of from one to six carbon atoms;
- (CH₂)_pCOOR⁹, where p is 0 or an integer of from 1 to 4 and R⁹ is as defined above,
- (CH₂)_qNR⁷R⁸, where q is an integer of from 2 and 4 and R⁷ and R⁸ are as defined above,
- (CH₂)_pCOR⁹ where R⁹ is as defined above,
- (CH₂)_qOH,
- (CH₂)_pSO₂R⁹ where p and R⁹ are as defined above,
- (CH₂)_pSO₂NR⁷R⁸ where p, R⁷ and R⁸ are as defined above,
- (CH₂)_pCONR¹⁰R¹¹, where p is as defined above and R¹⁰ and R¹¹ are independently selected from
 - hydrogen,
 - alkyl of from one to six carbon atoms,
 - (CH₂)_rCOOR⁹, where r is an integer of from 1 to 4 and R⁹ is as defined above,
 - (CH₂)_rNR⁷R⁸ where r, R⁷ and R⁸ are as defined above,
 - (CH₂)_rOH,
 - (CH₂)_rSO₂R⁹ where r and R⁹ are as defined above, and
 - (CH₂)_rSO₂NR⁷R⁸ where r, R⁷ and R⁸ are as defined above,
- (CH₂)_pCN where p is as defined above;
- (CH₂)_p-1H-tetrazol-5-yl where p is as defined above;
- CONHNH₂, or,
- (CH₂)_r-phenyl, where r is as defined above and the phenyl moiety is optionally substituted by
 - halogen,
 - alkyl of from one to six carbon atoms, or
 - alkoxy of from one to six carbon atoms;

R³, R⁴, and R⁵ are independently selected from hydrogen or alkyl of from one to six carbon atoms;

X is selected from the group consisting of S, SO, SO₂, O, and CH₂;

Y is selected from the groups consisting of

- N,
- N⁺-R¹² where R¹² is an alkyl group of from one to six carbon atoms,

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$N^+ \rightarrow O^-$,

N^+-OR^{12} where R^{12} is as defined above,

$N^+-NR^7R^8$ where R^7 and R^8 are as defined above,

$N^+-NHCONR^7R^8$ where R^7 and R^8 are as defined above,

$N^+-NHCOR^9$ where R^9 is as defined above,

$N^+-CR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above,

$N^+-OCR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above,

$N^+-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above,

$N^+-O-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above; and

A is selected from the group consisting of

O,

NOR¹⁰,

NOCOR¹⁰,

NNR⁷R⁸,

where R^7 , R^8 and R^{10} are as defined above.

5. A pharmaceutical composition useful for inhibiting PAF in a mammal in need of such treatment comprising a PAF-inhibitive effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US92/05890 (22) International Filing Date: 14 July 1992 (14.07.92) (30) Priority data: 731,681 17 July 1991 (17.07.91) US (60) Parent Application or Grant (63) Related by Continuation US 731,681 (CIP) Filed on 17 July 1991 (17.07.91) (71) Applicant (for all designated States except US): ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SUMMERS, James, B. [US/US]; 1108 Crestfield Avenue, Libertyville, IL 60048 (US). DAVIDSEN, Steven, K. [US/US]; 840 Banbury Road, Mundelein, IL 60060 (US). HOLMS, James, H. [US/US]; 521 Magnolia, Gurnee, IL 60031 (US). PI-REH, Daisy [IR/US]; 12 Newcastle Lane, Lincolnshire, IL 60069 (US). HEYMAN, H., Robin [US/US]; 1350 North Wells, Apt. D203, Chicago, IL 60610 (US). MARTIN, Michael, B. [US/US]; 3770 Johns Manville, Waukegan, IL 60085 (US). STEINMAN, Douglas, H.		[US/US]; 7001 Foster Street, Morton Grove, IL 60053 (US). SHEPPARD, George, S. [US/US]; 504 Fifth Street, Apt. C1, Wilmette, IL 60091 (US). CARRERA, George, M., Jr. [US/US]; 9379 Bay Colony Drive, Des Plaines, IL 60016 (US). (74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, CHAD-0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US). (81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE). Published With international search report. 651243
(54) Title: PLATELET ACTIVATING FACTOR ANTAGONISTS (57) Abstract Indole compounds substituted at the 3-position by a 7-carbonyl(pyridin-3-yl)pyrrolo[1,2-c]thiazole, 7-carbonyl(pyridin-3-yl)pyrrolo[1,2-c]oxazoline, or 7-carbonyl(pyridin-3-yl)pyrrolo[1,2-c]pyrrole group are potent antagonists of PAF and are useful in the treatment of PAF-related disorders including asthma, shock, respiratory distress syndrome, acute inflammation, transplanted organ rejection, gastrointestinal ulceration, allergic skin diseases, delayed cellular immunity, parturition, fetal lung maturation, and cellular differentiation.		

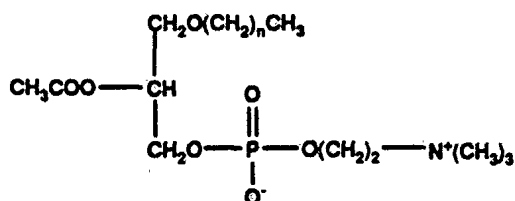
PLATELET ACTIVATING FACTOR ANTAGONISTS

Technical Field

This invention relates to compounds having pharmacological activity, to compositions containing these compounds, and to a medical method of treatment employing the compounds and compositions. More particularly, this invention concerns certain indolecarbonyl pyridylpyrrolothiazole compounds and their salts which have platelet activating factor (PAF) antagonist activity, to pharmaceutical compositions containing these compounds, and to a method of treating PAF-mediated disorders.

Background of the Invention

Platelet activating factor (PAF) is a phospholipid released from human and other animal cells and is an acetylglyceryl ether of phosphorylcholine as represented by the following formula:



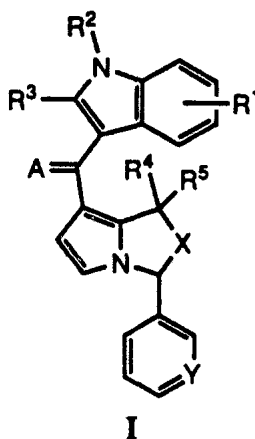
where n is 15 or 17.

PAF is physiologically active and causes contraction of the airway smooth muscle, increased vascular permeability, platelet aggregation, hypotension, and the like. It is now recognized as a powerful mediator of inflammation and may play a physiological or pathobiological role in a variety of clinical conditions, such as asthma and pulmonary dysfunction, acute inflammation, transplanted organ rejection, shock, thrombosis, anaphylaxis, gastrointestinal ulceration, allergic skin diseases, retinal and corneal diseases, chemically induced liver cirrhosis, and ovimplantation in pregnancy.

Several PAF antagonists have been reported (e.g., United States Patent 4,948,795, European Patent Application EP 279681, and U.S. 4,786,645) but none have received wide acceptance. Therefore, there is a continuing need for the development of potent, orally active antagonists of PAF.

Summary of the Invention

The present invention provides, in its principal aspect, compounds having PAF antagonist activity of the formula:



or a pharmaceutically acceptable salt thereof.

In the formula given above, R^1 is one or more groups independently selected from the group consisting of (A) hydrogen; (B) halogen; (C) alkyl of from one to six carbon atoms; (D) alkoxy of from one to six carbon atoms; (E) alkoyl of from one to seven carbon atoms; (F) phenyl, optionally substituted by (1) alkyl of from one to six carbon atoms, (2) alkoxy of from one to six carbon atoms, or (3) halogen; (G) NR^7R^8 where R^7 and R^8 are independently selected from (1) hydrogen, and (2) alkyl of from one to six carbon atoms, or (3) taken together with the nitrogen atom to which they are attached form a saturated 5- or 6-membered nitrogen-containing ring; (H) $-COOR^9$ where R^9 is independently selected from (1) hydrogen, and (2) alkyl of from one to six carbon atoms, (I) $-CONR^7R^8$ where R^7 and R^8 are as defined above; (J) $-SO_2NR^7R^8$ where R^7 and R^8 are as defined above; (K) 2- or 3-furyl, (L) 2- or 3-thienyl, (M) 2-, 4-, or 5-thiazolyl, (N) 2-, 3-, or 4-pyridyl, (O) 2-, or 4-pyrimidyl, (P) benzoyl, wherein the phenyl moiety is optionally substituted by (1) halogen, (2) alkyl of from one to six carbon atoms, or (3) alkoxy of from one to six carbon atoms; (Q) phenoxy optionally substituted by (1) halogen, (2) alkyl of from one to six carbon atoms, or (3) alkoxy of from one to six carbon atoms; (R) phenylalkyloxy in which the alkyl portion contains from one to six carbon atoms and the phenyl is optionally substituted with (1) halogen, (2) alkyl of from one to six carbon atoms, or (3) alkoxy of from one to six carbon atoms, and (S) phenylalkoyl in which the alkoyl portion contains from one to seven carbon atoms and the phenyl moiety is optionally substituted by; (1) halogen, (2) alkyl of from one to six carbon atoms, or (3) alkoxy of from one to six carbon atoms.

The substituent group R^2 is selected from the group consisting of (A) hydrogen, (B) alkyl of from one to six carbon atoms; (C) $-(CH_2)_pCOOR^9$, where p is 0 or an integer of from 1 to 4 and R^9 is as defined above, (D) $-(CH_2)_qNR^7R^8$, where q is an integer of from 2 and 4 and R^7 and R^8 are as defined above, (E) $-(CH_2)_pCOR^9$ where R^9 is as defined above; (F) $-(CH_2)_qOH$ where q is as defined above; (G) $-(CH_2)_pSO_2R^9$ where p and R^9 are as defined above, (H) $-(CH_2)_pSO_2NR^7R^8$ where p , R^7 and R^8 are as defined above, (I) $-(CH_2)_pCONR^{10}R^{11}$, where p is as defined above and R^{10} and R^{11} are independently selected from (1) hydrogen, (2) alkyl of from one to six carbon atoms, (3) $-(CH_2)_rCOOR^9$, where r is an integer of from 1 to 4 and R^9 is as defined above, (4) $-(CH_2)_rNR^7R^8$ where r , R^7 and R^8 are as defined above, (5) $-(CH_2)_rOH$, (6) $-(CH_2)_rSO_2R^9$ where r and R^9 are as defined above, (7) $-(CH_2)_rSO_2NR^7R^8$ where r , R^7 and R^8 are as defined above, (8) $-(CH_2)_pCN$ where p is as defined above; (9) $-(CH_2)_p-1H$ -tetrazol-5-yl where p is as defined above; (10) $-CONHNH_2$, and (11) $-(CH_2)_r$ -phenyl, where r is as defined above and the phenyl moiety is optionally substituted by halogen, alkyl of from one to six carbon atoms, or alkoxy of from one to six carbon atoms.

The groups R^3 , R^4 , and R^5 are independently selected from hydrogen or alkyl of from one to six carbon atoms.

X represents an atom or group of atoms selected from the group consisting of S, SO, SO_2 , O, and CH_2 .

Y represents an atom or group selected from the group consisting of (A) N, (B) N^+-R^{12} where R^{12} is an alkyl group of from one to six carbon atoms, (C) $N^+ \rightarrow O^-$, (D) N^+-OR^{12} where R^{12} is as defined above, (E) $N^+-NR^7R^8$ where R^7 and R^8 are as defined above, (F) $N^+-NHCONR^7R^8$ where R^7 and R^8 are as defined above, (G) $N^+-NHCOR^9$ where R^9 is as defined above, (H) $N^+-CR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above, (I) $N^+-OCR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above, (J) $N^+-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above, and (K) $N^+-O-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above.

A represents O, N^+OR^{10} , N^+OCOR^{10} , or $N^+NR^7R^8$, where R^7 , R^8 and R^{10} are as defined above.

The pharmaceutically acceptable salts and individual stereoisomers of compounds of structural formula I above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

In another aspect, the present invention provides pharmaceutical compositions useful for the treatment of PAF-mediated disorders comprising a therapeutically

effective amount of a compound of formula I above in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of inhibiting PAF activity by administering to a host mammal in need of such treatment an effective amount of a PAF-inhibiting compound having structure I above.

In yet another aspect of the present invention, there is provided a method of treating PAF-mediated disorders including asthma, shock, respiratory distress syndrome, acute inflammation, delayed cellular immunity, parturition, fetal lung maturation, and cellular differentiation by administering to a host mammal in need of such treatment a therapeutically effective amount of a compound of structure I above.

Detailed Description and Preferred Embodiments

In a preferred embodiment, compounds of the present invention are represented by formula I wherein:

R^1 is phenyl, optionally substituted by (a) alkyl of from one to six carbon atoms, (b) alkoxy of from one to six carbon atoms, or (c) halogen; R^2 is as defined above; R^3 , R^4 , and R^5 are hydrogen; X is -S-; Y is selected from the groups consisting of (a) -N-, (b) >N-O, (c) >N-CR⁸OCOR¹², or (d) >N-OCR⁷R⁸OCOR¹²; A is selected from the groups consisting of (a) =O, or (b) =NOH. Preferred compounds of Formula I are those in which X is -S-, -SO-, or -SO₂-; R^2 is hydrogen, carbamoyl, alkyl of from one to six carbon atoms, -COOR⁸, or -SO₂R⁸; R^3 is hydrogen or alkyl of from one to six carbon atoms; and R^1 is hydrogen, phenyl, or phenylalkoxy or a pharmaceutically acceptable salt thereof.

In a particularly preferred embodiment, compounds of the present invention are represented by Formula I wherein R^1 is phenyl or 4-fluorophenyl; R^2 is CONH₂, CONHCH₃, or CON(CH₃)₂; and R^3 , R^4 , X, Y, and A are as defined immediately above.

Examples of compounds contemplated as falling within the scope of the present invention include, but are not necessarily limited to:

3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(5-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-(7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-
c]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-5-phenylmethoxyindol-3-
yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 5 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylmethoxyindol-3-
yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-7-phenylmethoxyindol-3-
yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-
10 pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(morpholin-4-ylcarbonyl)indol-3-yl]carbonyl-1*H*,3*H*-
pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-
15 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 2-oxide-3-(pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 2-oxide-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole;
- 20 3-(pyridin-3-yl)-7-(1-*N,N*-diisopropylcarbamoyl-6-phenylmethoxyindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 1,1-dimethyl-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-
c]thiazole;
- 3-(pyridin-3-yl)-7-(1-carbomethoxycarbamoyl-6-phenylmethoxyindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 25 1,1-dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-indol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N*-methyl-*N*-phenylcarbamoyl-6-phenylmethoxyindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 30 3-(pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylmethoxyindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 2-oxide-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 35 1,1-dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 1,1-dimethyl-3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 5 3-(pyridin-3-yl)-7-(1-carbophenoxy-6-phenylmethoxyindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 10 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 15 1,1-dimethyl-3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-
6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-methylpyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 20 3-(1-oxide-pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 25 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylmethoxyindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 30 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-pyrid-3-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo-
[1,2-*c*]thiazole;
- 35 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-pyrid-4-ylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 5 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)-indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 10 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3,4,5-trimethoxyphenyl)-indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-carboxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-sulfamylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 15 3-(pyridin-3-yl)-7-[1-methanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride;
- 20 3-(pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)-indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole hydrochloride;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 25 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3-aminophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-*tert*-butoxycarbonylaminoethyl)-6-(4-fluorophenyl)-indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 30 3-(1-oxide-pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 35 3-(pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-[1-*N*-(2-hydroxyethyl)carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-bromoindol-3-ylcarbonyl)-
5 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 10 3-(1-amino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-methanesulfonylaminoethyl)-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-hydrazinocarbonyl-6-(4-fluorophenyl)indol-3-yl-
15 carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride;
- 3-(pyridin-3-yl)-7-[1-ethanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 20 3-(pyridin-3-yl)-7-[1-(2-hydroxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-pyrimid-2-ylindol-
25 3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-
6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 30 3-(1-carbamoylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-pyrid-3-oylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-(2-aminosulfonylethyl)-6-(4-fluorophenyl)indol-
35 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3-aminosulfonylphenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-[1-(2-*N*-methylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 5 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(*N*-methyl-*N*-(dimethylaminoethyl))carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N*-carboxymethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 10 3-(1-methyl-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-thiazol-2-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 15 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(2-aminopyrimid-5-yl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 20 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-hydrazinylcarbonylphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-acetoxymethylpyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 25 3-(pyridin-3-yl)-7-[1-*N*-methyl-*N*-hydroxymethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-cyanomethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 30 3-(pyridin-3-yl)-7-[1-carbamoylmethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-carboxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(1*H*-tetrazol-5-ylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 35 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(2,4(1*H*,3*H*)-pyrimidinedion-5-yl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 5 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-thiophen-2-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-(4-hydroxymethyl)-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 2-oxide-3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indole-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 10 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylhydrazone]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N*-(2-(4-imidazolyl)ethyl)carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole; and
 15 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylsemicarbazide]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

or a pharmaceutically acceptable salt of each thereof.

As used throughout this specification and the appended claims, the following terms have the meanings ascribed to them:

- 20 The term "alkenyl" as used herein refers to straight or branched chain groups of 2 to 6 carbon atoms containing a carbon-carbon double bond. Representative examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, and the like.

The term "alkoxy" as used herein refers to an alkyl group, as defined herein, which is bonded to the parent molecular moiety through an oxygen atom.

- 25 Representative examples of alkoxy groups include methoxy, ethoxy, *tert*-butoxy, and the like.

- The term "alkoyl" as used herein refers to formyl and radicals of the structure -C(O)-alkyl in which the alkyl portion is a straight or branched alkyl group of from one to six carbon atoms. Representative examples of alkoyl groups include formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, and the like.

- 30 The term "alkyl" as used herein refers to straight or branched chain radicals derived from saturated hydrocarbons by the removal of one hydrogen atom. Representative examples of alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like.

- 35 The term "alkylsulfonyl" is used herein to mean -SO₂(alkyl) where the alkyl group is as defined above. Representative examples of alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, and the like.

The term "benzyl" as used herein refers specifically to a phenyl substituted methyl in which the phenyl group may be substituted with 1, 2, or 3 substituents independently selected from halo, nitro, cyano, alkyl of from one to six carbon atoms, alkoxy, and halo-substituted alkyl and the like.

5 The term "carboalkoxy" as used herein refers to a structure of formula -C(O)OR wherein R is a straight or branched alkyl radical of from one to six carbon atoms, benzyl, or substituted benzyl. Representative examples of carboalkoxy groups include carbomethoxy, carboethoxy, carbo(*iso*-propoxy), carbobutoxy, carbo(*sec*-butoxy), carbo(*iso*-butoxy), carbo(*tert*-butoxy), benzyloxycarbonyl, and the like.

10 The term "nitrogen heterocycle" as used herein refers to any 5- or 6-membered saturated ring containing from one to three heteroatoms independently selected from the group consisting of one, two, or three nitrogens, one oxygen and one nitrogen, and one sulfur and one nitrogen; wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, wherein the nitrogen heteroatom may be optionally quaternized,
15 and wherein one or more carbon or nitrogen atoms may be substituted with alkyl of from one to six carbon atoms. Representative nitrogen heterocycles include, but are not limited to, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, and the like.

20 The term "carbamoyl" refers to a structure of formula -CONR'R" wherein R' and R" are independently selected from hydrogen, a straight or branched alkyl radical of from one to six carbon atoms, or taken together may form a nitrogen heterocycle, as previously defined. Representative examples of carbamoyl groups, include -C(O)NH₂, *N,N*-dimethylcarbamoyl, *N-tert*-butylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, (morpholin-4-yl)carbonyl, (piperidin-1-yl)carbonyl, (4-methylpiperazin-1-yl)carbonyl
25 and the like.

The term "phenylalkoxy" is used herein to mean a phenyl group appended to an alkoxy radical as previously defined. Representative examples of phenylalkoxy groups include phenylmethoxy (*i.e.* benzyloxy), 1-phenylethoxy, 2-phenylethoxy, 2-phenylpropoxy, and the like.

30 The term "phenylalkoyl" is used herein to mean a phenyl group appended through an alkyl or alkenyl group of from one to six carbon atoms or a valence bond to a formyl radical of the structure -C(O)- in which the phenyl group may optionally be substituted with alkyl of from one to six carbon atoms, halogen, or alkoxy as previously defined. Representative examples of phenylalkoyl groups include benzoyl,
35 phenylacetyl, cinnamoyl, phenylpropionyl, and the like.

The terms "PAF-related disorders" and "PAF-mediated disorders" are used herein to mean disorders related to PAF or mediated by PAF, including asthma, shock,

respiratory distress syndromes, acute inflammation, gastric ulceration, transplant organ rejection, psoriasis, allergic skin disease, ischemia and reperfusion injury, delayed cellular immunity, parturition, fetal lung maturation, and cellular differentiation.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66: 1-19 (1977) which is incorporated herein by reference.)

Individual enantiomeric forms of compounds of the present invention can be separated from mixtures thereof by techniques well known in the art. For example, a mixture of diastereomeric salts may be formed by reacting the compounds of the present invention with a optically pure form of an acid, followed by purification of the mixture of diastereomers by recrystallization or chromatography and subsequent recovery of the resolved compound from the salt by basification. Alternatively, the enantiomers of the compounds of the present invention can be separated from one another by chromatographic techniques employing separation on a chiral chromatographic medium.

The present invention also provides pharmaceutical compositions which comprise one or more of the compounds of formula I above formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions as well as sterile powders for reconstitution into sterile

injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose,

sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, ca. boxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and

sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments, and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

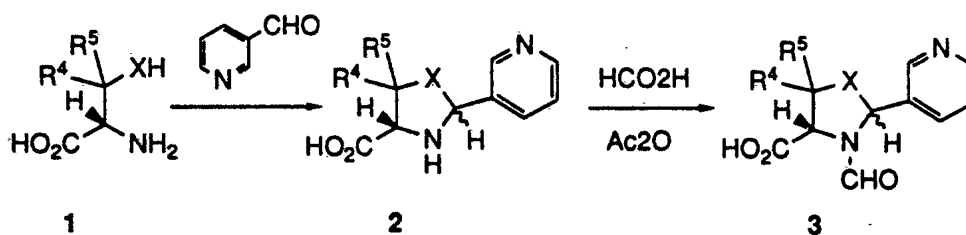
Generally dosage levels of about 0.001 to about 100 mg, more preferably of about 0.01 to about 20 mg, and most preferably about 0.1 to about 10 mg of active compound per kilogram of body weight per day are administered orally to a mammalian

patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

In general, the compounds of the present invention are synthesized by reaction Schemes 1 through 15 as illustrated below. It should be understood that X, A, R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, and R¹² as used herein correspond to the groups identified by Formula I.

The compounds of Formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and other portions of the molecule must be consistent with the chemical transformation proposed. This will frequently necessitate judgement as to the order of synthetic steps, protecting groups required, and deprotection conditions.

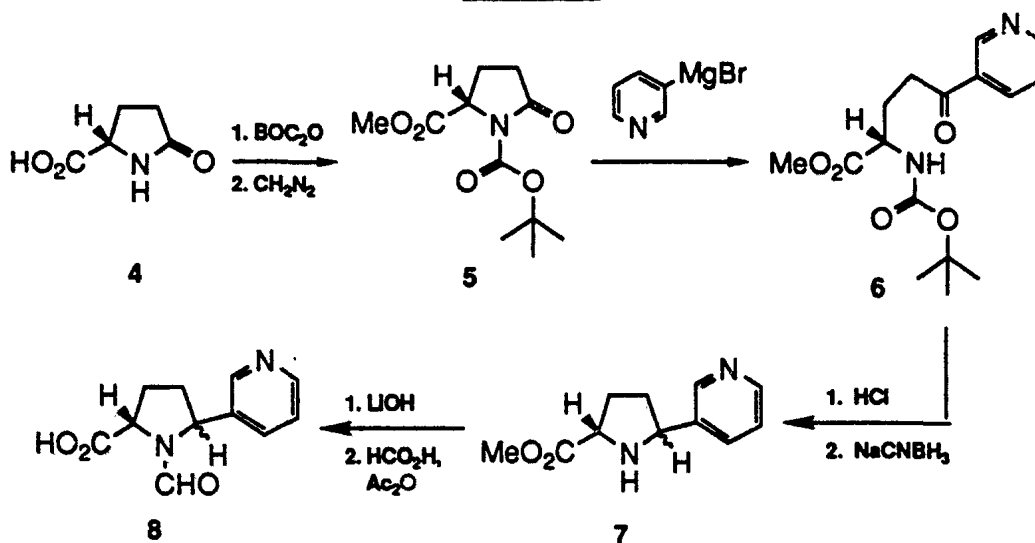
Scheme 1



Scheme 1

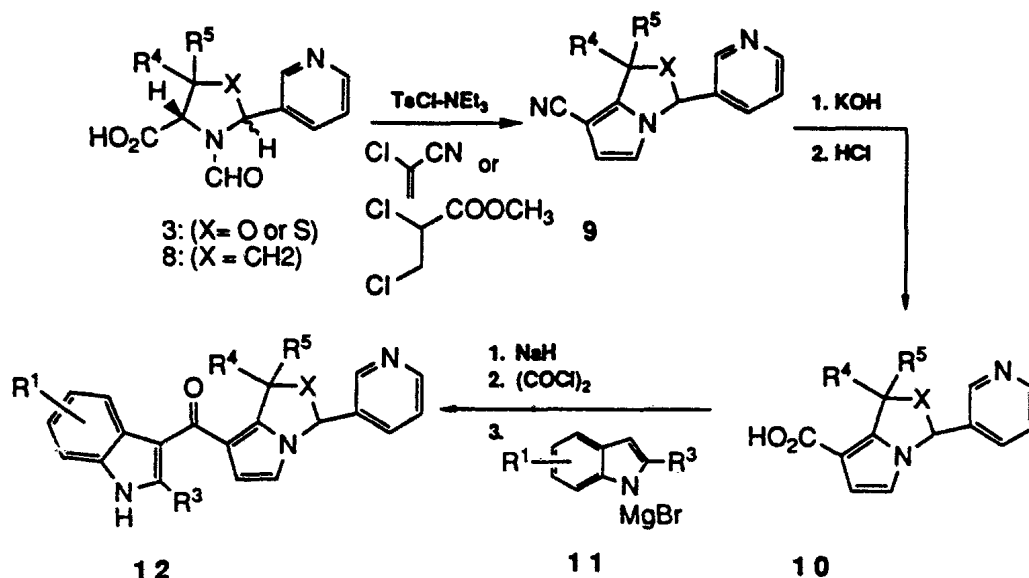
According to the foregoing reaction Scheme 1, L-Cysteine, L-Serine, L-Penicillamine, or a related amino acid (1) is condensed with nicotinaldehyde to produce the thiazolidine or oxazolidine acids 2. The secondary nitrogen atom is then formylated by the action of formic acid/acetic anhydride to yield the N-formyl heterocycles 3.

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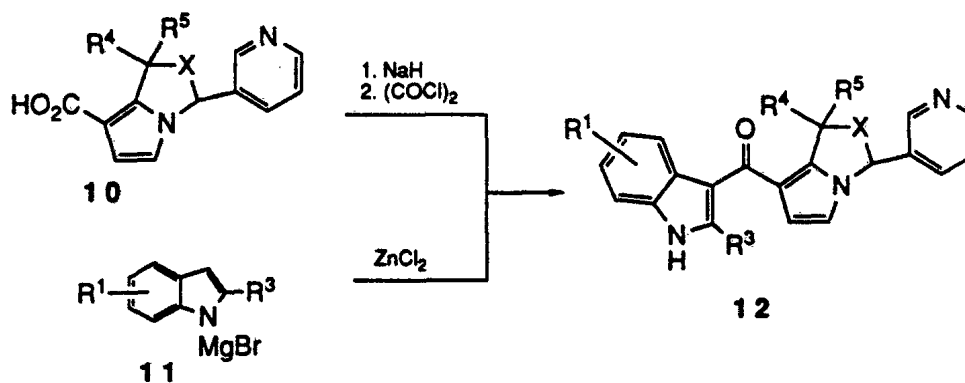
Scheme 2**Scheme 2**

- According to the foregoing reaction Scheme 2, the nitrogen atom of L-pyrroglutamic acid may be protected with an appropriate group, preferably *tert*-butyloxycarbonyl (BOC) with di-*tert*-butyl dicarbonate followed by methyl ester formation which gives lactam 5. Addition of 3-pyridylmagnesium bromide cleaves the heterocyclic ring and gives ketone 6. The nitrogen atom is deprotected under acidic conditions and reductive cyclization is achieved upon treatment with sodium cyanoborohydride. Hydrolysis of the methyl ester followed by formylation with formic acid/acetic anhydride gives the *N*-formyl pyrrolidine 8.

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Scheme 3**Scheme 3**

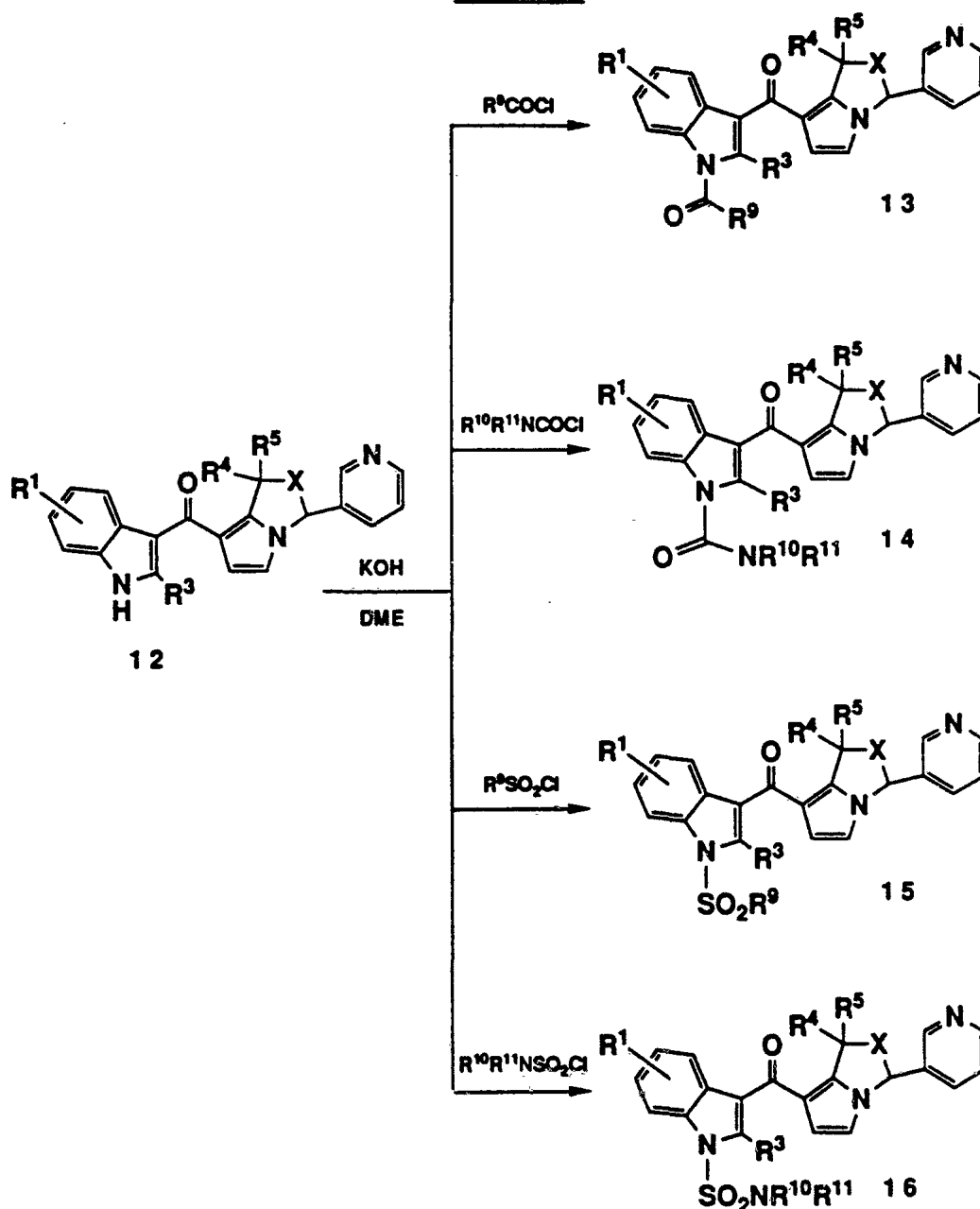
- According to the foregoing reaction Scheme 3, *N*-formyl heterocycles 3 and 8 may be heated independently with 2-chloroacrylonitrile in the presence of triethylamine and *p*-toluenesulfonyl chloride to afford the corresponding fused bicyclic heterocycle 9. Base catalyzed hydrolysis of the nitrile group followed by acidification affords acid 10. The indole group is introduced by treatment of the anhydrous acid chlorides (prepared from 10 by treatment with sodium hydride followed by oxalyl chloride) with indole Grignard 11 derived from the reaction of the appropriate substituted indole and ethylmagnesium bromide.

Scheme 4

Scheme 4

According to the foregoing reaction Scheme 4, the appropriately substituted indole group is also introduced by treatment of magnesium indole salt with zinc chloride in ether followed by reaction with the anhydrous acid chloride of 10.

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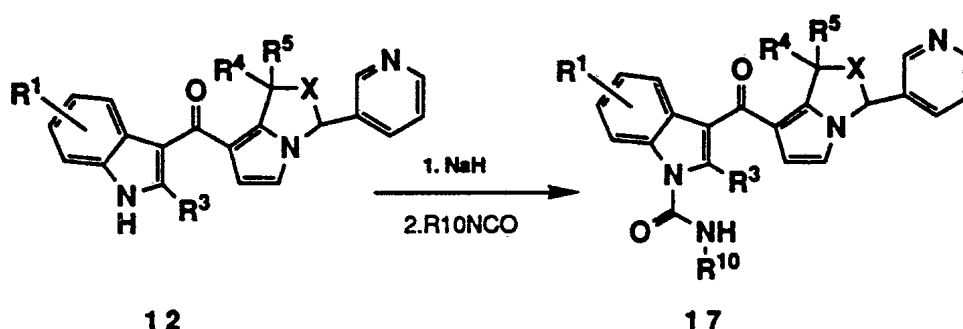
Scheme 5**Scheme 5**

According to the foregoing reaction Scheme 5, the indole nitrogen atom of the bicyclic heterocycle 12 may be functionalized with an amide group by reaction with the

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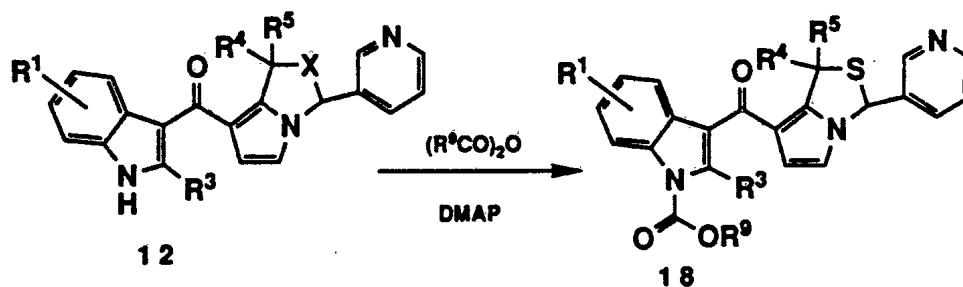
corresponding acid chloride, preferably using potassium hydroxide in 1,2-dimethoxyethane, giving N-acyl indoles 13. Alternatively, compound 12 may be treated independently with the appropriate carbamoyl chloride under similar conditions to give urea 14. Treatment of a potassium hydroxide solution of 12 in 1,2-dimethoxyethane with the appropriate sulfonyl chloride gives the corresponding sulfonamide 15. Finally, 12 in a potassium hydroxide solution with the appropriate sulfamoyl chloride gives the sulfonylurea 16.

Scheme 6

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Scheme 6

According to the foregoing reaction Scheme 6, 3-acyl indole heterocycle 12 are treated with the appropriate isocyanate to give the urea substituted indole 17.

Scheme 7

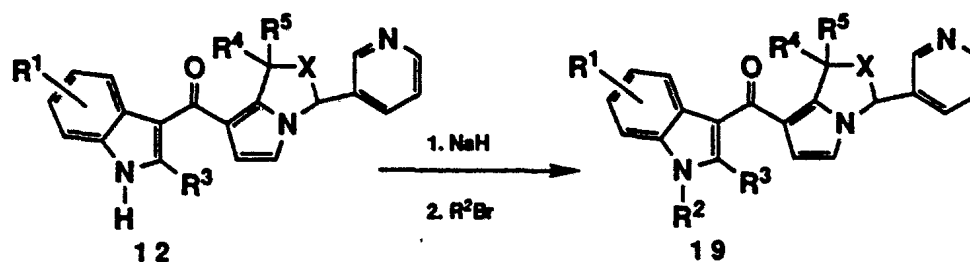
15

Scheme 7

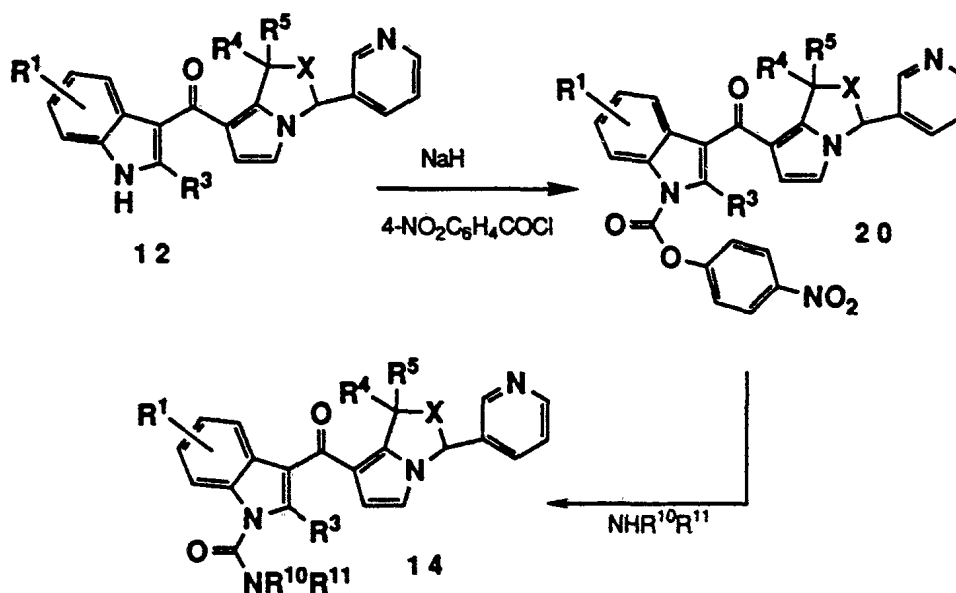
According to the foregoing reaction Scheme 7, 3-acyl indole heterocycle 12 is treated with the appropriate alkyl dicarbonate in the presence of 4-dimethylaminopyridine to give the corresponding N-carboalkoxy indole 18.

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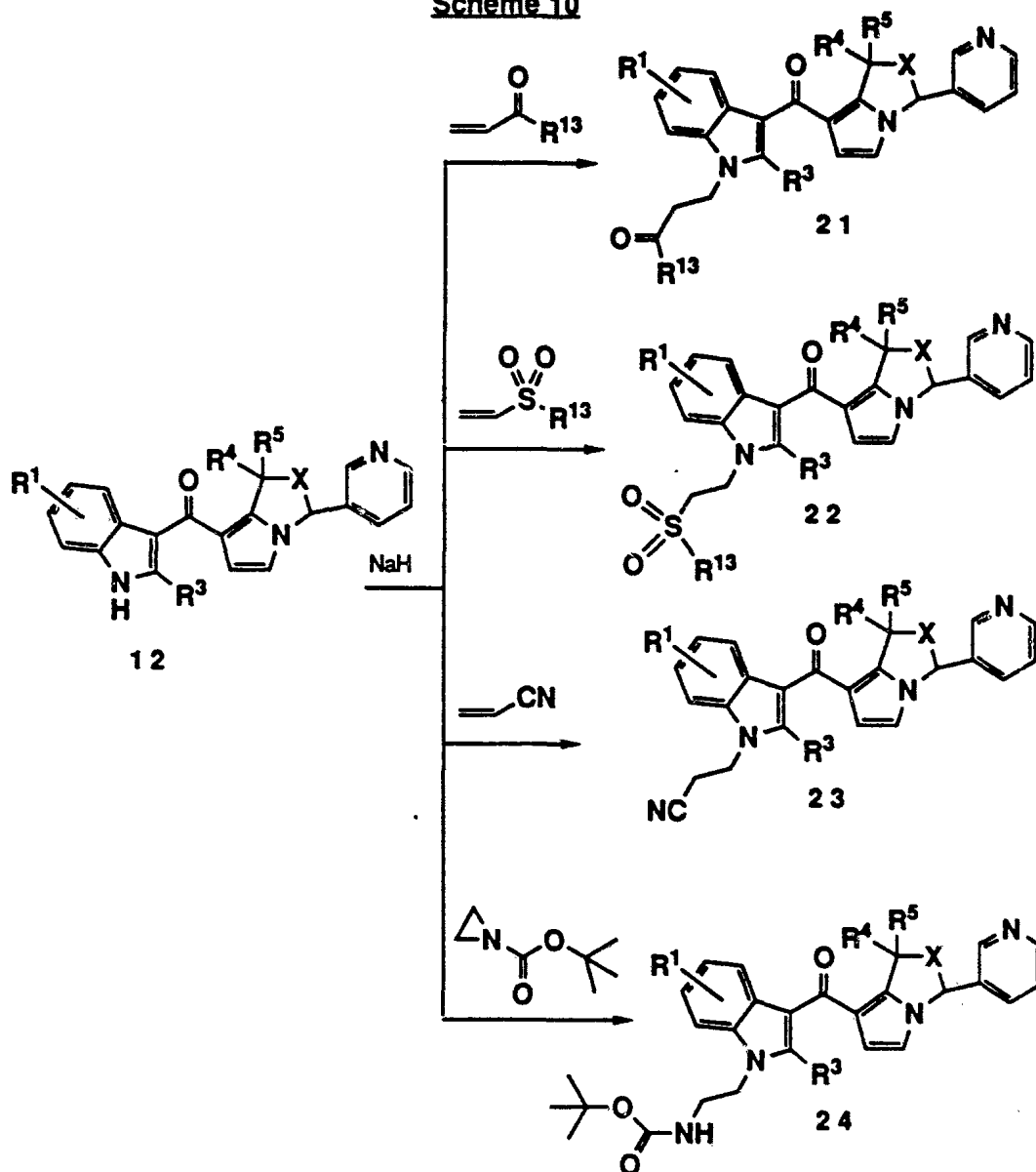
Scheme 8**Scheme 8**

According to the foregoing reaction Scheme 8, 3-acyl indole heterocycle 12 is treated with sodium hydride followed by the addition of the appropriate alkyl halide to give the corresponding N-alkyl indole 19.

Scheme 9**Scheme 9**

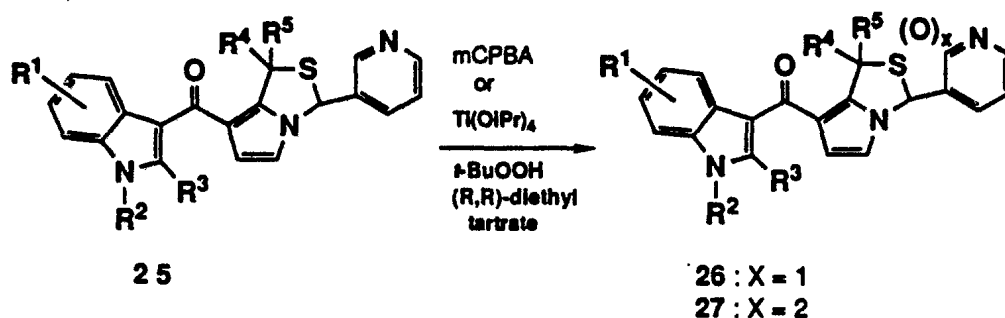
According to the foregoing reaction Scheme 9, 3-acyl indole heterocycle 12 is treated with 4-nitrophenylchloroformate to give the activated acylindole derivative 20 that is subsequently reacted with an appropriately substituted amine to afford urea 14.

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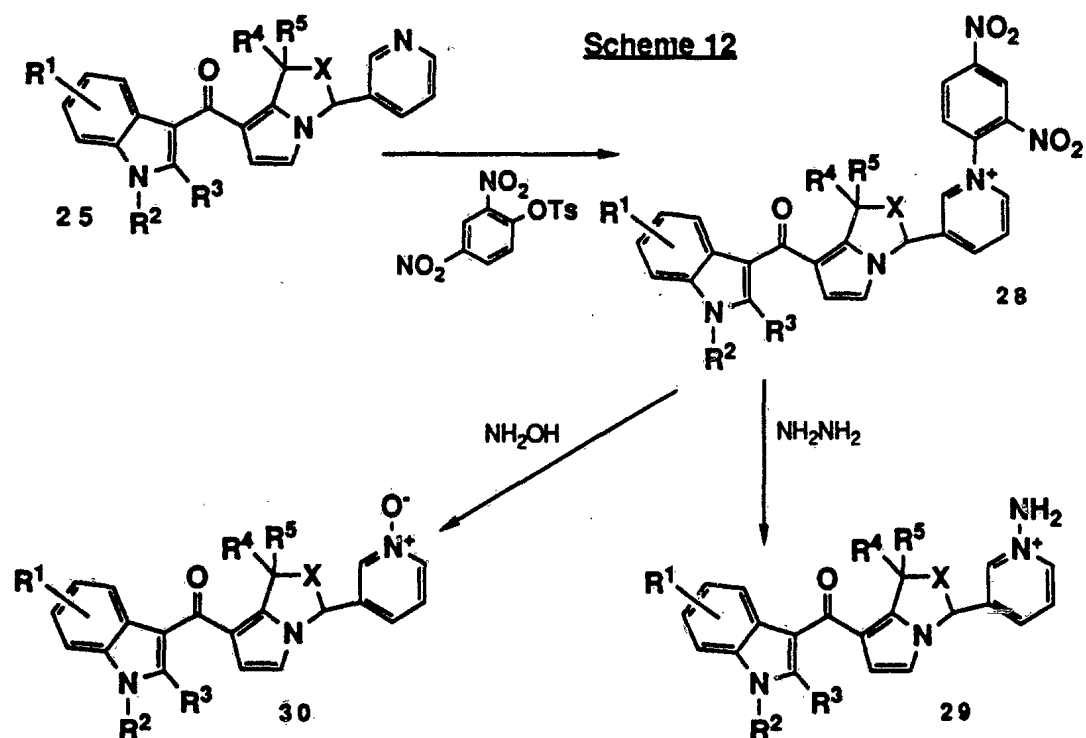
Scheme 10**Scheme 10**

According to the foregoing reaction Scheme 10, 3-acyl indole heterocycle 12 is
 5 treated with sodium hydride and then reacted with an α,β unsaturated carbonyl
 compound to give 21, with an α,β unsaturated sulfonyl compound to give 22, with an
 α,β unsaturated nitrile to give 23, or with an acyl aziridine to afford 24. R^{13} in 21
 and 22 is used herein to indicate R^9 , OR^9 , or $NR^{10}R^{11}$.

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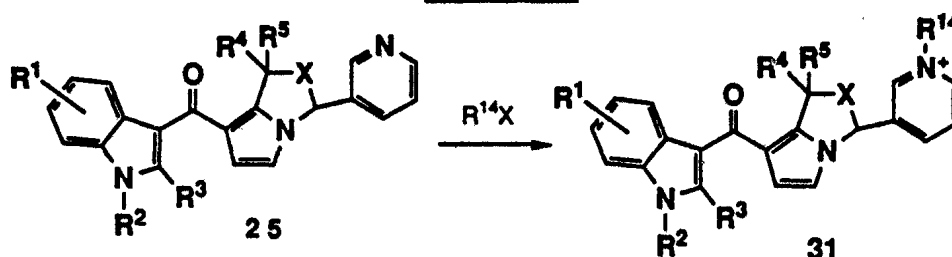
Scheme 11**Scheme 11**

According to the foregoing reaction Scheme 11, the 3-acyl indole heterocycle **25** is treated with *tert*-butyl hydroperoxide, titanium tetraisopropoxide, and (R,R)-diethyl tartrate, or with *m*-chloroperoxybenzoic acid to give the corresponding sulfoxide **26** or sulfone **27**.

**Scheme 12**

According to the foregoing reaction Scheme 12, the 3-acyl indole heterocycle **25** is treated with 2,4-dinitrophenyl 4-toluenesulfonate to the pyridinium salt **28**. The salt is treated with hydroxylamine to give N-oxide **30** or alternatively with hydrazine to give **29**.

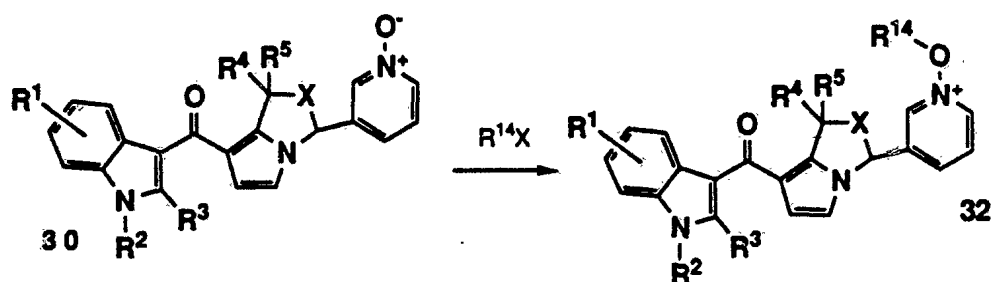
Scheme 13



Scheme 13

5 According to the foregoing reaction Scheme 13, the 3-acyl indole heterocycle 25 is treated with an alkyl halide to give pyridinium salt 30. R¹⁴ is used herein to indicate R¹² or CR⁷R⁸OCOR⁸.

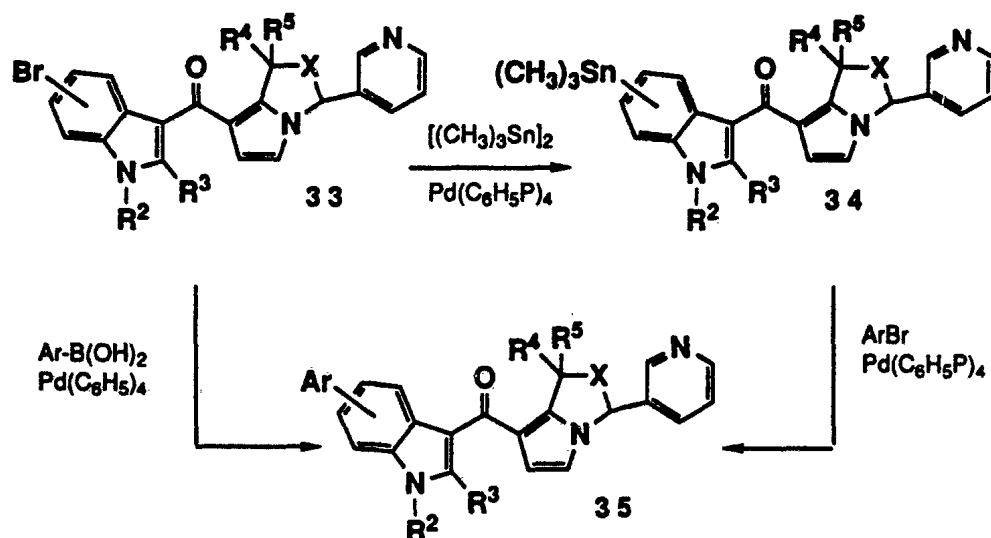
Scheme 14



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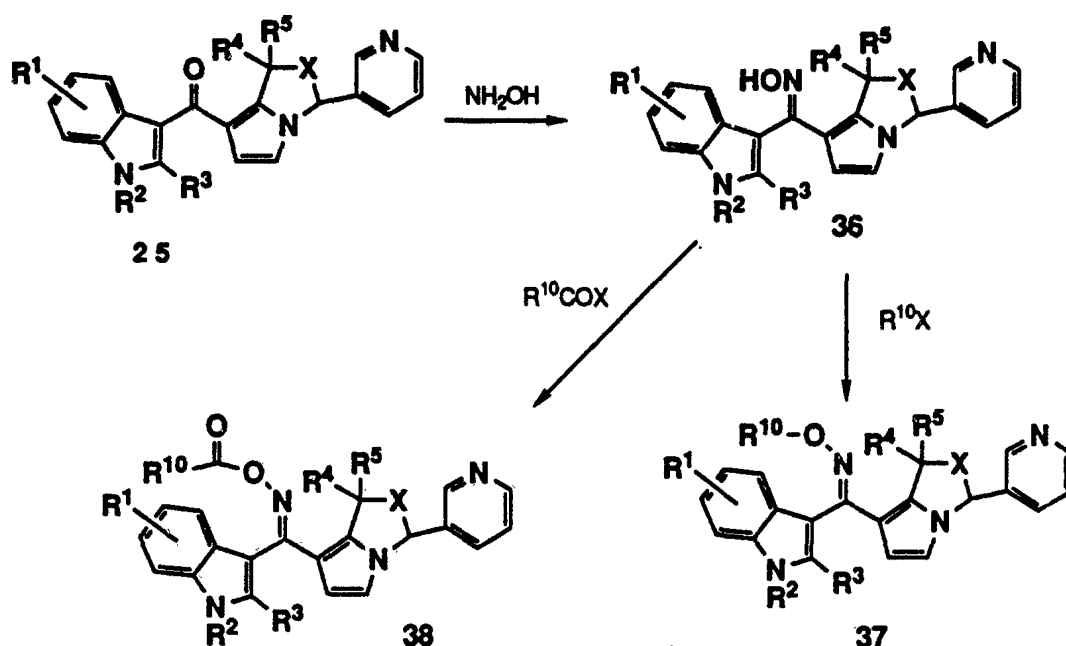
Scheme 14

According to the foregoing reaction Scheme 14, the 3-acyl indole *N*-oxide heterocycle **30** is treated with an alkyl halide to give pyridinium salt **32**.

Scheme 15**Scheme 15**

According to the foregoing reaction Scheme 15, the bromo indole heterocycle 33 (prepare as described in reaction Scheme 4) is treated with hexamethyltin in the presence of tetrakis(triphenylphosphine)palladium to give 34. This tin reagent is then treated with an aryl halide also in the presence of tetrakis(triphenylphosphine)palladium to afford the aryl indole 35. Alternatively 33 may be converted to 35 directly using the appropriate arylboronic acid in the presence of tetrakis(triphenylphosphine)palladium. Ar is used herein to indicate substituted or unsubstituted phenyl, thiazolyl, pyridyl, pyrimidyl, and the like.

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Scheme 16Scheme 16

According to the foregoing reaction Scheme 16, the indole heterocycle **25** is treated with hydroxylamine to give oxime **36**. This oxime can be alkylated with an appropriate alkyl halide to give **37**, or acylated with an activated acyl compound to give **38**.

PAF Inhibitory Activity of the Compounds of the Present Invention

The ability of representative compounds of the present invention to inhibit PAF activity was determined in an *in vitro* test using the following method.

Citrated whole rabbit blood was obtained from Pel-Freez (Rogers, AR). Rabbit platelets were prepared by centrifugation and washing. The platelets were lysed by freeze-thawing and sonication; platelet membranes were prepared by centrifugation and washing. Final membrane preparations were stored frozen in 10 mM Tris/5 mM MgCl_2 /2 mM EDTA (TME buffer, pH 7.0) with 0.25 M sucrose added for membrane stabilization.

The standard PAF receptor binding assay contained 10 μg platelet membrane protein, 0.6 nM $[^3\text{H}]\text{C}_{18}\text{-PAF}$ (from Amersham or New England Nuclear; specific activity 120-180 Ci/mmol), with and without test compound, in "binding buffer" consisting of TME with 0.25% bovine serum albumin added (Sigma, RIA grade). The final volume of the assay was 100 μl . The assay was conducted in Millititre-GVTM

(Millipore Corp.) filtration plates; incubation time was for 60 minutes at room temperature (22-23°C.). "Specific binding" was operationally defined as the arithmetic difference between "total binding" of 0.6 nM [³H]C₁₈-PAF (in the absence of added PAF) and "nonspecific binding" (in the presence of 1 μM PAF). After the prescribed incubation, platelet membranes were filtered under vacuum and washed with 1 millilitre of "binding buffer". The filters were dried and removed. The bound radioactivity was quantitated with a Berthold TLC-Linear Analyzer model LB2842.

Dose-response curves of inhibition of specific [³H]C₁₈-PAF binding by test compounds were conducted in triplicate, with at least four doses covering the active range. Experiments were repeated at least once. IC₅₀ values (concentration producing 50% inhibition) were determined by point-to-point evaluation. K_i values of inhibitory binding constants were calculated according to the method of Cheng and Prusoff [Biochem. Pharmacol. 22 (1973) 3099-3108] whereby

$$\begin{aligned}
 K_i &= \frac{IC_{50}}{1 + ([^3H]PAF)/K_d[^3H]PAF)} \\
 &= \frac{IC_{50}}{1 + (0.6 \text{ nM}/0.6 \text{ nM})} \\
 &= \frac{IC_{50}}{2}
 \end{aligned}$$

The values of K_i for representative compounds of the present invention appear in Table 1.

Table 1
PAF Receptor Binding Activity

Example	K _i (nM)	Example	K _i (nM)	Example	K _i (nM)	Example	K _i (nM)
1	53.	28	75	55	940.	82	0.3
2	2,000	29	7.5	56	110	83	10.7
3	180.	30	135	57	38	84	6.9
4	64.	31	10	58	49	85	129.
5	90.	32	150	59	27	86	4,000
6	120.	33	2,800	60	210	87	71
7	17.	34	14	61	1,100	88	680
8	170.	35	44	62	7.4	89	280
9	110.	36	1,100	63	580	90	480
10	95	37	10	64	15.3	91	20
11	225.	38	1,000	65	89	92	19
12	23.	39	3.3	66	38	93	0.8
13	2,200.	40	26	67	2,000	94	40
14	2,400.	41	2,000	68	9.6	95	10
15	5,600.	42	10.5	69	25	96	18
16	85.	43	26	70	2.6	97	19
17	1,200.	44	40	71	244	98	240
18	35.	45	4.1	72	5	99	19
19	100.	46	10	73	211	100	>300
20	180.	47	590	74	84	101	0.95
21	15.	48	8	75	7.5	102	16
22	9.	49	160	76	6.1	103	85
23	95.	50	3.3	77	100	104	2.2
24	51.	51	120	78	123	105	4.3
25	272	52	16	79	18.	106	8.0
26	55	53	0.7	80	45.		
27	200	54	17	81	1.12		

5 The foregoing may be better understood from the following Examples, which are presented for the purpose of illustration and not intended to limit the scope of the inventive concept.

Example 1

Preparation of 3-(Pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylic acid, prepared as described in United States Patent 4,529,728, (1.00 g) in anhydrous tetrahydrofuran (THF) (50 mL) under dry nitrogen was added sodium hydride, 60% oil dispersion (0.18 g, 1.1 equivalents) and stirred 1.0 hour at ambient temperature. To the resulting suspension was added a catalytic amount of dimethylformamide (DMF) followed by the dropwise addition of oxalyl chloride (0.43 mL, 1.2 equivalents). After the reaction mixture had stirred 2.0 hours at ambient temperature, the solvent was evaporated *in vacuo* at 45°C. The residue was suspended in a mixture of methylene chloride and benzene (3:1 v/v, 30 mL).

In a separate flask, a 3.0 *M* solution of methyl magnesium bromide in ether (2.0 mL, 1.5 equivalents) was added dropwise to a solution of indole (0.72 g, 1.5 equivalents) in benzene (30 mL) at room temperature and stirred 0.75 hour. The resulting green indolylmagnesium bromide solution was cannulated into the suspension of acid chloride described above. The reaction mixture was stirred at room temperature for 18 hours and then quenched with water (equal volume) and extracted with ether (2 x equal volume). The combined organic phases were dried over magnesium sulfate and concentrated *in vacuo* at 45°C to afford crude product which was purified by flash chromatography (15 p.s.i.) on 250 g silica gel eluting with 1:1 THF/hexane. The resulting yellow solid was triturated with methylene chloride, filtered, and dried at 50° *in vacuo* to afford the title compound as a white powder (112 mg, 8 %). m.p. 237-238°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.45 (d, *J* = 15Hz, 1H), 4.63 (dd, *J* = 15, 2Hz, 1H), 6.69 (d, *J* = 3Hz, 1H), 6.77 (d, *J* = 1.5Hz, 1H), 6.88 (d, *J* = 3Hz, 1H), 7.20 (dqintet, *J* = 7.5Hz, 1H), 7.43 (dd, *J* = 7.5, 5.3Hz, 1H), 7.48 (d, *J* = 8Hz, 1H), 7.65 (dt, *J* = 2, 8.4Hz, 1H), 8.21 (d, *J* = 3Hz, 1H), 8.24-8.28 (m, 1H), 8.53-8.58 (m, 2H), 11.86 (s, 1H). MS (DCI/NH₃) *m/e* 346 (M+H)⁺.

Example 2

Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

3-(Pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole prepared as described in Example 1, (0.11 g) was dissolved in dimethoxyethane (DME) (20 mL) and powdered potassium hydroxide (0.09 g, 5 equivalents) was added in one portion. After stirring at ambient temperature for 0.5 hour, *N,N*-dimethylcarbamoyl chloride (0.038 g, 1.1 equivalents) was added dropwise and the reaction was stirred for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with ether (2 x 50

mL). The combined extracts were dried over magnesium sulfate and concentrated *in vacuo* at 50°C to afford crude product as an amber oil. The crude product was dissolved in the minimal amount of toluene (2 mL) and ether was added until cloudy (20 mL). After standing for 18 hours at -20°C, the supernatant was decanted from a yellow precipitate. The desired product was then precipitated from the supernatant with the addition of excess pentane (50 mL). The white flocculent precipitate was dried *in vacuo* at 50°C to afford the title compound as a white powder (28 mg, 21%). m.p. 241-243°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.05 (s, 6H), 4.48 (d, J = 15Hz, 1H), 4.66 (dd, J = 15, 2Hz, 1H), 6.73 (d, J = 3Hz, 1H), 6.79 (d, J = 1Hz, 1H), 6.89 (d, J = 3Hz, 1H), 7.28-7.47 (m, 3H), 7.60-7.70 (m, 2H), 8.23-8.28 (m, 1H), 8.32 (s, 1H), 8.55-8.59 (m, 2H). MS (DCI/NH₃) m/e 417 (M+H)⁺. IR (KBr) 1600, 1687, 2930, 3440 cm⁻¹.

Example 3

Preparation of 3-(Pyridin-3-yl)-7-(5-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 1 except 5-phenylmethoxyindole was used instead of indole. The crude product was purified by flash chromatography (15 p.s.i.) on 250 g silica gel eluting with 3:2 THF/hexane to afford the title compound. m.p. 178-179°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, 1H, J = 15Hz), 4.62 (dd, 1H, J = 15, 2Hz), 5.13 (s, 2H), 6.68 (d, 1H, J = 3Hz), 6.76 (d, 1H, J = 1Hz), 6.87 (d, 1H, J = 3Hz), 6.94 (dd, 1H, J = 9, 3Hz), 7.29-7.53 (m, 7H), 7.65 (dt, 1H, J = 2.4, 8.4Hz), 7.91 (d, 1H, J = 2.5Hz), 8.18 (d, 1H, J = 3Hz), 8.53-8.58 (m, 2H), 11.77 (d, 1H, J = 2.5Hz). Anal calcd for C₂₇H₂₁N₃O₂S: C, 71.82; H, 4.69; N, 9.31. Found: C, 71.41; H, 4.78; N, 9.19. MS (DCI/NH₃) m/e 452 (M+H)⁺. IR (KBr) 1422, 1585, 3400 cm⁻¹.

Example 4

Preparation of 3-(Pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 1 using 6-phenylmethoxyindole instead of indole. The crude product was purified by flash chromatography (15 p.s.i.) on 250 g silica gel eluting with 3:2 THF/hexane and then recrystallized from THF, a minimum of methanol, and excess ether to afford the title compound. m.p. 229-231°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, J = 15Hz, 1H), 4.62 (dd, J = 15, 2Hz, 1H), 5.15 (s, 2H), 6.67 (d, J = 3Hz, 1H), 6.75 (d, J = 2Hz, 1H), 6.85 (d, J = 3Hz, 1H), 6.91 (dd, J = 9, 2.5Hz, 1H), 7.04 (d, J = 2.5Hz, 1H), 7.30-7.52 (m, 6H), 7.65 (dt, J = 8, 2Hz, 1H), 8.09 (s, 1H), 8.13 (d, J =

9Hz, 1H), 8.53-8.58 (m, 2H), 11.68 (m, 1H). Anal calcd for $C_{27}H_{21}N_3O_2S$: C, 71.82; H, 4.69; N, 9.31. Found: C, 71.72; H, 4.78; N, 9.16. MS (DCI/NH₃) m/e 452 (M+H)⁺. IR (KBr) 1520, 1570, 1620, 3200, 3420 cm⁻¹.

5

Example 5

Preparation of 3-(Pyridin-3-yl)-7-(7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 1 using 7-phenylmethoxyindole instead of indole. The crude product was purified by
10 flash chromatography (15 p.s.i.) on 250 g silica gel eluting with 1:1 THF/hexane and then recrystallized from ethyl acetate/ether to afford the title compound. m.p. 184-188°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, J = 15Hz, 1H), 4.62 (dd, J = 15, 2Hz, 1H), 5.30 (s, 2H), 6.68 (d, J = 3Hz, 1H), 6.76 (d, J = 1Hz, 1H), 6.85 (d, J = 3Hz, 1H), 6.89 (d, J = 8Hz, 1H), 7.08 (t, J = 8Hz, 1H), 7.31-7.46 (m, 4H), 7.56-
15 7.67 (m, 3H), 7.83 (d, J = 8Hz, 1H), 8.03 (d, J = 3Hz, 1H), 8.53-8.58 (m, 2H), 12.06 (d, J = 3Hz). Anal calcd for $C_{27}H_{21}N_3O_2S$: C, 71.82; H, 4.69; N, 9.31. Found: C, 71.33; H, 4.70; N, 9.16. MS (DCI/NH₃) m/e 452 (M+H)⁺.

Example 6

Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-5-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 3, 3-(pyridin-3-yl)-7-(5-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-
25 (pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. The product was recrystallized from ethyl acetate/pentane to give the title compound. m.p. 87-91°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.04 (s, 6H), 4.48 (d, J = 15Hz, 1H), 4.65 (dd, J = 2, 15Hz, 1H), 5.16 (s, 2H), 6.72 (d, J = 3Hz, 1H), 6.79 (d, J = 1Hz, 1H), 6.89 (d, J = 3Hz, 1H), 7.06 (dd, J = 15, 3Hz, 1H), 7.30-7.56 (m, 7H), 7.66 (dt, H = 8, 2Hz,
30 1H), 7.88 (d, J = 3Hz, 1H), 8.28 (s, 1H), 8.55-8.59 (m, 2H). Anal calcd for $C_{30}H_{26}N_4O_3S$: C, 68.95; H, 5.01; N, 10.72. Found: C, 68.44; H, 5.17; N, 10.43. MS (DCI/NH₃) m/e 523 (M+H)⁺.

Example 7**Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 4, 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. The product was recrystallized from toluene/ether/excess pentane to give the title compound. m.p. 85-91°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.01 (s, 6H), 4.47 (d, *J* = 15Hz, 1H), 4.55 (dd, *J* = 15, 2Hz, 1H), 5.17 (s, 2H), 6.71 (d, *J* = 3Hz, 1H), 6.78 (d, *J* = 1Hz, 1H), 6.88 (d, *J* = 3Hz, 1H), 7.30-7.52 (m, 6H), 7.66 (dt, *J* = 8, 2Hz, 1H), 8.12 (d, *J* = 15Hz, 1H), 8.19 (s, 1H), 8.54-8.58 (m, 2H). Anal calcd for C₃₀H₂₆N₄O₃S: C, 68.95; H, 5.01; N, 10.72. Found: C, 68.66; H, 5.04; N, 10.55. MS (DCI/NH₃) *m/e* 523 (M+H)⁺.

Example 8**Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 5, 3-(pyridin-3-yl)-7-(7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. The product was recrystallized from methylene chloride/THF/hexane to give the title compound. m.p. 210-211°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.70 (d, *J* = 21Hz, 6H), 4.45 (d, *J* = 15Hz, 1H), 4.54 (dd, *J* = 15, 2Hz, 1H), 5.21 (s, 2H), 6.70 (d, *J* = 3Hz, 1H), 6.78 (d, *J* = 1Hz, 1H), 6.88 (s, 1H), 7.05 (d, *J* = 8Hz, 1H), 7.23 (t, *J* = 8Hz, 1H), 7.33-7.53 (m, 6H), 7.66 (dt, *J* = 8, 2Hz, 1H), 7.89 (d, *J* = 8Hz, 1H), 8.28 (s, 1H), 8.52-8.58 (m, 2H). MS (DCI/NH₃) *m/e* 523 (M+H)⁺.

Example 9**Preparation of 3-(Pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The compound resulting from Example 1 was reacted with di-*t*-butyl-dicarbonate in acetonitrile in the presence of 4-dimethylaminopyridine to give, after recrystallization from ether/pentane at -20 °C, the title compound. m.p. 150-151°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.66 (s, 9H), 4.48 (d, *J* = 15Hz, 1H), 4.65 (dd, *J* = 15, 2Hz, 1H), 6.75 (d, *J* = 3Hz, 1H), 6.83 (d, *J* = 3Hz, 1H), 7.34-7.48 (m, 3H), 7.69 (dt, *J* = 9, 2Hz, 1H), 8.12 (d, *J* = 9Hz, 1H), 8.26 (s, 1H), 8.56-8.60 (m, 2H).

Anal calcd for $C_{25}H_{23}N_3O_3S$: C, 67.40; H, 5.20; N, 9.43. Found: C, 67.26; H, 5.53; N, 9.10. MS (DCI/ NH_3) m/e 446 ($M+H$)⁺. IR(KBr) 1540, 1605, 1735, 2980 cm^{-1} .

Example 10

5 Preparation of 3-(Pyridin-3-yl)-7-(6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 1 using 6-phenylindole instead of indole. The product was recrystallized from THF/methanol/ether and then triturated in methylene chloride to afford the title
10 compound. m.p. 258°C. ¹H NMR (DMSO- d_6 , 300 MHz) δ 4.48 (d, J = 15Hz, 1H), 4.65 (dd, J = 15, 2Hz, 1H), 6.71 (d, J = 3Hz, 1H), 6.78 (s, 1H), 6.90 (d, J = 3Hz, 1H), 7.32-7.53 (m, 5H), 7.64-7.73 (m, 4H), 8.27 (d, J = 3Hz, 1H), 8.33 (d, J = 9Hz, 1H), 8.54-8.59 (m, 2H), 11.96 (d, J = 3Hz, 1H). Anal calcd for $C_{26}H_{19}N_3OS$: C, 74.09; H, 4.54; N, 9.97. Found: C, 73.93; H, 4.57; N, 9.92. MS (DCI/ NH_3)
15 m/e 422 ($M+H$)⁺. IR(KBr) 1505, 1522, 1550, 1580, 3180, 3420 cm^{-1} .

Example 11

Preparation of 3-(Pyridin-3-yl)-7-[1-(morpholin-4-ylcarbonyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

20 The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 1, 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, and (morpholin-4-yl)chloroformate to give, after recrystallization from ethyl acetate/ether, the title compound. m.p. 161-163°C. ¹H NMR (DMSO- d_6 , 300 MHz) δ 3.53-3.58 (m, 4H), 3.66-3.72 (m, 4H), 4.48 (d, J
25 = 15Hz, 1H), 4.65 (d, J = 15Hz, 1H), 6.75 (d, J = 2Hz, 1H), 6.80 (s, 1H), 6.90 (d, J = 3Hz, 1H), 7.28-7.47 (m, 3H), 7.68 (d, J = 8Hz, 2H), 8.22-8.30 (m, 2H), 8.55-8.59 (m, 2H). MS (DCI/ NH_3) m/e 459 ($M+H$)⁺. IR(CDCl₃) 1540, 1605, 1690, 2850, 2920, 2970 cm^{-1} .

Example 12

30 Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 10, 3-(pyridin-3-yl)-7-(6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. The crude product was purified by flash
35 chromatography (15 p.s.i.) on 250 g silica gel eluting with ethyl acetate to give the title compound as an amorphous solid. m.p. 115-125°C. ¹H NMR (DMSO- d_6 , 300 MHz)

δ 3.09 (s, 6H), 4.50 (d, $J = 15$ Hz, 1H), 4.68 (dd, $J = 15, 2$ Hz, 1H), 6.74 (d, $J = 3$ Hz, 1H), 6.80 (d, $J = 1$ Hz, 1H), 6.92 (d, $J = 3$ Hz, 1H), 7.34-7.53 (m, 4H), 7.84 (d, $J = 1$ Hz, 1H), 8.33 (d, $J = 9$ Hz, 1H), 8.38 (s, 1H), 8.57-8.60 (m, 2H). MS (DCI/NH₃) m/e 493 (M+H)⁺. IR (CDCl₃) 1540, 1610, 1690, 2930 cm⁻¹.

5

Example 13

Preparation of 2-Oxide-3-(pyridin-3-yl)-7-(1-*tert*-butyloxycarbonylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(pyridin-3-yl)-7-(1-*tert*-butyloxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (270mg, 0.61 mmol) prepared as described in example 9, in CHCl₃ (50 mL) at -20°C was added a solution of 3-chloroperbenzoic acid in CHCl₃ (50 mL). The reaction mixture was stirred for three hours at -20°C and then was partitioned between CHCl₃ and saturated aqueous NaHCO₃. The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated.

Purification by flash chromatography on silica gel (ethyl acetate) afforded the desired sulfoxide (150 mg). m.p. 155-157°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 1.67 (s, 9H), 4.27 (d, 1H, $J=17$ Hz), 4.68 (d, 1H, $J=17$ Hz), 6.72 (s, 1H), 6.97 (d, 1H, $J=3$ Hz), 7.12 (d, 1H, $J=3$ Hz), 7.36-7.50 (m, 4H), 8.11-8.16 (m, 1H), 8.20-8.24 (m, 1H), 8.31 (s, 1H), 8.45 (m, 1H), 8.61 (dd, 1H, $J=2, 4$ Hz). MS (DCI/NH₃) m/e 462 (M+H)⁺, 479 (M+NH₄)⁺, 414. IR (CDCl₃) 2980, 1740, 1620, 1545. Anal calcd for C₂₅H₂₃N₃O₄S: C, 65.06; H, 5.02; N, 9.10. Found: C, 63.92; H, 5.16; N, 8.72.

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Example 14

Preparation of 2-Oxide-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 13 using the compound resulting from Example 1, 3-(Pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(1-*tert*-butyloxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 158°C (decomp). ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.25 (d, 1H, $J=18$ Hz), 4.67 (d, 1H, $J=18$ Hz), 6.68 (s, 1H), 7.00 (d, 1H, $J=3$ Hz), 7.06 (d, 1H, $J=3$ Hz), 7.16-7.27 (m, 2H), 7.39-7.52 (m, 3H), 8.25-8.29 (m, 2H), 8.42 (d, 1H, $J=2$ Hz), 8.59-8.62 (m, 1H), 11.92 (s, 1H). MS (DCI/NH₃) m/e 362 (M+H)⁺, 379 (M+NH₄)⁺, 346, 315. IR (KBr) 3420, 2920, 1592, 1422. Anal calcd for C₂₀H₁₅N₃O₂S: C, 66.47; H, 4.18; N, 11.63. Found: C, 63.69; H, 4.64; N, 10.39.

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Example 15**Preparation of 3-(Pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole.**

The desired compound was prepared according to the method of Example 1, except substituting 3-(3-pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-carboxylic acid, prepared from 3-pyridinecarboxaldehyde and L-serine as described in United States Patent 4,529,728, for 3-(3-pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-carboxylic acid. ¹H NMR (DMSO-*d*₆) δ 5.28 (dd, 1H, *J* = 1.5, 13.0Hz), 5.44 (dd, 1H, *J* = 2.0, 13.0Hz), 6.80 (d, 1H, *J* = 3.0Hz), 6.84 (s, 1H), 6.90 (d, 1H, *J* = 3.0Hz), 7.19 (pd, 2H, *J* = 1.5, 7.0Hz), 7.47 (d, 1H, *J* = 7.0Hz), 7.49 (m, 1H), 7.825 (m, 2H), 8.68 (dd, 1H, *J* = 2.0, 5.0Hz), 8.71 (d, 1H, *J* = 2.0Hz). MS (DCI/NH₃) *m/e* 330 (M+1)⁺.

Example 16**Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-diisopropylcarbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 4, 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using diisopropylcarbamoylchloride instead of dimethylcarbamoylchloride. ¹H NMR (CDCl₃, 300 MHz) δ 1.30 (d, 12H, *J*=7 Hz), 3.63 (m, 2H), 4.47 (d, 1H, *J*=15 Hz), 4.65 (d, 1H, *J*=15 Hz), 5.18 (s, 2H), 6.72 (d, 1H, *J*=3 Hz), 6.78 (s, 1H), 6.88 (d, 1H, *J*=3 Hz), 6.97 (s, 1H), 7.04 (d, 1H, *J*=10 Hz), 7.29-7.50 (m, 6H), 7.62-7.69 (m, 1H), 8.15 (d, 1H, *J*=9 Hz), 8.19 (s, 1H), 8.53-8.58 (m, 2H). MS (DCI/NH₃) *m/e* 579 (M+H)⁺, 457. IR (CDCl₃) 2970, 1685, 1616. Anal calcd for C₃₄H₃₄N₄O₃S: C, 70.56; H, 5.92; N, 9.68. Found: C, 69.08; H, 5.84; N, 9.39.

Example 17**Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.****Step 1. 2-(3-pyridinyl)-5,5-dimethyl-4-thiazolidinecarboxylic acid.**

To a suspension of DL-penicillamine (50g, 335 mmol) in 1:1 aqueous ethanol (500 mL) was added 3-pyridinecarboxaldehyde (36g, 335 mmol). The resulting clear-yellow solution was stirred for 17 hours at ambient temperature during which time a white precipitate formed. The white solid was filtered off and rinsed with 3:1 H₂O, ethanol and ether to give 2-(3-pyridinyl)-5,5-dimethyl-4-thiazolidinecarboxylic acid (51g, 64%).

Step 2. 2-(3-pyridinyl)-3-formyl-5,5-dimethyl-4-thiazolidinecarboxylic acid.

Formic acid (17g, 378 mmol) and acetic anhydride (13g, 126 mmol) were combined at 0°C. A slurry of 2-(3-pyridinyl)-5,5-dimethyl-4-thiazolidinecarboxylic acid (10g, 42 mmol), prepared as in step 1, in THF (250 mL) was added over five minutes. The resulting clear-yellow solution was warmed slowly to ambient temperature and stirred for 17 hours, during which time it became a white suspension. The THF was removed *in vacuo*, and the resulting slurry was filtered to yield a white solid. The solid was rinsed with ether to give 2-(3-pyridinyl)-3-formyl-5,5-dimethyl-4-thiazolidinecarboxylic acid (10g) which was used without further purification.

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Step 3. methyl 1,1-dimethyl-3-(pyrid-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylate.

To a solution of p-toluenesulfonyl chloride (18g, 95 mmol) and methyl 2,3-dichloropropionate (15g, 95 mmol) in refluxing CH₂Cl₂ (125 mL) was added a mixture of 2-(3-pyridinyl)-3-formyl-5,5-dimethyl-4-thiazolidinecarboxylic acid (5.1g, 19 mmol) and triethylamine (2.3g, 22 mmol) in CH₂Cl₂ (125 mL). After one hour at reflux triethylamine (4.6g, 44 mmol) was added and the reaction mixture was refluxed for a further 17 hours. The reaction mixture was cooled to ambient temperature and partitioned between cold 1N aqueous NaOH and ethyl acetate. The organic phase was washed with cold 1N aqueous NaOH and brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was dissolved in 5% aqueous HCl and the solution was extracted twice with ether. The aqueous phase was neutralized with solid Na₂CO₃ and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. Chromatography on silica gel (150g, 1:1 ethyl acetate, hexanes), afforded methyl 1,1-dimethyl-3-(pyrid-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylate (1.1g, 20%) as an off-white powder.

Step 4. 1,1-dimethyl-3-(pyrid-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylic acid.

A mixture of methyl 1,1-dimethyl-3-(pyrid-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylate (1.1g, 3.8 mmol), 1N aqueous NaOH (19 mmol), and methanol (40 mL) was refluxed for 17 hours. The reaction mixture was cooled to ambient temperature and taken to pH 4 with concentrated HCl. The thick solution was extracted twice with 9:1 CHCl₃, isopropanol. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give a yellow powder. The powder was triturated with ether to afford 1,1-dimethyl-3-(pyrid-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylic acid as a pale-yellow powder.

35

Step 5. 1,1-Dimethyl-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-
c]thiazole.

The desired compound was prepared according to the method of Example 1,
5 except substituting 1,1-dimethyl-3-(pyrid-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-
carboxylic acid (1.0g, 3.6 mmol) for 3-(pyridin-3-yl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7-
carboxylic acid to give 1,1-Dimethyl-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-
pyrrolo[1,2-*c*]thiazole
(183mg, 14%). m.p. 254-257°C. ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (s, 3H), 2.07
10 (s, 3H), 6.19 (d, J=3Hz, 1H), 6.50 (s, 1H), 6.70 (d, J=3 Hz, 1H), 7.29 (m, 2H),
7.35 (m, 1H), 7.43 (m, 1H), 7.70 (dt, J=9.0, 1.5 Hz, 1H), 7.82 (d, J=3 Hz, 1H),
8.53 (bs, 1H), 8.64 (dd, J=6.0, 1.5 Hz, 2H). MS (DCI/NH₃) m/e 374 (M+1)⁺, 253,
141, 124.

Example 18

15 Preparation of 3-(Pyridin-3-yl)-7-(1-carbomethoxycarbamoyl-6-phenylmethoxyindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The desired compound was prepared according to the method of Example 2,
except substituting 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-
pyrrolo[1,2-*c*]thiazole, prepared as in Example 4 for 3-(pyridin-3-yl)-7-(indol-3-
20 yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and substituting methyl chloroformate for
N,N-dimethylcarbamoyl chloride. m.p. 152-153°C. ¹H NMR (DMSO-*d*₆, 300 MHz)
δ 4.03 (s, 3H), 4.47 (d, 1H, J=15 Hz), 4.63 (dd, 1H, J=2, 15 Hz), 5.20 (s, 2H),
6.73 (d, 1H, J=3 Hz), 6.80 (d, 1H, J=2 Hz), 6.81 (d, 1H, J=3 Hz), 7.12 (dd, 1H,
J=3, 9 Hz), 7.30-7.52 (m, 6H), 7.67 (dt, 1H, J=8, 2 Hz), 7.79 (d, 1H, J=3 Hz), 8.08
25 (d, 1H, J=9 Hz), 8.16 (s, 1H), 8.55-8.59 (m, 2H). MS (DCI/NH₃) m/e 510 (M+H)⁺.
Anal calcd for C₂₉H₂₃N₃O₄S: C, 68.35; H, 4.55; N, 8.25. Found: C, 67.84; H, 4.63;
N, 8.04.

Example 19

30 Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-indol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2
using the compound resulting from Example 17, 1,1-dimethyl-3-(pyridin-3-yl)-7-
(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(Pyridin-3-yl)-7-
(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (CDCl₃, 300 MHz) δ
35 2.05 (s, 3H), 2.06 (s, 3H), 3.13 (s, 6H), 6.20 (d, 1H, J=3Hz), 6.51 (s, 1H), 6.72 (d,
1H, J=3Hz), 7.36 (m, 3H), 7.58 (m, 1H), 7.69 (dt, 1H, J=7.5, 1.5Hz), 7.91 (s, 1H),
8.34 (m, 1H), 8.64 (b, 2H). MS (DCI/NH₃) 445(M+H)⁺, 322, 124.

Example 20**Preparation of 3-(Pyridin-3-yl)-7-(1-N-methyl-N-phenylcarbamoyl-6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole.**

5 The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 4, 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole and using *N*-methyl-*N*-phenylcarbamoylchloride instead of *N,N*-dimethylcarbamoylchloride. ¹H
10 NMR (DMSO-d₆, 300 MHz) δ 3.49 (s, 3H), 4.34 (d, 1H, J=15Hz), 4.52 (dd, 1H, J=15, 2Hz), 5.18 (s, 2H), 5.72 (d, 1H J=3Hz), 6.55 (d, 1H, J=3Hz), 6.72 (d, 1H, J=2Hz), 7.00 (dd, 1H, J=9, 3Hz), 7.18-7.55 (m, 12H), 7.60-7.66 (m, 2H), 7.98 (d, 1H, J=8Hz), 8.52 (d, 1H, J=2Hz), 8.58 (dd, 1H, J=2, 8Hz). MS (DCI/NH₃) m/e
15 585 (M+H)⁺, 463, 452, 372. IR (KBr) 1690, 1610, 1592, 1540, 1485. Anal calcd for C₃₅H₂₈N₄O₃S: C, 71.90; H, 4.83; N, 9.58. Found: C, 71.43; H, 4.95; N, 9.45.

Example 21**Preparation of 3-(Pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole.**

20 The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 4, 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole and using methyl iodide instead of *N,N*-dimethylcarbamoylchloride. m.p. 172-173°C. ¹H NMR
25 (DMSO-d₆, 300 MHz) δ 3.84 (s, 3H), 4.45 (d, 1H, J=5Hz), 4.62 (dd, 1H, J=15, 2Hz), 5.18 (s, 2H), 6.69 (d, 1H, J=3Hz), 6.76 (d, 1H, J=1Hz), 6.90 (d, 1H, J=3Hz), 6.95 (dd, 1H, J=9, 2Hz), 7.20 (d, 1H, J=2Hz), 7.32-7.53 (m, 6H), 7.65 (dt, 1H, J=8, 2Hz), 8.15 (d, 1H, 9Hz), 8.17 (s, 1H), 8.53-8.58 (m, 2H). MS (DCI/NH₃) m/e 466 (M+H)⁺, 436, 374, 345. IR (CDCl₃) 1595, 1570, 1525, 1245, 1080. Anal
30 calcd for C₂₈H₂₃N₃O₂S: C, 72.24; H, 4.98; N, 9.03. Found: C, 72.34; H, 5.06; N, 8.88.

Example 22**Preparation of 3-(Pyridin-3-yl)-7-(1-N-methylcarbamoyl-6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole.**

35 The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 4, 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1H,3H-pyrrolo[1,2-c]thiazole, instead of 3-

(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoylchloride. m.p. 212-214°C. ¹H NMR (DMSO-*d*₆) δ 3.84 (s, 3H), 4.45 (d, 1H, *J*=5Hz), 4.62 (dd, 1H, *J*=15, 2Hz), 5.18 (s, 2H), 6.69 (d, 1H, *J*=3Hz), 6.76 (d, 1H, *J*=1Hz), 6.90 (d, 1H, *J*=3Hz), 6.95 (dd, 1H, *J*=9, 2Hz), 7.20 (d, 1H, *J*=2Hz), 7.327.53 (m, 6H), 7.65 (dt, 1H, *J*=8, 2Hz), 8.15 (d, 1H, 9Hz), 8.17 (s, 1H), 8.53-8.58 (m, 2H). MS (DCI/NH₃) *m/e* 509 (M+H)⁺, 452. Anal calcd for C₂₉H₂₄N₄O₃S: C, 68.49; H, 4.76; N, 11.02. Found: C, 68.43; H, 4.31; N, 11.47.

Example 23

10 Preparation of 2-Oxide-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 13 using the compound resulting from Example 12, 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.09 (s, 0.12H), 3.11 (s, 0.88H), 4.29 (d, 0.12H, *J*=17Hz), 4.30 (d, 0.88H, *J*=17Hz), 4.72 (d, 0.88H, *J*=17Hz), 4.82 (d, 0.12H, *J*=17Hz), 6.72 (s, 0.88H), 6.77 (d, 0.12H, *J*=3Hz), 6.81 (s, 0.12), 6.96 (d, 0.12, *J*=3Hz), 7.05 (d, 0.88H, *J*=3Hz), 7.35-7.44 (m, 1H), 7.45-7.53 (m, 4H), 7.65 (dd, 1H, *J*=9, 2Hz), 7.72 (dd, 2H, *J*=9, 1Hz), 7.86 (m, 1H), 8.34 (d, 1H, *J*=9Hz), 8.43 (m, 2H), 8.62 (dd, 0.88H, 4, 2Hz), 8.69 (dd, 0.12H, 4Hz, 2Hz). MS (DCI/NH₃) *m/e* 526 (M+NH₄)⁺, 509 (M+H)⁺, 461, 403, 388. Anal calcd for C₂₉H₂₄N₄O₃S: C, 68.49; H, 4.76; N, 11.02. Found: C, 70.44; H, 5.33; N, 12.05.

25 Example 24

Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 19 using, 6-phenylindole instead of indole. ¹H NMR (CDCl₃, 300 MHz) δ 2.04 (s, 3H), 2.07 (s, 3H), 6.22 (d, 1H, *J*=3Hz), 6.53 (s, 1H), 6.75 (d, 1H, *J*=3Hz), 7.36 (m, 1H), 7.47 (m, 2H), 7.60 (dd, 1H, *J*=7.5, 1.5Hz), 7.67 (m, 2H), 7.81 (m, 2H), 7.92 (s, 1H), 8.37 (d, 1H, *J*=9Hz), 8.67 (2H). MS (DCI/NH₃) *m/e* 521(M+H)⁺, 398.

Example 25**Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.****Step 1. Preparation of 6-(4-methoxyphenyl)-1-*tert*-butoxycarbonylindole.**

- 5 To a solution of 1-*tert*-butoxycarbonyl-6-bromoindole (5.0g, 17 mmol) in toluene (200 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.94g, 0.84 mmol), 2N aqueous Na₂CO₃ (100 mL), and a solution of 4-methoxyboronic acid in ethanol (50 mL). The 2-phase mixture was heated at 110-125°C for two hours. The reaction mixture was cooled to ambient temperature and the layers were separated. The aqueous phase was extracted twice with ether. The combined organic layers were
10 washed twice with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to give a brown oil. Chromatography on silica gel (250g, 5% ether, hexanes) afforded 6-(4-methoxyphenyl)-1-*tert*-butoxycarbonylindole (3.2g, 58%).

15 **Step 2. Preparation of 6-(4-methoxyphenyl)indole.**

- To a suspension of 6-(4-methoxyphenyl)-1-*tert*-butoxycarbonylindole (3.9g, 12 mmol) in methanol (50 mL) was added 1N methanolic NaOH (60 mL) and CH₂Cl₂ (20 mL). The reaction was stirred for one hour at ambient temperature and 1.5 hours at reflux. The reaction mixture was cooled to ambient temperature and H₂O (50 mL) was
20 added to dissolve all solids. The two-phase mixture was poured into CHCl₃ and the layers were separated. The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (100g, 25% ethyl acetate, hexanes) afforded 6-(4-methoxyphenyl)indole as white flakes (2.2g, 81%).

25

Step 3. Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

- The title compound was prepared by the procedure described in Example 17 using 6-(4-methoxyphenyl)indole instead of indole. m.p. 236-239°C. ¹H NMR
30 (CDCl₃, 300 MHz) δ 2.06 (s, 3H), 2.08 (s, 3H), 4.06 (s, 3H), 6.19 (d, J=3 Hz, 1H), 6.49 (s, 1H), 6.70 (d, J=3 Hz, 1H), 6.99 (d, J=9 Hz, 2H), 7.36 (dd, J=7.5, 6.0 Hz, 1H), 7.51 (dd, J=7.5, 1.5 Hz, 1H), 7.58 (m, 3H), 7.71 (dt, J=9.0, 1.5 Hz, 1H), 7.81 (d, J=3 Hz, 1H), 8.40 (d, J=9 Hz, 1H), 8.62 (b, 3H). MS (DCI/NH₃) m/e 480 (M+1)⁺.

Example 26**Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl]-6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 25, 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 271-273°C. ¹H NMR (CDCl₃, 300 MHz) δ 2.06 (s, 3H), 2.07 (s, 3H), 3.15 (s, 3H), 3.86 (s, 3H), 6.20 (d, J=3 Hz, 1H), 6.51 (s, 1H), 6.73 (d, J=3 Hz, 1H), 6.99 (dd, J=9.0, 6.0 Hz, 2H), 7.37 (m, 1H), 7.55 (dd, J=9.0, 1.5 Hz, 1H), 7.59 (d, J=9 Hz, 2H), 7.70 (dt, J=9.0, 1.5 Hz, 1H), 7.73 (d, J=1.5 Hz, 1H), 7.89 (s, 1H), 8.34 (d, J=9 Hz, 1H), 8.64 (b, 2H). MS (DCI/NH₃) m/e 551 (M+1)⁺, 428. Anal calcd for C₃₂H₃₀N₄O₃S: C, 69.80; H, 5.49; N, 10.17. Found: C, 69.57; H, 5.59; N, 9.89.

15

Example 27**Preparation of 3-(Pyridin-3-yl)-7-(1-carbophenoxy-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The desired compound was prepared according to the method of Example 2, except substituting 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 4 for 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and substituting phenyl chloroformate for *N,N*-dimethylcarbamoyl chloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, 1H, J=15Hz), 4.62 (dd, 1H, J=15Hz, 2Hz), 5.16 (s, 2H), 6.69 (d, 1H, J=3Hz), 6.76 (s, 1H), 6.85 (d, 1H, J=3Hz), 7.12 (dd, 1H, J=9Hz, 3Hz), 7.26-7.52 (m, 11H), 7.60-7.68 (m, 1H), 7.77 (d, 1H, J=3Hz), 8.08 (d, 1H, J=9Hz), 8.30 (s, 1H), 8.51-8.54 (m, 2H). MS (DCI/NH₃) m/e 572 (M+H)⁺.

25

Example 28**Preparation of 3-(Pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

30

Step 1. Preparation of 6-(4-fluorophenyl)indole.

The desired compound was prepared according to the method of Example 25, step 1, except substituting 4-fluorophenylboronic acid for 4-methoxyphenylboronic acid, and 6-bromoindole for 1-*tert*-butoxy-6-bromoindole.

35

Step 2. Preparation of 3-(Pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

3-(Pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was prepared according to the method of Example 1, except substituting 6-(4-fluorophenyl)indole for indole. m.p. 248-252°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.47 (d, 1H, J=15Hz), 4.64 (dd, 1H, J=15Hz, 2Hz), 6.71 (d, 1H, J=3Hz), 6.78 (s, 1H), 6.90 (d, 1H, J=3Hz), 7.30 (t, 2H, J=9Hz), 7.41-7.50 (m, 2H), 7.63-7.78 (m, 4H), 8.27 (d, 1H, J=3Hz), 8.31 (d, 1H, J=8Hz), 8.55-8.60 (m, 2H), 11.96 (d, 1H, J=3Hz). MS (DCI/NH₃) m/e 440 (M+H)⁺, 406, 315, 212. IR (KBr) 3420, 1590, 1510, 1425, 1230, 860. Anal calcd for C₂₆H₁₈N₃OSF: C, 71.05; H, 4.13; N, 9.56. Found: C, 70.06; H, 4.19; N, 9.31.

Example 29

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 28, 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 212-214°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.08 (s, 6H), 4.50 (d, 1H, J=15Hz), 4.67 (dd, 1H, J=15, 2Hz), 6.73 (d, 1H, J=3Hz), 6.80 (d, 1H, J=1Hz), 6.92 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.44 (dd, 1H, J=5, 8Hz), 7.61 (dd, 1H, J=9, 1Hz), 7.68 (dt, 1H, J=8, 1Hz), 7.72-7.84 (m, 3H), 8.32 (d, 1H, J=9Hz), 8.37 (s, 1H), 8.55-8.60 (m, 2H). MS (DCI/NH₃) m/e 511 (M+H)⁺, 465, 387. IR (KBr) 1690, 1605, 1540, 1515, 1480. Anal calcd for C₂₉H₂₃FN₄O₂S: C, 68.22; H, 4.54; N, 10.97. Found: C, 67.46; H, 4.58; N, 10.67.

Example 30

Preparation of 3-(Pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 10, 3-(pyridin-3-yl)-7-(6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. m.p. 238-240°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.89 (d, 3H, J=4Hz), 4.51 (d, 1H, J=Hz), 4.68 (dd, 1H, J=15, 2Hz), 6.77 (d, 1H, J=3Hz), 6.81 (d, 1H, J=1Hz), 7.06 (d, 1H, 3Hz), 7.35-7.53 (m, 4H), 7.63 (dd, 1H, J=9, 1Hz), 7.66 (m, 3H), 8.32 (d, 1H, J=9Hz), 8.53-8.63 (m, 5H). MS (DCI/NH₃)

m/e 479 (M+H)⁺, 422, 298. IR (KBr) 1710, 1600, 1530, 1470. Anal calcd for C₂₈H₂₂N₄O₂S: C, 70.27; H, 4.63; N, 11.71. Found: C, 69.63; H, 4.87; N, 11.20.

Example 31

5 Preparation of 3-(Pyridin-3-yl)-7-[1-N-methylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 28, 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using
10 methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. m.p. 227-228°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.89 (d, 3H, J=4Hz), 4.51 (d, 1H, J=15Hz), 4.67 (dd, 1H, J=15, 2Hz), 6.78 (d, 1H, J=3Hz), 6.81 (d, 1H, J=1Hz), 7.05 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.45 (dd, 1H, J=8, 5Hz), 7.61 (dd, 1H, J=9, 1Hz),
15 7.65-7.77 (m, J=3H), 8.31 (d, 1H, J=8Hz), 8.50-8.63 (m, 5H). MS (DCI/NH₃) m/e 497 (M+H)⁺, 440. IR (KBr) 1712, 1600, 1535, 1510, 1430. Anal calcd for C₂₈H₂₁N₄O₂SF: C, 67.73; H, 4.26; N, 11.28. Found: C, 67.05; H, 4.31; N, 10.94.

20

Example 32

Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-[1-N-methylcarbamoyl-6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 25, 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of
25 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. ¹H NMR (CDCl₃, 300 MHz) δ 2.03 (s, 6H), 3.12 (s, 3H), 3.14 (s, 3H), 3.86 (s, 3H), 6.16 (b, 1H), 6.19 (d, 1H, J=3Hz), 6.51 (s, 1H), 6.70 (d, 1H, J=3Hz), 6.96 (d, 2H, J=9Hz), 7.49 (m,
30 1H), 7.50-7.60 (c, 3H), 7.73 (d, 1H, J=9Hz), 7.96 (s, 1H), 8.06 (s, 1H), 8.24 (d, 1H, J=9Hz), 8.58-8.70 (b, 2H). MS (DCI/HN₃) 537(M+H)⁺, 480.

Example 33**Preparation of 3-(1-methylpyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

To a solution of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (100mg, 0.20 mmol), prepared as in Example 11, in acetone (15 mL) was added iodomethane (19μL, 0.30 mmol) via syringe. The reaction mixture was stirred at reflux for 18 hours. The reaction mixture was cooled to ambient temperature and iodomethane (7μL) was added and the reaction mixture was warmed back to reflux and stirred for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in methanol. Crude material was precipitated by addition of ether. Pure 3-(1-Methylpyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (38 mg), was obtained by recrystallization from methanol, ether. m.p. 171-174C. ¹H NMR (D₃COD, 300 MHz) δ 3.17 (s, 6H), 4.44 (s, 3H), 4.57 (d, 1H, J=15Hz), 4.76 (dd, 1H, J=15, 2Hz), 6.76 (d, 1H, J=3Hz), 6.87 (d, 1H, J=2Hz), 6.98 (d, 1H, J=3Hz), 7.35 (t, 1H, J=8Hz), 7.47 (t, 2H, J=8Hz), 7.62 (dd, 1H, J=9, 2Hz), 7.65-7.72 (m, 2H), 7.81-7.82 (m, 1H), 8.10 (dd, 1H, J=6, 8Hz), 8.25 (s, 1H), 8.32 (d, 1H, J=9Hz), 8.45 (d, 1H, J=9Hz), 8.91 (d, 1H, J=6Hz), 8.97 (s, 1H). MS (FAB) m/e 507 (M+1)⁺. IR (KBr) 1690, 1610, 1535, 1475. Anal calcd for C₃₀H₂₇N₄O₂S: C, 56.79; H, 4.29; N, 8.83. Found: C, 54.50; H, 4.12; N, 8.45.

Example 34**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.****Step 1. Preparation of 3-[1-(2,4-dinitrophenyl)pyridin-3-yl]-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

A mixture of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (500 mg, 1.01 mmol), prepared as described in Example 12, and 2,4-dinitrophenyl-*p*-toluenesulfonate (515 mg, 1.5 mmol), prepared according to the method described in J. Amer. Chem. Soc., **74**, 5859 (1952), in acetonitrile (10 mL) was heated at 100-110°C for 23 hours. The heterogeneous reaction mixture was cooled to ambient temperature, ether (30 mL) was added, and the slurry was stirred for 10 min. The solid was filtered off and recrystallized from methanol to afford 3-[1-(2,4-dinitrophenyl)pyridin-3-yl]-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (608 mg) as a tan solid.

Step 2. Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a suspension of 3-[1-(2,4-dinitrophenyl)pyridin-3-yl]-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (250
5 mg, 0.30 mmol), prepared as in step 1, in methanol (6 ml) was added aqueous hydroxylamine (1*N*, 0.60 mmol) and the reaction mixture was heated at 90°C for three hours. The reaction mixture was concentrated *in vacuo* and triturated with ether to give a reddish powder. Pure 3-(1-Oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was obtained by flash
10 chromatography on silica gel (24:1 CH₂Cl₂, 5% aqueous methanol). ¹H NMR (CD₃OD, 300 MHz) δ 3.18 (s, 6H), 4.52 (d, 1H, *J* = 15.0Hz), 4.68 (dd, 1H, *J* = 1.5, 15.0Hz), 6.69 (d, 1H, *J* = 1.0Hz), 6.72 (d, 1H, *J* = 3.0Hz), 6.95 (d, 1H, *J* = 3.0Hz), 7.34 (m, 1H), 7.43-7.50(c, 3H), 7.55 (dd, 1H, *J* = 7.0, 8.5Hz), 7.61 (dd, 1H, *J* = 1.5, 9.0Hz), 7.69 (d, 2H, *J* = 8.0Hz), 7.82 (d, 1H, *J* = 1.0Hz), 8.25 (s, 1H), 8.28
15 (br s, 1H), 8.30 (d, 1H, *J* = 8.0Hz), 8.31 (m, 1H). MS (DCI/NH₃) 509 (M+1), 493.

Example 35

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound is prepared by the procedure described in Example 34 using
20 the compound resulting from Example 30, 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (CD₃OD, 300 MHz) δ 3.00 (s, 3H), 4.52 (d,
25 1H, *J* = 15.0Hz), 4.66 (dd, 1H, *J* = 1.5, 15.0Hz), 6.69 (d, 1H, *J* = 1.0Hz), 6.73 (d, 1H, *J* = 3.0Hz), 7.03 (d, 1H, *J* = 3.0Hz), 7.34 (m, 1H), 7.45-7.48 (c, 3H), 7.55 (dd, 1H, *J* = 7.0, 9.0Hz), 7.61 (dd, 1H, *J* = 1.5, 9.0Hz), 7.70 (d, 2H, *J* = 8.0Hz), 8.23 (d, 1H, *J* = 1.5Hz), 8.29 (d, 1H, *J* = 8.0Hz), 8.30 (dd, 1H, *J* = 1.5, 7.0Hz), 8.49 (s, 1H), 8.50 (s, 1H). MS (FAB) 495 (M+1)⁺ 479.

30

Example 36

Preparation of 1,1-Dimethyl-3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 17
35 using 6-(4-fluorophenyl)indole, prepared as in Example 28, instead of indole. ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (s, 6H), 6.18 (d, 1H, *J*=3Hz), 6.51 (s, 1H), 6.69 (d, 1H, *J*=3Hz), 7.13 (t, 2H, *J*=14.9Hz), 7.43 (m, 1H), 7.49 (dd, 1H, *J*=9, 1.5Hz), 7.58

(m, 3H), 7.78 (m, 1H), 7.80 (d, 1H, J=3Hz), 8.42 (d, 1H, J=9Hz), 8.61 (d, 1H, J=1.5Hz), 8.65 (m, 1H), 8.98 (bs, 1H). MS (DCI/NH₃) 468 (M+H)⁺.

Example 37

5 Preparation of 3-(Pyridin-3-yl)-7-(1-carbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

Step 1. Preparation of 3-(Pyridin-3-yl)-7-[1-(4-nitrophenoxy carbonyl)-6-phenylmethoxyindol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

To a solution of 3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-
10 1H,3H-pyrrolo[1,2-c]thiazole (200 mg, 0.443 mmol), prepared as in Example 4, in DMF (12 mL) was added NaH (60% oil dispersion, 19 mg, 0.465 mmol) and the reaction mixture was stirred for 7 min at ambient temperature. 4-nitrophenyl chloroformate (94 mg, 0.45 mmol) was added and the amber solution was stirred for two hours at ambient temperature. The reaction mixture was partitioned between H₂O
15 and ethyl acetate. The organic phase was dried over MgSO₄, filtered, and concentrated. The title compound (98 mg) was purified by flash chromatography on silica gel (60 g, 1:1 ethyl acetate, hexanes).

20 Step 2. Preparation of 3-(Pyridin-3-yl)-7-(1-carbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

Several drops of anhydrous ammonia were condensed into a solution of 3-(Pyridin-3-yl)-7-[1-(4-nitrophenoxy carbonyl)-6-phenylmethoxyindol-3-ylcarbonyl]-
1H,3H-pyrrolo[1,2-c]thiazole (50 mg) in 1:1 THF methanol (4 mL) at -78°C. The reaction mixture was stirred for 1 hour at -78°C. The reaction mixture was warmed to
25 ambient temperature and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (50 g, ethyl acetate) to yield 32 mg of 3-(Pyridin-3-yl)-7-(1-carbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.48 (d, 1H, J=15Hz), 4.55 (dd 1H, J=15, 2Hz), 5.15 (s, 2H), 6.74 (d, 1H, J=3Hz), 6.79 (d, 1H, J=1Hz), 7.01 (d, 1H, J=3Hz), 7.04 (dd, 1H, J=3, 9Hz) 7.30-7.52 (m, 6H), 7.68 (dt, 1H, J=8, 2Hz), 7.89
30 (s, 2H), 7.98 (d, 1H, J=3Hz), 8.11 (d, 1H, J=9Hz), 8.41 (s, 1H), 8.55-8.59 (m, 2H). MS (DCI/NH₃) m/e 495 (M+H)⁺, 452. IR (KBr) 1710, 1600, 1540, 1480. Anal calcd for C₂₈H₂₂N₄O₃S: C, 68.00; H, 4.48; N, 11.33. Found: C, 67.14; H, 4.68; N, 10.87.

Example 38**Preparation of 3-(Pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The desired compound was prepared using the procedure of example 28, except
5 using 4-methoxybromobenzene instead of 4-fluorobromobenzene. m.p. 246-248°C.
¹H NMR (DMSO-*d*₆ 300 MHz) δ 3.81 (s, 3H), 4.47 (d, 1H, J=15Hz), 4.64 (dd,
1H, J=15Hz, 2Hz), 6.70 (d, 1H, J=3Hz), 6.77 (s, 1H), 6.90 (d, 1H, J=3Hz), 7.04
(d, 2H, J=2Hz), 7.41-7.48 (m, 2H), 7.61-7.69 (m, 4H), 8.23 (d, 1H, J=2Hz), 8.29
(d, 1H, J=9Hz), 8.53-8.59 (m, 2H), 11.90 (s, 1H). MS (DCI/NH₃) m/e 452
10 (M+H)⁺. IR (KBr) 1605, 1575, 1510. Anal calcd for C₂₇H₂₁N₃O₂S: C, 71.82; H,
4.69; N, 9.31. Found: C, 70.97; H, 4.74; N, 9.06.

Example 39**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound is prepared by the procedure described in Example 34 using
the compound resulting from Example 29, 3-(pyridin-3-yl)-7-[1-*N,N*-
N,N-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-yl]carbonyl-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-
20 dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H
NMR (CD₃OD, 300 MHz) δ 3.15 (s, 6H), 4.48 (d, 1H, J=15 Hz), 4.65 (1H, J=15,
2Hz), 6.68 (d, 1H, J=1Hz), 6.73 (d, 1H, J=3Hz), 6.95 (1H, J=4Hz), 7.2 (t, 2H,
J=9Hz), 7.45 (m, 1H), 7.5-7.6 (cm, 2H), 7.65-7.75 (m, 2H), 7.8 (d, 1H, J=1Hz),
8.23-8.33 (m, 4H). MS (FAB) m/e 527. IR (CDCl₃) 1690, 1600, 1540, 1510, 1480,
25 1440, 1390, 1225, 1180.

Example 40**Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2
30 using the compound resulting from Example 38, 3-(pyridin-3-yl)-
7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of
3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 204-
205°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.08 (s, 6H), 3.81 (s, 3H), 4.49 (d, 1H,
J=15Hz), 4.68 (dd, 1H, J=15, 2Hz), 6.73 (d, 1H, J=3Hz), 6.80 (s, 1H), 6.91 (d,
35 1H, J=3Hz), 7.05 (d, 2H, J=9Hz), 7.45 (dd, 1H, J=5, 8Hz), 7.58 (dd, 1H, J=1,
8Hz), 7.63-7.70 (m, 3H), 7.78 (s, 1H), 8.29 (d, 1H, J=9Hz), 8.33 (s, 1H), 8.55-
8.59 (m, 2H). MS (DCI/NH₃) m/e 523 (M+H)⁺. IR (KBr) 1690, 1605, 1540, 1520,

1480. Anal calcd for $C_{20}H_{26}N_4O_3S$: C, 68.95; H, 5.01; N, 10.72. Found: C, 67.22; H, 5.05; N, 9.93.

Example 41

Preparation of 3-(Pyridin-3-yl)-7-(6-pyrid-4-ylindol-3-ylcarbonyl)-

5 1H,3H-pyrrolo[1,2-c]thiazole.

Step 1. Preparation of 6-indolylboronic acid.

To a suspension of potassium hydride (35% oil dispersion, 0.84 g, 7.33 mmol) in THF (10 mL) at 0°C was added a solution of 6-bromoindole (1.43 g, 7.29 mmol) in THF (6 mL). The reaction mixture was stirred for 15 min at 0°C, then cooled to -78°C and *t*-butyllithium solution (1.7M in pentane, 14.6 mmol) was added quickly dropwise. After stirring for 20 min. at -78°C, a solution of tri-*n*-butyl borate (3.94 mL, 14.6 mmol) in THF (4 mL) was added quickly. The reaction mixture was stirred for 1 hour at -78°C and 2 hours at 0°C. The reaction was quenched by addition of 1N aqueous HCl (15 mL) and stirring for 30 min at 0°C. The reaction mixture was partitioned between H₂O and ether. The aqueous phase was extracted 3 times with ether. The combined ethereal extracts were washed 3 times with cold 1N aqueous NaOH, and then discarded. The basic aqueous extracts were acidified with 1N aqueous HCl and extracted 3 times with ether. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 6-indolylboronic acid (0.86 g) which was used without further purification.

Step 2. Preparation of 6-(3-pyridinyl)indole.

The desired compound was prepared according to the method of Example 25, step 1, except substituting 6-indolylboronic acid, prepared as in step 1 for 4-methoxyphenylboronic acid, and 3-bromopyridine for 1-*tert*-butoxycarbonyl-6-bromoindole.

Step 3. Preparation of 3-(Pyridin-3-yl)-7-(6-pyrid-3-ylindol-3-ylcarbonyl)-

1H,3H-pyrrolo[1,2-c]thiazole.

To a suspension of 3-(pyridin-3-yl)-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylic acid (0.84 g, 3.43 mmol), prepared as described in United States Patent 4,529,728, in dry CHCl₃ under N₂ was added NaH (60% oil dispersion, 151 mg, 3.77 mmol) in a single portion. The suspension was stirred for 30 min at ambient temperature, then 2 drops of DMF were added, followed by oxalyl chloride (0.34 mL, 3.77 mmol). The suspension was stirred for 30 min at ambient temperature.

In a separate flask, methylmagnesium bromide solution (3.0M in ether, 2.3 mL, 6.9 mmol) was added to a suspension of 6-(3-pyridinyl)indole, prepared in step 2, in

ether (35 mL). The yellow suspension was stirred for 30 min at ambient temperature, after which zinc chloride solution (1.0M in ether, 6.9 mmol) was added quickly and the suspension was stirred for a further 20 min.

The solution of acid chloride in CHCl_3 was cannulated into the indolylzinc chloride suspension and the reaction mixture was stirred for 18 hours at ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with THF, ethyl acetate, and again with THF. The combined organic layers were dried over MgSO_4 , filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (200 g, 7% methanol, CHCl_3) afforded 3-(Pyridin-3-yl)-7-(6-pyrid-3-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (116 mg). m.p. 270-271°C. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 4.48 (d, 1H, $J=15\text{Hz}$), 4.65 (dd, 1H, $J=2, 15\text{Hz}$), 6.71 (d, 1H, $J=3\text{Hz}$), 6.78 (d, 1H, $J=1\text{Hz}$), 6.91 (d, 1H, $J=3\text{Hz}$), 7.45 (dd, 1H, $J=8, 5\text{Hz}$), 7.50 (dd, 1H, $J=5, 8\text{Hz}$), 7.55 (dd, 1H, $J=9, 2\text{Hz}$), 7.66 (dt, 1H, $J=9, 2\text{Hz}$), 7.79 (d, 1H, $J=2\text{Hz}$), 8.30 (s, 1H), 8.37 (d, 1H, $J=9\text{Hz}$), 8.53-8.59 (d, 1H, $J=9\text{Hz}$), 8.53-8.59 (m, 3H), 8.94 (d, 1H, $J=2\text{Hz}$). MS (DCI/NH_3) m/e 423 ($\text{M}+\text{H}$)⁺, 223, 195. IR (KBr) 3180, 1585, 1575, 1540. Anal calcd for $\text{C}_{25}\text{H}_{18}\text{N}_4\text{OS}$: C, 71.07; H, 4.29; N, 13.26. Found: C, 70.14; H, 4.28; N, 12.93.

Example 42

20 Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-pyrid-4-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 41, 3-(pyridin-3-yl)-7-(6-pyrid-4-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 3.09 (s, 6H), 4.50 (d, 1H, $J=15\text{Hz}$), 4.68 (dd, 1H, $J=2, 15\text{Hz}$), 6.74 (d, 1H, $J=3\text{Hz}$), 6.80 (d, 1H, $J=1\text{Hz}$), 6.92 (d, 1H, $J=3\text{Hz}$), 7.45 (dd, 1H, $J=5, 8\text{Hz}$), 7.51 (dd, 1H, $J=5, 8\text{Hz}$), 7.65-7.71 (m, 2H), 7.90 (d, 1H, $J=1\text{Hz}$), 8.14 (dt, 1H, $J=2, 8\text{Hz}$), 8.36 (d, 1H, $J=8\text{Hz}$), 8.40 (s, 1H), 8.56-8.61 (m, 3H), 8.95 (d, 1H, $J=2\text{Hz}$). MS (DCI/NH_3) m/e 494 ($\text{M}+\text{H}$)⁺, 387, 337. IR (KBr) 2920, 1690, 1602, 1530, 1480. Anal calcd for $\text{C}_{28}\text{H}_{23}\text{N}_5\text{O}_2\text{S}$: C, 68.14; H, 4.70; N, 14.19. Found: C, 67.27; H, 4.75; N, 14.06.

Example 43**Preparation of 3-(Pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 38, 3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. m.p. 251°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.89 (d, 3H, J=5Hz), 3.81 (s, 3H), 4.51 (d, 1H, J=15Hz), 4.68 (dd, 1H, J=2, 15Hz), 6.78 (d, 1H, J=3Hz), 6.81 (d, 1H, J=1Hz), 7.03-7.08 (m, 3H), 7.45 (dd, 1H, J=5, 8Hz), 7.59 (dd, 1H, J=1, 9Hz), 7.61-7.71 (m, 3H), 8.28 (d, 1H, J=9Hz), 8.48-8.52 (m, 2H), 8.56-8.62 (m, 3H). MS (DCI/NH₃) *m/e* 509 (M+H)⁺, 452. IR (KBr) 1705, 1605, 1530, 1515, 1475. Anal calcd for C₂₉H₂₄N₄O₃S: C, 68.49; H, 4.76; N, 11.02. Found: C, 67.56; H, 4.96; N, 10.58.

Example 44**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 2, 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.05 (s, 6H), 4.46 (d, 1H, J=15Hz), 4.65 (dd, 1H, J=2, 15Hz), 6.70 (d, 1H, J=2Hz), 6.86 (d, 1H, J=3Hz), 6.91 (d, 1H, J=3Hz), 7.13 (d, 1H, J=8Hz), 7.28-7.47 (m, 3H), 7.62 (d, 1H, J=8Hz), 8.18-8.28 (m, 3H), 8.33 (s, 1H). IR (KBr) 2920, 1690, 1600, 1535, 1480.

Example 45**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 40, 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.09 (s, 6H), 3.81 (s, 3H), 4.47 (d, 1H, J=15Hz),

4.67 (dd, 1H, J=2, 15Hz), 6.71 (d, 1H, J=1Hz), 6.87 (d, 1H, J=3Hz), 6.94 (d, 1H, J=3Hz), 7.05 (d, 2H, J=9Hz), 7.15 (d, 1H, J=8Hz), 7.40-7.46 (m, 1H), 7.59 (dd, 1H, J=2, 9Hz), 7.63-7.70 (m, 2H), 7.78 (d, 1H, J=1Hz), 8.19-8.22 (m, 2H), 8.29 (d, 1H, J=9Hz), 8.34 (s, 1H). MS (DCI/NH₃) m/e 523 (M+H)⁺, 539.

5

Example 46

Preparation of 3-(Pyridin-3-yl)-7-[1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

Sodium hydride (95%, 37.4 mg, 1.48 mmol) was added to a solution of 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (0.50 g, 1.14 mmol), prepared according to the method of Example 28, in DMF (30 mL). The reaction mixture was stirred for 30 min. at ambient temperature, and then methyl acrylate (0.40 mL, 4.56 mmol) was added. The reaction mixture was poured into brine and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. 3-(Pyridin-3-yl)-7-[1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (190 mg, 32%) was obtained by flash chromatography on silica gel (5g, 40%, then 60%, then 80% ethyl acetate, hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 2.93 (t, 2H, J=6, 8Hz), 3.68 (s, 3H), 4.53 (dd, 3H, J=6, 11Hz), 4.7 (dd, 1H, J=2, 15Hz), 6.38 (d, 1H, J=3Hz), 6.43 (s, 1H), 6.78 (d, 1H, J=3Hz), 7.15 (t, 2H, J=9, 10Hz), 7.35 (dd, 1H, J=5, 8Hz), 7.5 (dd, 2H, J=3, 10Hz), 7.6-7.1 (m, 3H), 7.95 (s, 1H), 8.45 (dd, 1H, J=1, 9Hz), 8.6-8.68 (m, 2H). MS (DCI/NH₃) m/e 526 (M+H)⁺.

Example 47

Preparation of 3-(Pyridin-3-yl)-7-(6-chloroindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared by the procedure of Example 28, using 6-chloroindole instead 6-phenylindole. m.p. 263-265°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.45 (d, 1H, J=15Hz), 4.62 (dd, 1H, J=2, 15Hz), 6.70 (d, 1H, J=3Hz), 6.77 (s, 1H), 6.89 (d, 1H, J=3Hz), 7.20 (dd, 1H, J=2, 9Hz), 7.43 (dd, 1H, J=5, 7Hz), 7.52 (d, 1H, J=2Hz), 7.65 (dt, 1H, J=1, 8Hz), 8.25 (d, 1H, J=9Hz), 8.28 (d, 1H, J=2Hz), 8.53-8.58 (m, 2H), 11.98 (s, 1H). MS (DCI/NH₃) m/e 380 (M+H)⁺, 350. Anal calcd for C₂₀H₁₄ClN₃OS: C, 63.24; H, 3.71; N, 11.06. Found: C, 61.98; H, 2.89; N, 10.73.

35

Example 48**Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3,4,5-trimethoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the method of Example 2, using 3-(pyridin-3-yl)-7-[6-(3,4,5-trimethoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared according to the methods of Example 28, except using 3,4,5-trimethoxybromobenzene instead of 4-fluorobromobenzene, instead of 3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 194-196°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.09 (s, 6H), 3.71 (s, 3H), 3.89 (s, 6H), 4.50 (d, 1H, J=15Hz), 4.68 (dd, 1H, J=2, 15Hz), 6.74 (d, 1H, J=3Hz), 6.80 (s, 1H), 6.91-6.95 (m, 3H), 7.45 (dd, 1H, J=5, 8Hz), 7.62 (dd, 1H, J=1, 9Hz), 7.68 (dt, 1H, J=1, 9Hz), 7.82 (s, 1H), 8.30 (d, 1H, J=8Hz), 8.36 (s, 1H), 8.55-8.60 (m, 2H). MS (DCI/NH₃) m/e 583 (M+H)⁺, 461, 387. IR (KBr) 2940, 1690, 1605, 1580, 1535. Anal calcd for C₃₂H₃₀N₄O₅S: C, 65.96; H, 5.19; N, 6.92. Found: C, 64.28; H, 4.06; N, 9.26.

Example 49**Preparation of 3-(Pyridin-3-yl)-7-[1-(2-carboxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.****Step 1. Preparation of 3-(pyridin-3-yl)-7-[1-(2-carboethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The desired compound was prepared according to the method of Example 46, except substituting ethyl acrylate for methyl acrylate.

Step 2. Preparation of 3-(Pyridin-3-yl)-7-[1-(2-carboxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

A mixture of 3-(pyridin-3-yl)-7-[1-(2-carboethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (90 mg, 0.17 mmol), and lithium hydroxide (11 mg), were stirred in 33% aqueous THF (15 mL) for 45 min. The reaction mixture was diluted with H₂O and taken to pH 4 with 1M aqueous HCl. The reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. 3-(Pyridin-3-yl)-7-[1-(2-carboxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (63 mg), was crystallized from ethyl acetate, hexanes. ¹H NMR (CDCl₃, 300MHz) δ 2.95 (t, 2H, J=6, 7Hz), 4.5-4.65 (m, 4H), 6.14 (d, 1H, J=3Hz), 6.45 (s, 1H), 6.73 (d, 1H, J=3Hz), 7.15 (t, 2H, J=9, 11Hz), 7.38-7.43 (m, 1H), 7.52 (d, 2H, J=8Hz), 7.6-7.7 (m, 3H), 8.05 (s, 1H), 8.46 (d, 1H, J=9Hz),

8.57 (bs, 2H). MS (DCI/NH₃) m/e 512 (M+H)⁺. Anal calcd for C₂₉H₂₂N₃O₃SF: C, 68.09; H, 4.33; N, 8.21. Found: C, 67.78; H, 3.90; N, 8.06.

Example 50

5 Preparation of 3-(Pyridin-3-yl)-7-[1-(2-sulfamylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 46 using vinylsulfonamide instead of methyl acrylate. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.6 (t, 2H, J=7, 9Hz), 4.48 (d, 1H, J=15Hz), 4.65 (d, 1H, J=15Hz), 4.77 (t, 2H, J=6, 8Hz), 6.73 (d, 1H, J=3Hz), 6.78 (s, 1H), 6.95 (d, 1H, J=3Hz), 7.13 (s, 2H), 10 7.33 (t, 2H, J=9, 10Hz), 7.45 (dd, 1H, J=5, 9Hz), 7.54 (d, 1H, J=9Hz), 7.67 (d, 1H, J=8Hz), 7.8-7.88 (m, 3H), 8.32 (d, 1H, J=9Hz), 8.39 (s, 1H), 8.55-8.6 (m, 2H). MS (DCI/NH₃) m/e 547 (M+H)⁺. Anal calcd for C₂₈H₂₃N₄O₃S₂F: C, 61.52; H, 4.24; N, 15 10.25. Found: C, 60.82; H, 3.95; N, 9.95.

Example 51

Preparation of 3-(Pyridin-3-yl)-7-[1-methanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

20 The desired compound was prepared according to the method of Example 29, except substituting methanesulfonyl chloride for *N,N*-dimethylcarbonyl chloride. ¹H NMR (DMSO -d₆) δ 3.76 (s,3H), 4.48 (d, 1H, J =15Hz), 4.66 (dd, 1H, J =15, 1.5Hz), 6.78 (d, 1H, J =3Hz), 6.82 (bs, 1H), 6.9 (d, 1H, J =3Hz), 7.35 (t, 2H, J =9Hz), 7.45 (dd, 1H, J =4.5, 6Hz), 7.65-7.74 (cm, 2H), 7.82 (dd, 2H, J =6, 3Hz), 25 8.08 (bs, 1H), 8.2 (s, 1H), 8.3 (d, 1H, J =9Hz), 8.55-9.0 (cm, 2H). MS (DCI/NH₃) m/e 517 (M+H)⁺ 440. Anal calcd for C₂₇H₂₀FN₃O₃S₂·0.75H₂O: C, 51.06; H, 4.08; N, 7.91. Found: C, 51.14; H, 3.69; N, 7.62.

Example 52

30 Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbonyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride.

A solution of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbonyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 12, was treated at ambient temperature with excess 4N HCl in dioxane. After stirring for two hours, 35 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbonyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride was isolated by filtration. ¹H NMR

(CD₃OD, 300 MHz) δ 3.17 (s, 6H), 4.55 (d, 1H, J = 15.0Hz), 4.72 (dd, 1H, J = 15.0, 1.0Hz), 6.72 (d, 1H, J = 3.0Hz), 6.89 (d, 1H, J = 1.0Hz), 6.98 (d, 1H, J = 3.0Hz), 7.36 (t, 1H, J = 7.5Hz), 7.46 (t, 2H, J = 7.5Hz), 7.61 (dd, 1H, J = 9.0, 1.0Hz), 7.69 (d, 2H, J = 8.0Hz), 7.81 (bs, 1H), 8.09 (dd, 1H, J = 9.0, 6.0Hz), 8.24 (s, 1H), 8.31 (d, 1H, J = 9.0Hz), 8.49 (dt, 1H, J = 8.5, 1.0Hz), 8.84 (bs, 1H), 8.85 (m, 1H). IR (KBr) 3450, 1695, 1540, 1390. Anal calcd for C₂₉H₂₅ClN₄O₂S: C, 65.84; H, 4.76; N, 10.59. Found: C, 65.96; H, 4.91; N, 10.48.

Example 53

10 Preparation of 3-(Pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The desired compound was prepared according to the method of Example 46, except substituting *N,N* dimethylchloroacetamide for methyl acrylate. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.88 (s, 3H), 3.15 (s, 3H), 4.48 (d, 1H, J=15 Hz), 4.65 (dd, 1H, J=15, 2 Hz), 5.37 (s, 2H), 6.72 (d, 1H, J=3 Hz), 6.78 (bs, 1H), 6.85 (d, 1H, J=3 Hz), 7.31 (t, 2H, J=12 Hz), 7.44 (cm, 2H), 7.52 (dd, 2H, J=12, 2Hz), 7.66 (cm, 1H), 7.78 (cm, 3H), 8.25 (s, 1H), 8.32 (d, 1H, J=12 Hz), 8.57 (cm, 2H). MS (DCI/NH₃) m/e 525 (M+H)⁺, 542 (M+ NH₄)⁺. IR (KBr) 1600(s), 1660(s). Anal calcd for C₃₀H₂₅N₄O₂SF: C, 68.69; H, 4.80; N, 10.68. Found: C, 68.20; H, 4.63; N, 10.68.

Example 54

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole hydrochloride.

The title compound was prepared by the procedure described in Example 52 using the compound resulting from Example 34, 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 122-130°C. ¹H NMR (CD₃OD, 300 MHz) δ 3.16 (s, 6H), 4.53 (d, 1H, J = 15.0Hz), 4.69 (d, 1H, J = 15.0Hz), 6.73 (s, 1H, J = 3.0Hz), 6.74 (bs, 1H), 6.97 (d, 1H, J = 3.0Hz), 7.33 (t, 1H, J = 7.5Hz), 7.45 (t, 2H, J = 7.5Hz), 7.62 (dd, 1H, J = 9.0, 1.0Hz), 7.68 (d, 2H, J = 7.5Hz), 7.81 (m, 2H), 8.23 (s, 1H), 8.31 (d, 1H, J = 9.0Hz), 8.58 (bs, 1H), 8.60 (m, 1H). IR (KBr) 3410, 1695, 1535, 1395.

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Example 55

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 51, using *N,N*-dimethylaminosulfonylchloride instead of methanesulfonylchloride. m.p. 100°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.35 (s, 6H), 4.48 (d, 1H, J=15Hz), 4.67 (d, 1H, J=15Hz), 6.75-6.77 (m, 1H), 6.82 (d, 2H, J=3Hz), 7.35 (t, 2H, J=9Hz), 7.42-7.46 (dd, 1H, J=4.5, J=3Hz), 7.65-7.73 (cm, 2H), 7.75 (dd, 2H, J=6, 3Hz), 8.08 (m, 1H), 8.22 (s, 1H), 8.3 (d, 1H, J=9Hz), 8.58 (m, 2H). MS (FAB) *m/e* 546 (M+1), 563. Anal calcd for C₂₈H₂₃FN₄O₃S₂·0.75H₂O: C, 60.04; H, 4.41; N, 10.00. Found: C, 60.84; H, 4.75; N, 9.66.

Example 56

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl]-6-(3-aminophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(pyridin-3-yl)-7-(6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (370 mg, 0.75 mmol), prepared as in Example 64, in DME (15 mL), was added a solution of 3-aminophenylboronic acid (182 mg, 1.2 mmol). The reaction mixture was warmed to reflux, diluted with DME (15 mL), and stirred at reflux for 17 hours. The reaction mixture was cooled to ambient temperature and partitioned between saturated aqueous NaHCO₃ and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate, then once with 3% methanol, methylene chloride. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification by chromatography on silica gel (3% methanol, methylene chloride) gave 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl)-6-(3-aminophenyl)indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole as a pale-yellow foam. m.p. 86-88°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 8.57 (m, 2H), 8.28 (d, 1H, J=8.1Hz), 7.77 (m, 1H), 7.68 (m, 1H), 7.60 (m, 6H), 7.56 (m, 1H), 6.91 (d, 1H, J=3.0Hz), 6.79 (bds, 1H), 6.73 (d, 1H, J=3.3Hz), 5.19 (bds, 2H), 4.67 (dd, 1H, J=2.2, 14.7Hz), 4.49 (d, 1H, J=14.7Hz), 3.08 (s, 6H). MS (DCI/NH₃) *m/e* 508 (M+H)⁺ (75), 182 (100). Anal calcd for C₂₉H₂₅N₅O₂S: C, 68.62; H, 4.96; N, 13.80. Found: C, 67.20; H, 4.88; N, 11.08.

Example 57

Preparation of 3-(Pyridin-3-yl)-7-[1-(2-*tert*-butoxycarbonylaminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

Step 1. *N*-*tert*-butoxycarbonylazide.

- 5 The desired compound was prepared according to the method of Example 9, except substituting aziridine for 3-(Pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole

Step 2. 3-(Pyridin-3-yl)-7-[1-(2-*tert*-butoxycarbonylaminoethyl)-

- 10 6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

- The desired compound was prepared according to the method of Example 46, except substituting *N*-*tert*-butoxycarbonylaziridine, prepared in step 1 for methyl acrylate. ¹H NMR (CDCl₃, 300 MHz) δ 1.5-1.7 (bs, 2H), 3.25 (t, 2H, J=6, 8Hz), 4.3 (t, 2H, J=6, 7Hz), 4.56 (d, 1H, J=15Hz), 4.70 (dd, 1H, J=15, 3Hz), 6.35 (d, 1H, J=3Hz), 6.42 (s, 1H), 6.78 (d, 1H, J=3Hz), 7.15 (t, 2H, J=9, 12Hz), 7.35 (dd, 1H, J=5, 9Hz), 7.5 (m, 2H), 7.62 (dd, 3H, J=7, 9Hz), 7.93 (s, 1H), 8.45 (d, 1H, J=9Hz), 8.6 (d, 1H, J=3Hz) 8.65 (dd, 1H, J=3, 5Hz). MS (DCI/NH₃) m/e 483 (M+H)⁺. Anal calcd for C₂₈H₂₃N₄OSF: C, 69.69; H, 4.80; N, 11.61. Found: C, 69.41; H, 4.55; N, 11.46.

20

Example 58

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

- The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 21, 3-(pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbonyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 98-100°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.22 (m, 1H), 8.18 (bds, 1H), 8.16 (m, 1H), 8.13 (s, 1H), 7.51 (m, 2H), 7.41 (m, 3H), 7.36 (m, 1H), 7.20 (d, 1H, J= 2Hz), 7.12 (bdd, 1H, J= 7.2Hz), 6.94 (dd, 1H, J= 2.8, 6.9Hz), 6.92 (d, 1H, J= 3.0Hz), 6.92 (d, 1H, J= 3.0Hz), 6.67 (bds, 1H), 5.18 (s, 2H), 4.62 (bdd, 1H, J= 15.1Hz), 4.43 (d, 1H, J= 15.1Hz), 3.85 (s, 3H). MS (DCI/NH₃) m/e 499(M+NH₄)⁺ (30), 482 (M+H)⁺ (50), 466 (100).

Example 59**Preparation of 3-(Pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

A solution of 3-(pyridin-3-yl)-7-[1-(2-*tert*-butoxycarbonylaminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (104 mg), prepared as in Example 57, in CH₂Cl₂ at 0°C was treated with 4*N* HCl/dioxane (1 mL). The reaction mixture was stirred for 15 min at 0°C and then concentrated *in vacuo*. The resulting solid was azeotroped three times with CH₂Cl₂ to give 3-(Pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole hydrochloride (115 mg). ¹H NMR (D₃CO, 300 MHz) δ 3.48-3.60 (m, 3H), 3.64-3.75 (m, 4H), 4.53 (d, 1H, J=15Hz), 4.68-4.77 (m, 3H), 6.76 (d, 1H, J=3Hz), 6.9 (d, 1H, J=1.5Hz), 7.55 (dd, 1H, J=1.5, 9Hz), 7.75 (dd, 2H, J=6, 8Hz), 7.83 (s, 1H), 8.13 (dd, 1H, J=6, 8Hz), 8.30 (s, 1H), 8.35 (d, 1H, J=9Hz), 8.49 (d, 1H, J=9Hz), 8.87 (d, 2H, J=7Hz). MS (DCI/NH₃) *m/e* 483 (M+H)⁺.

Example 60**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 55, 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. *m.p.* 118°C. ¹H NMR (CDCl₃, 300 MHz) δ 2.95 (s, 6H), 4.57 (d, 1H, J=15Hz), 4.67 (dd, 1H, J=12, 3Hz), 6.34 (s, 1H), 6.48 (d, 1H, J=3Hz), 6.82 (d, 1H, J=3Hz), 7.13-7.2 (m, 3H), 7.26 (s, 1H), 7.32 (t, 1H, J=6Hz), 7.58-7.64 (cm, 3H), 8.11 (d, 2H, J=4.5Hz), 8.19 (d, 1H, J=6Hz), 8.37 (d, 1H, J=9Hz). MS (DCI/NH₃) *m/e* 562 (M+H)⁺, 547.

Example 61**Preparation of 3-(Pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 51, using phenylsulfonylchloride instead of methane sulfonyl chloride. *m.p.* 115-116°C. ¹H NMR (CDCl₃, 300 MHz) δ 4.55 (d, 1H, J=12Hz), 4.67 (dd, 1H, J=12, 1.5Hz), 6.42 (d, 1H, J=3Hz), 6.46 (s, 1H), 6.8 (m, 1H), 7.13-7.2 (cm, 1H), 7.25 (s, 1H), 7.38 (dd, 1H, J=4.5, 0.75Hz), 8.14 (s, 1H), 8.2 (m, 1H), 8.28 (d, 1H, J=9Hz), 8.62 (s, 1H), 8.66 (d, 1H, J=3Hz). MS (FAB) *m/e* 508 (M+H)⁺, 307. Anal calcd for

$C_{32}H_{22}FN_3O_3S_2 \cdot 0.25H_2O$: C, 65.79; H, 3.88; N, 7.19. Found: C, 65.68; H, 3.93; N, 6.81.

Example 62

5 Preparation of 3-(Pyridin-3-yl)-7-[1-N-(2-hydroxyethyl)carbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The desired compound was prepared according to the method of Example 37 except substituting 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 28, for 3-(Pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, and substituting
10 ethanolamine for ammonia. ^1H NMR (DMSO- d_6 , 300 MHz) δ 3.32-3.42 (m, 2H), 3.60 (q, 2H, $J=6$ Hz), 4.51 (d, 1H, $J=15$ Hz), 4.68 (dd, 1H, $J=2, 15$ Hz), 4.88 (t, 1H, $J=6$ Hz), 6.79 (d, 1H, $J=3$ Hz), 6.81 (d, 1H, $J=1$ Hz), 7.09 (d, 1H, $J=3$ Hz), 7.32 (t, 2H, $J=9$ Hz), 7.45 (dd, 1H, $J=5, 8$ Hz), 7.61 (dd, 1H, $J=1, 8$ Hz), 7.69 (dt, 1H, $J=1, 8$ Hz), 7.71-7.76 (m, 2H), 8.32 (d, 1H, $J=8$ Hz), 8.51 (d, 1H, $J=1$ Hz), 8.56-8.61 (m, 15 3H), 8.47 (t, 1H, $J=6$ Hz). MS (FAB) m/e 527 ($M+H$) $^+$, 440. IR (KBr) 1701, 1601, 1530, 1510, 1475. Anal calcd for $C_{29}H_{23}FN_4O_3S$: C, 66.15; H, 4.40; N, 10.64. Found: C, 64.93; H, 4.14; N, 10.00.

Example 63

20 Preparation of 3-(Pyridin-3-yl)-7-(6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 1, using 6-bromoindole instead of indole. m.p. 265°C. ^1H NMR (DMSO- d_6 , 300 MHz) δ 4.45 (d, 1H, $J=15$ Hz), 4.52 (dd, 1H, $J=1, 15$ Hz), 6.70 (d, 1H, $J=3$ Hz), 6.77 (s, 1H), 6.89 (d, 1H, $J=3$ Hz), 7.31 (dd, 1H, $J=1, 9$ Hz), 7.43 (dd, 1H, $J=5, 8$ Hz), 7.61-7.69 (m, 2H), 8.20 (d, 1H, $J=9$ Hz), 8.27 (d, 1H, $J=3$ Hz), 8.53-8.59 (m, 2H), 11.98 (s, 1H). MS (DCI/ NH_3) m/e 443 ($M+NH_4$) $^+$, 441 ($M+NH_4$) $^+$, 426 ($M+H$) $^+$, 424 ($M+H$) $^+$, 394. IR (KBr) 1582, 1560, 1530, 1510, 1480. Anal calcd for $C_{20}H_{14}BrN_3OS$: C, 56.61; H, 3.33; N, 9.90. Found: C, 55.82; H, 3.25; N, 9.54.

30

Example 64

Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2
35 using the compound resulting from Example 63, 3-(pyridin-3-yl)-7-(6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-

yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. m.p. 199-201°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.05 (s, 6H), 4.48 (d, 1H, *J*=15Hz), 4.55 (dd, 1H, *J*=2, 15Hz), 6.73 (d, 1H, *J*=3Hz), 6.79 (d, 1H, *J*=1Hz), 6.90 (d, 1H, *J*=3Hz), 7.40-7.50 (m, 2H), 7.68 (dt, 1H, *J*=2, 8Hz), 7.82 (d, 1H, *J*=1Hz), 8.19 (d, 1H, *J*=9Hz), 8.37 (s, 1H), 8.55-8.59 (m, 2H). MS (DCI/NH₃) *m/e* 497 (M+H)⁺, 495 (M+H)⁺. IR (KBr) 3100, 2920, 1680, 1590, 1530. Anal calcd for C₂₃H₁₉BrN₄O₂S: C, 55.76; H, 3.87; N, 11.31. Found: C, 55.63; H, 3.59; N, 11.06.

10

Example 65Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 2 using the compound resulting from Example 47, 3-(pyridin-3-yl)-7-(6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, instead of 3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole and using methylisocyanate instead of *N,N*-dimethylcarbamoyl chloride. m.p. 214-215°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.05 (s, 6H), 4.48 (d, 1H, *J*=15Hz), 4.56 (dd, 1H, *J*=2, 15Hz), 6.73 (d, 1H, *J*=3Hz), 6.79 (d, 1H, *J*=1Hz), 6.90 (d, 1H, *J*=3Hz), 7.36 (dd, 1H, *J*=2, 8Hz), 7.43 (dd, 1H, *J*=5, 8Hz), 7.65-7.70 (m, 2H), 8.24 (d, 1H, *J*=9Hz), 8.38 (s, 1H), 8.55-8.59 (m, 2H). MS (DCI/NH₃) *m/e* 451 (M+H)⁺, 329, 141, 124. Anal calcd for C₂₃H₁₉ClN₄O₂S: C, 61.26; H, 4.25; N, 12.42. Found: C, 60.99; H, 4.16; N, 12.13.

Example 66Preparation of 3-(1-Oxide-Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 65, 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 192-193°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.06 (s, 6H), 4.45 (d, 1H, *J*=2, 15Hz), 4.55 (dd, 1H, *J*=2, 15Hz), 6.70 (d, 1H, *J*=1Hz), 6.87 (d, 1H, *J*=3Hz), 6.92 (d, 1H, *J*=3Hz), 7.14 (d, 1H, *J*=8Hz), 7.36 (dd, 1H, *J*=2, 9Hz), 7.39-7.45 (m, 1H), 7.69 (d, 1H, *J*=2Hz), 8.18-8.27 (m, 3H), 8.40 (s, 1H). MS (DCI/NH₃) *m/e* 484 (M+NH₄)⁺, 467 (M+H)⁺, 451. Anal calcd for C₂₃H₁₉ClN₄O₃S: C, 59.16; H, 4.10; N, 12.00. Found: C, 57.61; H, 3.96; N, 11.53.

Example 67**Preparation of 3-(1-Amino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

5 The desired compound was prepared according to the method of Example 34, except substituting 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 29, for 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, and aqueous hydrazine for aqueous hydroxylamine. m.p. 253-258°C. ¹H NMR (CD₃OD, 300 MHz) δ 2.36(s, 3H), 3.17(s, 6H), 4.55(d, 1H, J= 15.0Hz), 4.71 (d, 1H, J= 15.0, 1.0Hz), 6.78 (d, 1H, J= 3.0Hz), 6.82 (d, 1H, J= 1.0Hz), 6.98 (d, 1H, J= 3.0Hz), 7.20 (t, 2H, J= 7.5Hz), 7.22 (d, 2H, J= 8.5Hz), 7.58 (dd, 1H, J= 9.0, 1.0Hz), 7.69 (d, 2H, J= 8.5Hz), 7.71 (m, 2H), 7.79 (bs, 1H), 7.99 (dd, 1H, J= 7.5, 6.0Hz), 8.17 (d, 1H, J= 8.5Hz), 8.25 (s, 1H), 8.31 (d, 1H, J= 9.0Hz), 8.66 (bs, 1H), 8.71 (bd, 1H, J= 6.0Hz). MS (FAB) m/e 526 (M+1)⁺. IR (KBr) 3410, 1695, 1610, 1210. Anal calcd for C₂₉H₂₅FN₅O₂S: C, 61.18; H, 4.71; N, 9.91. Found: C, 61.19; H, 4.72; N, 9.95.

Example 68**Preparation of 3-(Pyridin-3-yl)-7-[1-(2-methanesulfonylaminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

To a solution of 3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (0.20 g, 0.062 mmol), prepared according to the method of Example 59, and triethylamine (13 μL, 0.093 mmol) in THF (15 mL) was added methanesulfonyl chloride (6 μL, 0.074 mmol). The reaction mixture was stirred for two hours at ambient temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. 3-(Pyridin-3-yl)-7-[1-(2-methanesulfonylaminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (66 mg) was obtained by flash chromatography on silica gel (98:2 CHCl₃, methanol). ¹H NMR (CDCl₃, 300 MHz) δ 2.83 (s, 3H), 3.6 (d, 2H, J=6Hz), 4.42-4.52 (m, 3H), 4.65 (d, 1H, J=15Hz), 5.57 (bs, 1H), 6.38 (bs, 1H), 6.46 (bs, 1H), 6.8 (d, 1H, J=3Hz), 7.15 (t, 2H, J=9Hz, 11Hz), 7.47 (d, 2H, J=7Hz), 7.52 7.65 (m, 3H), 7.8 (d, 1H, J=9Hz), 7.95 (s, 1H), 8.38 (d, 1H, 9Hz), 8.55 (bs, 2H). MS (DCI/NH₃) m/e 561 (M+H)⁺. Anal calcd for C₂₉H₂₅FN₄O₃S₂: C, 62.13; H, 4.49; N, 9.99. Found: C, 61.37; H, 4.57; N, 9.58.

Example 69**Preparation of 3-(Pyridin-3-yl)-7-[1-hydrazinocarbonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

5 The title compound was prepared by the procedure described in Example 62 using hydrazine instead of ethanolamine. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.50 (d, 1H, J=15Hz), 4.60 (bs, 2H), 4.68 (dd, 1H, J=2, 15Hz), 6.78 (d, 1H, J=3Hz), 6.81 (d, 1H, J=1Hz), 7.09 (s, 1H), 7.33 (t, 2H, J=9Hz), 7.45 (dd, 1H, J=5, 8Hz), 7.61 (dd, 1H, J=1, 9Hz), 7.65-7.76 (m, 3H), 8.31 (d, 1H, J=9Hz), 8.47-8.51- (m, 2H),
10 8.56 8.60 (m, 2H), 9.90 (bs, 1H). MS (DCI/NH₃) m/e 498 (M+H)⁺, 440. Anal calcd for C₂₇H₂₀FN₅O₂S: C, 65.18; H, 4.05; N, 14.08. Found: C, 64.18; H, 4.03; N, 13.79.

Example 70**Preparation of 3-(Pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride.**

15 The title compound was prepared by the procedure described in Example 52 using the compound resulting from Example 59, 3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbonyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (CDCl₃, 300 MHz) δ 1.35 (s, 9H), 3.57 (q, 2H, J=15Hz), 4.35-4.45 (m, 2H), 4.57 (d, 1H, J=15Hz), 4.63 (m, 1H), 4.7 (dd, 1H, J=3Hz), 7.15 (t, 2H, J=9Hz, 11Hz), 7.35 (dd, 1H, J=6, 11Hz), 7.5 (m, 2H), 7.6-7.7 (m, 3H), 7.83 (s, 1H), 8.45 (d, 1H, J=9Hz), 8.60 (d, 1H, J=2Hz), 8.65 (d, 1H, J=5Hz). MS (DCI/NH₃) m/e 583 (M+H)⁺.

25

Example 71**Preparation of 3-(Pyridin-3-yl)-7-[1-ethanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

30 The title compound was prepared by the procedure described in Example 51, using ethanesulfonylchloride instead of methanesulfonylchloride. m.p. 132°C. ¹H NMR (CDCl₃, 300 MHz) δ 1.25 (cm, 2H), 3.4-3.52 (m, 3H), 4.57 (d, 1H, J=13.5Hz), 4.7 (dd, 1H, J=1.5, 13.5Hz), 6.42 (d, 1H, J=3Hz), 6.52 (bs, 1H), 6.8 (m, 1H), 7.16 (t, 2H, J=6Hz), 7.55-7.68 (cm, 5H), 7.8 (d, 1H, J=4.5Hz), 8.05-8.12 (m, 2H), 8.4 (d, 1H, J=7.5), 8.68 (bs, 1H). MS (DCI/NH₃) m/e 532 (M+H)⁺, 440,
35 534. Anal calcd for C₂₈H₂₂N₃FO₃S₂·1H₂O: C, 61.19; H, 4.40; N, 7.65. Found: C, 61.37; H, 4.40; N, 6.47.

Example 72**Preparation of 3-(Pyridin-3-yl)-7-[1-(2-hydroxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.****Step 1. Preparation of 3-(Pyridin-3-yl)-7-[1-(2-dimethyl-*tert*-butylsilyloxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The desired compound was prepared according to the method of Example 46, except substituting 2-bromoethoxydimethyl-*tert*-butylsilane for methyl acrylate.

Step 2. Preparation of 3-(Pyridin-3-yl)-7-[1-(2-hydroxyethyl)-**6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole**

To a solution of 3-(Pyridin-3-yl)-7-[1-(2-dimethyl-*tert*-butylsilyloxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (365 mg, 0.61 mmol) and 18-crown-6 (168 mg, 0.64 mmol) in acetonitrile (8 mL) was added cerium fluoride (695 mg, 4.6 mmol). The reaction mixture was stirred 17 hours at ambient temperature. The reaction mixture was quenched with H₂O and concentrated *in vacuo*. The residue was taken up in CH₂Cl₂ and filtered. The filtrate was concentrated *in vacuo*. 3-(Pyridin-3-yl)-7-[1-(2-hydroxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was obtained by flash chromatography on silica gel. m.p. 170-171°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 3.73 (dd, 2H, J=6, 6Hz), 4.37 (t, 2H, J=1.5, 13.5Hz), 4.41 (d, 1H, J=13.5Hz), 4.57 (dd, 1H, J=1.5, 13.5Hz), 4.89 (t, 1H, J=6Hz), 6.65 (d, 1H, J=3Hz), 6.70 (bs, 1H), 6.82 (d, 1H, J=3Hz), 7.20 (t, 2H, J=9Hz), 7.29-7.35 (c, 1H), 7.63-7.70 (c, 2H), 7.85 (bs, 1H), 8.15 (s, 1H), 8.19 (d, 1H, J=6Hz), 8.31-8.35 (c, 2H). MS (DCI/NH₃) m/e 484 (M+H)⁺. IR (KBr) 3440, 1590, 1510, 1480, 1380, 1230, 1230, 1180, 1160, 1080, 1070, 870, 820, 710. Anal calcd for C₂₈H₂₃FN₃O₂S: C, 68.27; H, 4.91; N, 8.53. Found: C, 68.57; H, 4.71; N, 8.42.

Example 73**Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.**

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 61, 3-(pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 135-137°C. ¹H NMR (CDCl₃, 300 MHz) δ 4.55 (d, 1H, J=13.5Hz), 4.62-4.69 (dd, 1H, J=13.5, 3Hz), 6.38 (s, 1H), 6.53 (d, 1H, J=3Hz), 6.85 (d, 1H, J=3Hz), 7.18 (t, 2H, J=7.5Hz), 7.25-7.32 (m, 1H), 7.43 (t,

1H, J=3Hz), 7.47-7.64 (cm, 6H), 7.95 (m, 1H), 7.97 (s, 1H), 8.15 (d, 1H, J=1.5Hz), 8.22 (s, 1H), 8.26 (s, 1H), 8.28-8.34 (m, 2H). MS (FAB) m/e 596 (M+1)⁺.

Example 74

5 Preparation of 3-(Pyridin-3-yl)-7-(6-pyrimid-2-ylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

Step 1. Preparation of 3-(pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-trimethylstannylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

3-(pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-bromoindol-3-ylcarbonyl)-
 10 1H,3H-pyrrolo[1,2-c]thiazole (2.00 g, 4.04 mmol), prepared according to the method of Example 64, and hexamethylditin (1.65 g, 5.04 mmol) were combined under N₂ in a dry flask. Toluene (81 mL) was added via syringe and tetrakis(triphenylphosphine)palladium(0) (0.34 g, 0.29 mmol) was added under a stream of N₂. The reaction mixture was warmed to reflux and stirred for 2.5 hours.
 15 The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and pH 7 K₂HPO₄/NaOH buffer. The organic phase was washed with buffer and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to a small volume. The suspension was filtered, and the filtrate concentrated *in vacuo* and azeotroped with ethanol and CH₂CL₂ to give an orange solid. Pure 3-(pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-trimethylstannylindol-3-ylcarbonyl)-
 20 1H,3H-pyrrolo[1,2-c]thiazole (1.88 g, 80%), was obtained as a pale-yellow foam by flash chromatography on silica gel (3:1 then 5:1 ethyl acetate, hexanes).

25 Step 2. Preparation of 3-(Pyridin-3-yl)-7-(6-pyrimid-2-ylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

3-(pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-trimethylstannylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole (0.23 g, 0.40 mmol), prepared in step 1, and 5-bromopyrimidine (76 mg, 0.48 mmol) were combined under N₂ in a dry flask. Toluene (4 mL) was added via syringe and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) was added under a stream of N₂. The reaction mixture was
 30 warmed to reflux and heated for 23 hours. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and pH 7 K₂HPO₄/NaOH buffer. The organic phase was washed once with buffer, and the combined aqueous layers were extracted once with ethyl acetate. The combined organic layers were washed with
 35 brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (100:1, then 65:1, then 40:1 then 20:1 CHCl₃, methanol) afforded pure 3-(Pyridin-3-yl)-7-(6-pyrimid-2-ylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole

(0.14 g, 70%). m.p. 125-128°C. ¹H NMR (CDCl₃, 300 MHz) δ 3.18 (s, 6H), 4.60 (d, 1H, J=15.1 Hz), 4.72 (dd, 1H, J=1.8, 15.1 Hz), 6.40 (d, 1H, J=2.9 Hz), 6.49 (s, 1H), 6.79 (d, 1H, J=2.9 Hz), 7.44 (dd, 1H, J=5.0, 7.9 Hz), 7.57 (dd, 1H, J=1.5, 8.5 Hz), 7.74 (d, 1H, J=8.1 Hz), 7.87 (s, 1H), 8.04 (s, 1H), 8.48 (d, 1H, J=8.1 Hz), 8.62-8.70 (c, 2H), 9.03 (s, 2H), 9.22 (s, 1H). MS (DCI/NH₃) m/e 495 (M+1)⁺. IR (KBr) 866 (s), 1181 (s), 1226 (m), 1386 (s), 1416 (s), 1484 (m), 1539 (s), 1612 (m), 1695 (s), 3437 (br). Anal calcd for C₂₇H₂₂N₆O₂S·0.75H₂O: C, 63.82; H, 4.67; N, 16.54. Found: C, 53.45; H, 4.31; N, 16.19.

10

Example 75

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 53, 3-(pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 180.7°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.55 (d, 1H, J=13.5Hz), 4.62-4.69 (dd, 1H, J=13.5, 3Hz), 6.38 (s, 1H), 6.53 (d, 1H, J=3Hz), 6.85 (d, 1H, J=3Hz), 7.18 (t, 2H, J=7.5Hz), 7.25-7.32 (m, 1H), 7.43 (t, 1H, J=3Hz), 7.47-7.64 (cm, 6H), 7.95 (m, 1H), 7.97 (s, 1H), 8.15 (d, 1H, J=1.5Hz), 8.22 (s, 1H), 8.26 (s, 1H), 8.28-8.34 (m, 2H). MS (FAB) m/e 541 (M+1)⁺. IR (KBr) 1600(s), 1660(s). Anal calcd for C₃₀H₂₅FN₄O₃S: C, 62.98; H, 5.02; N, 9.79. Found: C, 62.65; H, 3.97; N, 9.47.

25

Example 76

Preparation of 3-(Pyridin-3-yl)-7-[1-carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 37 using 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 28, instead of 3-(Pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.50 (d, 1H, J=15Hz), 4.68 (dd, 1H, J=2, 15Hz), 6.78 (d, 1H, J=3Hz), 6.81 (s, 1H), 7.05 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.45 (dd, 1H, J=5, 8Hz), 7.61 (dd, 1H, J=1, 9Hz), 7.66-7.77 (m, 3H), 8.00 (bs, 2H), 8.30 (d, 1H, J=9Hz), 8.53-8.60 (m, 4H). MS (DCI/NH₃) m/e 483 (M+H)⁺, 440. Anal calcd for C₂₇H₁₉FN₄O₂S: C, 67.21; H, 3.97; N, 11.61. Found: C, 66.92; H, 3.88; N, 11.44.

Example 77

Preparation of 3-(1-Carbamoylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

5 The title compound was prepared by the procedure described in Example 67 using semicarbazide instead of hydrazine. m.p. 156-163. ¹H NMR (CD₃OD, 300 MHz) δ 3.14 (s, 6H), 4.52 (d, 1H, J= 15.0Hz), 4.69 (dd, 1H, J= 15.0, 1.0Hz), 6.76 (d, 1H, J= 3.0Hz), 6.79 (d, 1H, J= 1.0Hz), 6.93 (d, 1H, J= 3.0Hz), 7.19 (t, 2H, J= 9.0Hz), 7.58 (dd, 1H, J= 1.0Hz), 7.70 (dd, 2H, J=9.0, 6.0Hz), 7.80 (d, 1H, J= 1.0Hz), 7.81 (m, 1H), 7.98 (d, 1H, J= 8.5Hz), 8.26 (s, 1H), 8.30 (d, 1H, J= 9.0Hz), 8.57 (d, 1H, J= 1.0Hz), 8.58 (m, 1H). IR (KBr) 3410, 1695, 1610, 1480, 1380. MS (FAB) m/e 569 (M+1)⁺ 552. Anal calcd for C₃₀H₂₅FN₆O₃S: C, 63.37; H, 4.43; N, 14.78. Found: C, 60.91; H, 4.99; N, 13.65.

15

Example 78

Preparation of 3-(1-Pyrid-3-oylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

 The title compound was prepared by the procedure described in Example 62 using 3-pyridinehydrazide instead of hydrazine. m.p. 140-149°C. ¹H NMR (CD₃OD, 20 300 MHz) δ 3.15 (s, 6H), 4.56 (d, 1H, J= 15.0Hz), 4.73 (dd, 1H, J= 15.0, 3.0Hz), 6.78 (d, 1H, J= 3.0Hz), 6.82 (d, 1H, J= 1.0Hz), 6.96 (d, 1H, J= 3.0Hz), 7.19 (t, 2H, J= 9.0Hz), 7.50 (dd, 1H, J= 8.5, 4.5Hz), 7.57 (dd, 1H, J= 9.0, 1.0Hz), 7.70 (dd, 1H, J= 8.5, 4.5Hz), 7.79 (d, 1H, J= 1.0Hz), 7.96 (dd, 1H, J= 8.5, 4.5Hz), 8.12 (d, 1H, J= 8.5Hz), 8.25 (s, 1H), 8.30 (d, 1H, J= 9.0Hz), 8.93 (dt, 1H, J= 8.5, 1.0Hz), 8.62 (dd, 1H, J= 4.5, 1.0Hz), 8.78 (bd, 1H, J= 6.5Hz), 8.80 (bs, 1H), 9.20 (bs, 1H). MS (FAB) m/e 631 (M+1)⁺. IR (KBr) 3410, 1695, 1600, 1540, 1480, 25 1390.

Example 79

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-(2-aminosulfonylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

30 The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 50, 3-(pyridin-3-yl)-7-[1-(2-sulfamylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 171-176°C. ¹H (NMR D₃COD, 300 MHz) δ 3.65 (t, 2H, J=7, 81Hz), 4.5 (d, 1H, J=15Hz), 4.65 (dd, 1H, J=2, 15Hz), 4.8 (m, 2H), 6.67 (d, 1H, J=2Hz), 6.73 (d, 1H, J=3Hz), 6.97 (d, 1H, J=3Hz), 7.2 (t, 2H,

J=9, 12Hz), 7.45 (d, 1H, J=9Hz), 7.52-7.6 (m, 2H), 7.7-7.78 (m, 3H), 8.24 (s, 1H), 8.25-8.34 (m, 3H). MS (FAB) m/e 563 (M+H)⁺. Anal calcd for C₂₈H₂₃N₄O₄S₂F: C, 59.77; H, 4.12; N, 9.96. Found: C, 58.83; H, 4.37; N, 9.57.

5

Example 80

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3-aminosulfonylphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 74, using 4-bromophenylsulfonamide instead of 2-bromopyrimidine. m.p. 155-160°C.

10 ¹H NMR (DMSO-d₆, 300 MHz) δ 3.09 (s, 6H), 4.50 (d, 1H, J=15.1 Hz), 4.68 (d, 1H, J=15.1 Hz), 6.74 (d, 1H, J=3.3 Hz), 6.81 (s, 1H), 6.94 (d, 1H, J=2.9 Hz), 7.42 (s, 2H), 7.44 (dd, 1H, J=5.0, 7.9 Hz), 7.66-7.73 (c, 2H), 7.93 (s, 5H), 8.36 (d, 1H, J=8.1 Hz), 8.41 (s, 1H), 8.57 (br s, 2H). MS (DCI/NH₃) m/e 572(M+H)⁺. IR 865 (s), 1163 (s), 1182 (s), 1226 (m), 1341 (m), 1388 (s), 1433 (m), 1483 (m), 1537 (s),
15 1595 (m), 1609 (m), 1693 (s), 3427 (br). Anal calcd for C₂₉H₂₅N₅O₄S₂·0.6H₂O: C, 67.09; H, 4.25; N, 11.25. Found C, 67.17; H, 4.15; N, 11.06.

Example 81

Preparation of 3-(Pyridin-3-yl)-7-[1-(2-*N*-methylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

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The title compound was prepared by the procedure described in Example 53, using *N*-methyl bromoacetamide instead of *N,N*-dimethyl bromoacetamide. m.p. 166-168°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.62 (d, 3H, J=5 Hz), 4.48 (d, 1H, J=15 Hz), 4.65 (dd, 1H, J=15, 2Hz), 5.02 (s, 2H), 6.72 (d, 1H, J=3 Hz), 6.78 (bs, 1H),
25 6.89 (d, 1H, J=3 Hz), 7.31 (t, 2H, J=12 Hz), 7.44 (dd, 2H, J=12, 8 Hz), 7.66 (cm, 1H), 7.77 (cm, 3H), 8.15 (bd, 1H, J=5 Hz), 8.33 (d, 2H, J=12 Hz), 8.57 (cm, 2H). MS (DCI/NH₃) m/e 511 (M+H)⁺, 528 (M+NH₄)⁺. IR (KBr) 1600(s), 1660(s). Anal calcd for C₂₉H₂₃FN₄O₂S: C, 66.46; H, 4.71; N, 10.69. Found: C, 66.74; H, 4.38; N, 10.22.

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Example 82

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (0.33 g, 0.64
35 mmol), prepared as in Example 29, in 1:1 pyridine, ethanol (8 mL) was added hydroxylamine hydrochloride (0.36 g, 5.2 mmol). The reaction mixture was heated for 30 min at 110°C. The reaction mixture was cooled to ambient temperature and

partitioned between ether and H₂O. The organic phase was washed with pH 7 buffer and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (3:1 hexanes, ethyl acetate, then ethyl acetate) afforded 3-

- 5 3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 132°C. ¹H NMR (D₃COD, 300 MHz) δ 3.1 (s, 3H), 3.13 (s, 3H), 3.93-4.0 (c, 2H), 6.35 (d, 0.5H, J=3Hz), 6.45 (d, 0.5H, J=3Hz), 6.51 (d, 0.5H, J=1.5Hz), 6.52 (s, 0.5H), 6.54 (s, 0.5H), 6.55 (d, 0.5H, J=4.5Hz), 7.11-7.19 (m, 2H), 7.38-7.45 (m, 2H), 7.53 (s, 1H), 7.61-7.7 (m, 2H), 7.8-7.84 (c, 2H), 7.95 (s, 0.5H), 7.97 (s, 0.5H), 8.43-8.53 (m, 2H). MS
10 (FAB) m/e 526 (M+1)⁺.

Example 83

Preparation of 3-(Pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

- The title compound was prepared by the procedure described in Example 82,
15 using 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 106-108°C. ¹H NMR (CDCl₃, 300 MHz) δ 3.94-4.21 (c, 2H), 6.36 (d, 0.5H, J=3Hz), 6.46 (d, 0.5H, J=3Hz), 6.54 (s, 0.5H), 6.55 (s, 0.5H), 6.56-
20 6.6 (c, 1H), 7.12-7.2 (m, 2H), 7.4-7.46 (m, 2H), 7.54 (s, 1H), 7.62-7.7 (m, 4H), 7.8-7.82 (br s, 1H), 7.95 (s, 0.5H), 7.98 (s, 0.5H), 8.42-8.54 (m, 2H). MS (DCI/NH₃) m/e 454 (M+H)⁺.

Example 84

- Preparation of 3-(Pyridin-3-yl)-7-[1-(*N*-methyl-*N*-(dimethylaminoethyl))carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

- The title compound was prepared by the procedure described in Example 62 using *N,N,N'*-trimethylethylenediamine instead of ethanolamine. m.p. 149-152°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.08 (s, 6H), 2.50 (m, 2H), 3.02 (s, 3H), 3.58 (t, 2H, J=6Hz), 4.49 (d, 1H, J=15Hz), 4.68 (dd, 1H, J=1, 15Hz), 6.73 (d, 1H, J=3Hz),
30 6.80 (s, 1H), 6.91 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.44 (dd, 1H, J=5, 8Hz), 7.49-7.79 (m, 4H), 7.88 (s, 1H), 8.32 (d, 1H, J=8Hz), 8.37 (s, 1H), 8.56-8.60 (m, 2H). MS (DCI/NH₃) m/e 568 (M+H)⁺, 440. IR (CDCl₃) 1685, 1600, 1540, 1510. Anal calcd for C₃₂H₃₀FN₅O₂S: C, 67.71; H, 5.33; N, 12.34. Found: C, 66.96; H, 5.10; N, 12.06.

Example 85

Preparation of 3-(Pyridin-3-yl)-7-[1-*N*-carboxymethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 62 using glycine instead of ethanolamine. m.p. 255°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.01 (d, 2H, J=6Hz), 4.52 (d, 1H, J=15Hz), 4.69 (dd, 1H, J=15, 2Hz), 6.79 (d, 1H, J=3Hz), 6.81 (d, 1H, J=1Hz), 7.06 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.45 (dd, 1H, J=5Hz, 8Hz), 7.63 (dd, 1H, J=1, 8Hz), 7.69 (dt, 1H, J=2, 9Hz), 7.72-7.78 (m, 2H), 8.32 (d, 1H, J=8Hz), 8.51 (d, 1H, J=1Hz), 8.5-8.61 (m, 3H), 9.12 (t, 1H, J=6Hz). MS (DCI/NH₃) m/e 541 (M+H)⁺, 440. IR (KBr) 1708, 1600, 1532, 1510, 1475. Anal calcd for C₂₉H₂₁FN₄O₄S: C, 64.44; H, 3.92; N, 10.36. Found: C, 63.53; H, 3.82; N, 10.08.

Example 86

Preparation of 3-(1-Methyl-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 33 using the compound resulting from Example 29, 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole instead of 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 168°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.08 (s, 6H), 4.37 (s, 3H), 4.54 (d, 1H, J=15Hz), 4.78 (dd, 1H, J=2, 15Hz), 6.83 (d, 1H, J=3Hz), 6.95 (d, 1H, J=1Hz), 6.99 (d, 1H, J=3Hz), 7.32 (t, 2H, J=6Hz), 7.61 (dd, 1H, J=2, 9Hz), 7.73-7.82 (m, 3H), 8.16 (dd, 1H, J=7, 9Hz), 8.32 (d, 1H, J=9Hz), 8.38 (s, 1H), 8.49 (d, 1H, J=8Hz), 8.98 (d, 1H, J=6Hz), 9.03 (s, 1H). MS (FAB) m/e 525 (M+H)⁺, 307, 289. Anal calcd for C₃₀H₂₆FIN₄O₂S: C, 55.22; H, 4.02; N, 8.59. Found: C, 53.97; H, 3.88; N, 8.39.

Example 87

Preparation of 3-(Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-thiazol-2-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 74, using 2-bromothiazole instead of 2-bromopyrimidine. m.p. 123-126°C. ¹H NMR (CDCl₃, 300 MHz) δ 3.17 (s, 6H), 4.58 (d, 1H, J=15.4 Hz), 4.71 (dd, 1H, J=2.2, 15.1 Hz), 6.38 (d, 1H, J=3.0 Hz), 6.47 (s, 1H), 6.80 (d, 1H, J=2.9 Hz), 7.36 (d, 1H, J=2.9 Hz), 7.42 (dd, 1H, J=5.0, 7.9 Hz), 7.72 (d, 1H, J=7.7 Hz), 7.88 (d, 1H, J=3.3 Hz), 7.92 (dd, 1H, J=1.6, 8.3 Hz), 8.07 (s, 1H), 8.25 (s, 1H), 8.42 (d, 1H,

J=8.1 Hz), 8.63 (br s, 1H), 8.65 (br s, 1H). MS (DCI/NH₃) m/e 500 (M+H)⁺. IR (KBr) 857 (s), 1181 (s), 1223 (m), 1388 (s), 1435 (s), 1482 (s), 1538 (s), 1612 (s), 1696 (s), 3439 (br). Anal calcd for C₂₆H₂₁N₅O₂S₂·0.4H₂O: C, 61.61; H, 4.34; N, 13.82. Found: C, 61.59; H, 3.95; N, 13.41.

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Example 88

Preparation of 3-(Pyridin-3-yl)-7-[1-N-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole

The title compound was prepared by the procedure described in Example 62 using taurine instead of ethanolamine. m.p. 238°C (dec). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.79(t,2H,J=6Hz), 4.51(d,1H,J=15Hz), 4.70 (d,1H,J=15Hz), 6.80 (d,1H,J=3Hz), 6.85 (s,1H),7.05(d,1H,J=3Hz), 7.32(t,2H,J=2Hz), 7.57-7.65(c,2H), 7.73-7.81 (c,2H),7.84-7.90 (c,2H), 8.31 (d,1H,J=9Hz), 8.49 (s,1H), 8.53 (s,1H), 8.67 (bs,2H), 8.75 (bs,1H). IR (KBr cm⁻¹) 3440, 1710, 1610, 1540, 1510, 1475, 1425,1220, 1040, 875, 820. MS (FAB) m/e 613(M+Na)⁺, 591(M+H)⁺, 207, 185, 115.

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Example 89

Preparation of 3-(Pyridin-3-yl)-7-[1-N,N-dimethylcarbamoyl-6-(2-aminopyrimid-5-yl)indol-3-yl)carbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 74, using 2-amino-5-bromopyrimidine instead of 2-bromopyrimidine. m.p. 145-148°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.07 (s, 6H), 4.49 (d, 1H, J=15.2 Hz), 4.66 (dd, 1H, J=1.6, 15.2 Hz), 6.73 (d, 1H, J=2.9 Hz), 6.77 (s, 2H), 6.80 (s, 1H), 6.91 (d, 1H, J=3.3 Hz), 7.44 (dd, 1H, J=4.9, 7.8 Hz), 7.56 (dd, 1H, J=1.6, 8.6 Hz), 7.68 (d, 1H, J=8.2 Hz), 7.76 (s, 1H), 8.29 (d, 1H, J=8.2 Hz), 8.33 (s, 1H), 8.58 (s, 2H), 8.62 (s, 2H). MS (DCI/NH₃) m/e 510 (M+H)⁺. IR (KBr) 863 (m), 1183 (m), 1225 (m), 1384 (m), 1437 (m), 1464 (s), 1539 (s), 1612 (s), 1693 (s), 3409 (br), 3438 (br). Anal calcd for C₂₇H₂₃N₇O₂S·H₂O: C, 51.47; H, 4.78; N, 18.58. Found: C, 51.87; H, 4.74; N, 18.12.

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Example 90

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 34 using the compound resulting from Example 59, 3-(Pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole instead of

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3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole. m.p. 178-190°C. ¹H NMR (CDCl₃, 300 MHz) δ 3.87 (t, 2H, J=9Hz), 4.44 (t, 2H, J=9Hz), 4.59 (d, 1H, J=15Hz), 4.69 (dd, 1H, J=15, 1Hz) 6.37 (bs, 1H), 6.48 (d, 1H, J=3Hz), 6.87 (d, 1H, J=3Hz), 7.15 (t, 2H, J=12Hz), 7.37 (cm, 2H), 7.47 (bs, 1H) 7.53 (bd, 1H, J=12Hz), 7.62 (cm, 2H), 7.92 (s, 1H), 8.32 (cm, 2H), 8.48 (d, 1H, J=12Hz). MS (FAB) m/e 499 (M+1)⁺. IR (KBr) 1515 (s), 1600 (s), 3430 (br). Anal calcd for C₂₈H₂₃N₄O₂S: C, 67.45; H, 4.65; N, 11.24. Found: C, 55.69; H, 4.63; N, 8.40.

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Example 91

Preparation of 3-(1-Oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-hydrazinylcarbonylphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

The title compound was prepared by the procedure described in Example 74, using 4-bromobenzoyl hydrazide instead of 2-bromopyrimidine. m.p. 151-154°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.09 (s, 6H), 4.50 (d, 1H, J=14.7 Hz), 4.52 (s, 2H), 4.68 (d, 1H, J=14.3 Hz), 6.74 (d, 1H, J=2.9 Hz), 6.80 (s, 1H), 6.92 (d, 1H, J=2.9 Hz), 7.44 (dd, 1H, J=4.8, 7.7 Hz), 7.68 (d, 2H, J=8.1 Hz), 7.82 (d, 1H, J=8.5 Hz), 7.83 (s, 1H), 7.92 (d, 2H, J=9.6 Hz), 7.95 (d, 1H, J=8.5 Hz), 8.34 (d, 1H, J=8.5 Hz), 8.39 (s, 1H), 8.57 (br s, 2H), 9.85 (br s, 1H). MS (DCI/NH₃) m/e 551 (M+H)⁺. IR (KBr) 864 (s), 1182 (m), 1226 (m), 1387 (s), 1433 (m), 1480 (s), 1538 (s), 1609 (s), 1692 (s), 3431 (br). Anal calcd for C₃₀H₂₆N₆O₃S·0.85H₂O: C, 63.66; H, 4.94; N, 14.85. Found: C, 63.99; H, 4.86; N, 14.47.

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Example 92

Preparation of 3-(1-Acetoxymethylpyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (206 mg, 0.41 mmol), prepared as in Example 29, in acetone (8 mL) was added bromomethyl acetate (60 μL, 0.62 mmol). The reaction mixture was warmed to reflux and stirred for four hours. The reaction mixture was cooled to ambient temperature and concentrated to a foam. The foam was dissolved in methanol, and 3-(1-Acetoxymethylpyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was precipitated by addition of ether. m.p. 218-223°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 2.18 (s, 3H), 3.09 (s, 6H), 4.55 (d, 1H, J=15.0Hz), 4.75 (dd, 1H, J=15.0, 1.0Hz), 6.41 (s, 2H), 6.86 (d, 1H, J=3.0Hz), 7.00 (d, 1H, J=3.0Hz), 7.01 (s, 1H), 7.32 (t, 2H, J=8.5Hz), 7.62 (dd, 1H, J=8.5,

1.0Hz), 7.77 (m, 2H), 7.81 (bs, 1H), 8.26 (dd, 1H, J= 8.5, 1.0Hz), 8.31 (d, 1H, J= 8.5Hz), 8.39 (s, 1H), 8.61 (bd, 1H, J= 8.5Hz), 9.20 (d, 1H, J= 6.0Hz), 9.22 (bs, 1H). MS (FAB) m/e 583, 511. IR (KBr) 3450(br), 1685, 1480, 1220.

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Example 93

Preparation of 3-(Pyridin-3-yl)-7-[1-N-methyl-N-hydroxymethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

To a solution of 3-(pyridin-3-yl)-7-[1-(2-N-methylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (100 mg, 0.20 mmol), prepared as in Example 81, in THF (5 mL) was added a solution of K₂CO₃ (13 mg, 0.098 mmol) in H₂O (5 mL). Formaldehyde (37% aqueous solution, 10 mL, 123 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. The THF was removed *in vacuo* and the residue was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous NaHCO₃ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% methanol, ethyl acetate) afforded 3-(Pyridin-3-yl)-7-[1-N-methyl-N-hydroxymethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (32 mg). m.p. 172-182°C (decomp). ¹H NMR (DMSO-d₆, 300 MHz) δ 2.89 (s, 2.25H), 3.15 (s, 0.75H), 4.48 (d, 1H, J=15Hz), 4.62 (dd, 1H, J=15, 1Hz), 4.71 (d, 0.5H, J=10Hz), 4.92 (d, 1.5H, J=10Hz), 5.39 (s, 0.5H), 5.47 (s, 1.5H), 5.9 (t, 0.25, J=10Hz), 6.21 (t, 0.75H, J=10Hz), 6.71 (d, 1H, J=3Hz), 6.78 (s, 1H), 6.87 (d, 0.25H, J=3Hz), 6.88 (d, 0.75, J=3Hz), 7.312 (t, 2H, J=12Hz), 7.44 (cm, 1H), 7.51 (d, 1H, J=12Hz), 7.65 (d, 1H, J=12Hz), 7.75 (cm, 3H), 8.27 (s, 1H), 8.32 (d, 1H, J=12Hz), 8.57 (d, 2H, J=9Hz). MS (FAB) m/e 541 (M+1)⁺. Anal calcd for C₃₀H₂₅N₄O₃SF: C, 63.48; H, 4.97; N, 9.87. Found: C, 63.77; H, 5.87; N, 7.45.

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Example 94

Preparation of 3-(Pyridin-3-yl)-7-[1-cyanomethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 46, except substituting iodoacetonitrile for methyl acrylate. m.p. 219-223. ¹H NMR (DMSO-d₆, 300 MHz) δ 4.5 (d, 1H, J=1.5Hz), 4.65 (dd, 1H, J=1.5, 0.3Hz), 5.7 (s, 2H), 6.75 (d, 1H, J=0.3Hz), 6.8 (d, 1H, J=0.2Hz), 6.93 (d, 1H, J=0.3Hz), 7.35 (s, 2H, J=0.9, 1.2Hz), 7.4 (dd, 1H, 0.6, 0.9Hz), 7.63 (dd, 1H, J=0.9, 0.3Hz), 7.68 (dd, 1H, J=0.9, 0.3Hz), 7.83 (dd, 2H, J=0.3, 0.9Hz), 8.2 (s, 1H), 8.35 (d, 1H,

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$J=0.9\text{Hz}$), 8.48 (s, 1H), 8.55-8.60 (m, 2H). MS (DCI/ NH_3) m/e 479 ($M+H$)⁺. IR (KBr) 2200.

Example 95

5 Preparation of 3-(Pyridin-3-yl)-7-[1-carbamoylmethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

To a solution of 3-(pyridin-3-yl)-7-[1-cyanomethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (290 mg, 0.607 mmol), prepared as in Example 94, in 2:1 isopropanol, methanol (60 mL), was added a solution of borax (sodium tetraborate decahydrate, 0.693 g, 1.82 mmol) in H_2O (20 mL). The reaction mixture was heated for four hours at 80°C. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was taken up in CHCl_3 and filtered through a pad of celite. The organic phase was washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to give 3-(Pyridin-3-yl)-7-[1-carbamoylmethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (20 mg). m.p. 215-225°C. ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ 4.49 (d, 1H, $J=15\text{Hz}$), 4.65 (d, 1H, $J=15\text{Hz}$), 5.03 (s, 2H), 6.73 (d, 1H, $J=3\text{Hz}$), 6.79 (s, 1H), 6.9 (d, 1H, $J=3\text{Hz}$), 7.28-7.39 (m, 3H), 7.40-7.48 (m, 1H), 7.53 (d, 1H, $J=9\text{Hz}$), 7.6-7.8 (m, 5H), 8.33 (m, 1H), 8.58 (m, 1H). MS (DCI/ NH_3) m/e 497 ($M+H$)⁺. Anal calcd for $\text{C}_{28}\text{H}_{21}\text{FN}_4\text{O}_2\text{S}$: C, 67.73; H, 4.26; N, 11.28. Found: C, 65.63; H, 4.37; N, 10.31.

Example 96

25 Preparation of 3-(Pyridin-3-yl)-7-[1-carboxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

Step 1. Preparation of 3-(pyridin-3-yl)-7-[1-carboethoxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 46, except substituting ethyl chloroacetate for methyl acrylate.

30

Step 2. Preparation of 3-(Pyridin-3-yl)-7-[1-carboxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 49, step 2 except substituting 3-(pyridin-3-yl)-7-[1-carboethoxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole, prepared in step 1, for 3-(Pyridin-3-yl)-7-[1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole. m.p. 240-249°C. ^1H NMR ($\text{DMSO}-d_6$,

300 MHz) δ 4.45 (d, 1H, $J=1.5$ Hz), 4.65 (dd, 1H, $J=1.5, 0.3$ Hz), 4.84 (s, 2H), 6.7 (d, 1H, $J=0.3$ Hz), 6.78 (s, 1H), 6.87 (d, 1H, $J=0.3$ Hz), 7.3 (t, 2H, $J=0.9, 1.5$ Hz), 7.4-7.5 (m, 2H), 7.6-7.8 (m, 4H), 8.25-8.33 (m, 2H), 8.5-8.6 (m, 2H). MS (DCI/NH₃) m/e 498 (M+H)⁺.

5

Example 97

Preparation of 3-(Pyridin-3-yl)-7-[1-(1H-tetrazol-5-ylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

A mixture of 3-(pyridin-3-yl)-7-[1-cyanomethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (77 mg, 0.161 mmol), prepared as in
10 Example 94, dibutyltin oxide (40 mg, 0.161 mmol), and trimethylsilylazide (47.3 μ L, 0.322 mmol) in toluene (15 mL) was heated at reflux for three hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude product was azeotroped with CH₂Cl₂ and purified by flash chromatography on silica
15 gel (9:1 CHCl₃, methanol) to give 3-(Pyridin-3-yl)-7-[1-(1H-tetrazol-5-ylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (53 mg). m.p. 110-118°C. ¹H NMR (D₃COD, 300 MHz) δ 4.5 (d, 1H, $J=15$ Hz), 4.63 (dd, 1H, 15, 3Hz), 5.75 (s, 2H), 6.57 (d, 1H, $J=3$ Hz), 6.67 (bs, 1H), 6.98 (d, 1H, $J=3$ Hz), 7.15 (t, 2H, $J=9$ Hz), 7.45-7.51 (m, 2H), 7.67-7.77 (m, 3H), 7.79 (s, 1H), 8.25 (s, 1H),
20 8.31 (d, 1H, 9Hz), 8.55 (bs, 2H). MS (FAB) m/e 522 (M+H)⁺.

Example 98

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(2,4(1H,3H)-pyrimidinedion-5-yl)indol-3-yl]carbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 74,
25 using 5-bromouracil instead of 2-bromopyrimidine. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.06 (s, 6H), 4.48 (d, 1H, $J=15.1$ Hz), 4.66 (d, 1H, $J=15.4$ Hz), 6.72 (d, 1H, $J=3.3$ Hz), 6.79 (s, 1H), 6.90 (d, 1H, $J=2.9$ Hz), 7.40-7.47 (c, 2H), 7.65-7.70 (c, 2H), 7.83 (s, 1H), 8.20 (d, 1H, $J=8.1$ Hz), 8.32 (s, 1H), 8.55-8.59 (c, 2H), 11.17
30 (br s, 0.67H), 11.24 (br s, 0.33H), 11.27 (s, 0.67H), 11.52 (br s, 0.33H). MS (DCI/NH₃) m/e 527 (M+H)⁺.

Example 99

Preparation of 3-(Pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 62
35 using ethylamine instead of ethanolamine. m.p. 210-213°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 1.21 (t, 3H, $J=7$ Hz), 3.35-3.42 (m, 2H), 4.51 (d, 1H, $J=15$ Hz), 4.68

(dd, 1H, J=2, 15Hz), 6.78 (d, 1H, J=3Hz), 6.81 (s, 1H), 7.05 (d, 1H, J=3Hz), 7.32 (t, 2H, J=9Hz), 7.45 (dd, 1H, J=5, 8Hz), 7.61 (dd, 1H, J=1, 9Hz), 7.65 (m, 3H), 8.31 (d, 1H, J=8Hz), 8.50-8.61 (m, 4H), 8.68 (t, 1H, J=6Hz). MS (DCI/NH₃) m/e 511 (M+H)⁺, 441, 417. IR (KBr) 1710, 1600, 1532, 1512, 1475. Anal calcd for C₂₉H₂₃FN₄O₂S: C, 68.22; H, 4.54; N, 10.97. Found: C, 67.96; H, 4.42; N, 10.73.

Example 100

Preparation of 3-(Pyridin-3-yl)-7-[1-N-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The title compound was prepared by the procedure described in Example 62 using leucine instead of ethanolamine. m.p. 214-215°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.91 (bs, 6H), 1.24 (bs, 3H), 1.72 (bs, 3H), 4.25 (bs, 1H), 4.51 (bd, 1H, J=15Hz), 4.67 (bd, 1H, J=15Hz), 6.80 (bs, 2H), 7.09 (bs, 1H), 7.33 (t, 2H, J=9Hz), 7.40-7.48 (c, 1H), 7.61 (bd, 1H, J=9Hz), 7.67-7.81 (c, 3H), 8.32 (d, 1H, J=7.5Hz), 8.51-8.62(c, 4H). MS (DCI/NH₃) m/e 597 (M+H)⁺, 440, 228, 200. IR (KBr) 3420, 2950, 2940, 1710, 1600, 1535, 1515, 1480, 1430, 1380, 1220, 1160, 1140, 820, 710.

Example 101

Preparation of 3-(Pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-thiophen-2-ylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 74, except substituting 2-bromothiophene for 5-bromopyrimidine. m.p. 115-118°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.08 (s, 6H), 4.50 (d, 1H, J=15.1 Hz), 4.66 (dd, 1H, J=1.8, 15.1 Hz), 6.72 (d, 1H, J=2.9 Hz), 6.80 (d, 1H, J=1.5 Hz), 6.91 (d, 1H, J=3.3 Hz), 7.16 (dd, 1H, J=3.8, 5.0 Hz), 7.44 (dd, 1H, J=5.0, 7.9 Hz), 7.55 (d, 1H, J=5.5 Hz), 7.56 (d, 1H, J=3.7 Hz), 7.64 (dd, 1H, J=1.5, 8.4 Hz), 7.68 (dt, 1H, J=1.9, 8.1 Hz), 7.85 (dd, 1H, J=0.7, 1.5 Hz), 8.26 (d, 1H, J=8.4 Hz), 8.35 (s, 1H), 8.54-8.60 (c, 2H). MS (DCI/NH₃) m/e 499 (M+H)⁺. IR (KBr) 707 (m), 862 (m), 1180 (s), 1224 (m), 1387 (s), 1435 (m), 1483 (s), 1539 (s), 1611 (m), 1694 (s), 3439 (br). Anal calcd for C₂₇H₂₂N₄O₂S₂·0.1C₅H₁₂: C, 65.30; H, 4.62; N, 11.08. Found: C, 65.23; H, 4.73; N, 10.72.

Example 102

Preparation of 3-(Pyridin-3-yl)-7-(1-N,N-dimethylcarbamoyl-6-(4-hydroxymethyl)phenylindol-3-ylcarbonyl)-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 74, except substituting 4-bromobenzyl alcohol for 5-bromopyrimidine. m.p. 134-137°C.

¹H NMR (DMSO-d₆, 300 MHz) δ 3.08 (s, 6H), 4.50 (d, 1H, J=15.1 Hz), 4.56 (d, 2H, J=5.5 Hz), 4.67 (dd, 1H, J=2.0, 15.2 Hz), 5.20 (t, 1H, J=5.7 Hz), 6.74 (d, 1H, J=3.3 Hz), 6.80 (d, 1H, J=1.8 Hz), 6.92 (d, 1H, J=3.3 Hz), 7.41-7.47 (m, 1H), 7.42 (d, 2H, J=8.5 Hz), 7.62 (dd, 1H, J=1.8, 8.4 Hz), 7.66-7.71 (m, 1H), 7.68 (d, 2H, J=8.1 Hz), 7.83 (s, 1H), 8.30 (d, 1H, J=8.5 Hz), 8.35 (s, 1H), 8.56-8.59 (c, 2H). MS (FAB) m/e 523 (M+1)⁺. IR (KBr) 866 (s), 1182 (s), 1225 (m), 1388 (s), 1433 (m), 1482 (s), 1538 (s), 1610 (m), 1694 (s), 3436 (br). Anal calcd for C₃₀H₂₆N₄O₃S·0.75H₂O: C, 67.21; H, 5.17; N, 10.45. Found: C, 67.44; H, 4.83; N, 10.46.

10

Example 103

Preparation of 2-Oxide-3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indole-3-ylcarbonyl]-1*H,3H*-pyrrolo[1,2-*c*]thiazole.

The desired compound was prepared according to the method of Example 13, except substituting 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indole-3-ylcarbonyl]-1*H,3H*-pyrrolo[1,2-*c*]thiazole, prepared as in Example 39, for 3-(pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-yl)carbonyl-1*H,3H*-pyrrolo[1,2-*c*]thiazole. m.p. 187-206°C. ¹H NMR (DMSO-d₆, 300 MHz) δ 3.10 (s, 6H), 4.29 (d, 1H, J=17.0Hz), 4.75 (d, 1H, J=17.0Hz), 6.61 (s, 1H), 6.92 (bd, 1H, J=8.0Hz), 7.04 (d, 1H, J=3.0Hz), 7.18 (d, 1H, J=3.0Hz), 7.31 (t, 2H, J=8.5Hz), 7.45 (dd, 1H, J=7.0, 8.0Hz), 7.52 (dd, 1H, J=1.5, 8.5Hz), 7.78 (m, 2H), 7.82(d, 1H, J=1.5Hz), 8.09 (s, 1H), 8.24 (d, 1H, J=6.0Hz), 8.31(d, 1H, J=8.0Hz), 8.43 (s, 1H). MS (FAB) m/e 543 (M+1)⁺. IR (KBr) 1695, 1480.

20

Example 104

Preparation of 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylhydrazon]-1*H,3H*-pyrrolo[1,2-*c*]thiazole.

To a solution of 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H,3H*-pyrrolo[1,2-*c*]thiazole (0.30 g, 0.59 mmol), prepared as in Example 29, in *n*-butanol was added hydrazine hydrate (55% solution in H₂O, 0.20 mL, 2.9 mmol) and acetic acid (0.20 mL). The reaction mixture was heated at 80-90°C for 72 hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. 3-(Pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylhydrazon]-1*H,3H*-pyrrolo[1,2-*c*]thiazole was obtained by flash chromatography on silica gel. m.p. 150-151°C. ¹H NMR (D₃CO, 300 MHz) δ 3.1 (s, 6H), 3.95-4.1 (dd, 2H, J=1.5, 12Hz), 6.5 (d, 1H, J=3Hz), 6.63 (br s, 1H), 6.66 (d, 1H, J=3Hz), 7.13-7.2 (c, 2H), 7.35 (s, 1H), 7.42 (dd, 1H,

35

J=1.5, 6Hz), 7.45-7.5 (c, 1H), 7.64-7.59 (c, 2H), 7.75-7.78 (c, 1H), 7.79-7.8 (c, 1H), 8.08 (d, 1H, J=7.5Hz), 8.5 (br s, 1H), 8.54 (d, 1H, J=3Hz). MS (FAB) m/e 525 (M+1)⁺.

Example 105

5 Preparation of 3-(Pyridin-3-yl)-7-[1-N-(2-(4-imidazolyl)ethyl)carbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole.

The desired compound was prepared according to the method of Example 62, except substituting histamine for ethanolamine. m.p. 156-158°C. ¹H NMR (D₃COD, 300 MHz) δ 2.97 (t, 2H, J=7.5Hz), 3.68 (t, 2H, J=7.5Hz), 4.50 (d, 1H, J=15Hz),
10 4.65 (dd, 1H, J=3, 15Hz), 6.60 (d, 1H, J=3Hz), 6.79 (d, 1H, J=1.5Hz), 6.92 (bs, 1H), 6.96 (d, 1H, J=3Hz), 7.19 (t, 2H, J=9Hz), 7.45-7.51 (c, 1H), 7.55 (dd, 1H, J=1.5, 9Hz), 7.59 (d, 1H, J=1Hz), 7.63-7.70 (c, 2H), 7.75 (dt, 1H, J=1.5, 7.5Hz), 8.26 (d, 1H, J=7.5Hz), 8.34 (s, 1H), 8.37 (d, 1H, J=1Hz), 8.52 (d, 1H, J=1.5Hz), 8.55 (dd, 1H, J=1.5, 4.5Hz). MS (FAB) m/e 577 (M+H)⁺, 460, 440, 154, 136. IR
15 (KBr) 3410, 1710, 1600, 1530, 1510, 1475, 1430, 1220, 875, 820. Anal calcd for C₃₂H₂₇FN₆O₃S: C, 64.63; H, 4.58; N, 14.13. Found: C, 64.88; H, 4.28; N, 14.16.

Example 106

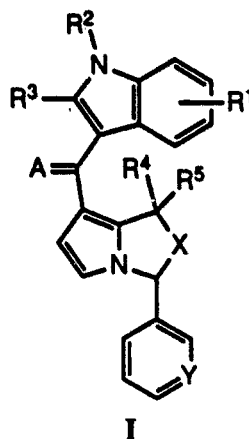
20 Preparation of 3-(pyridin-3-yl)-7-[1-N,N-dimethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonylsemicarbazide]-1H,3H-pyrrolo[1,2-c]thiazole.

To a suspension of 3-(pyridin-3-yl)-7-[1-N,N-dimethylcarbamoyl]-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1H,3H-pyrrolo[1,2-c]thiazole (0.62 g, 1.21 mmol), prepared as in Example 29, in 1:1 ethanol, pyridine (12 mL) was added semicarbazide hydrochloride (1.08 g, 9.72 mmol) and the reaction mixture was heated
25 for 24 hours at 105°C. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was taken up in CH₂Cl₂ and the solution was washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered, and concentrated. Flash chromatography on silica gel (20% methanol/acetone) provided 3-(pyridin-3-yl)-7-[1-N,N-dimethylcarbamoyl]-6-(4-fluorophenyl)indol-
30 3-ylcarbonylsemicarbazide]-1H,3H-pyrrolo[1,2-c]thiazole (30 mg). m.p. 160-161°C. ¹H NMR (D₃COD, 300 MHz) δ 3.3 (s, 6H), 4.03-4.35 (2H), 6.45-6.67 (3H), 7.07-7.2 (3H), 7.35-7.5 (4H), 7.6-7.75 (4H), 8.4-8.53 (2H). MS (FAB) m/e 567 (M+1)⁺.

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WE CLAIM

1. A compound of the formula:



5 or a pharmaceutically acceptable salt thereof wherein

R^1 is one or more groups independently selected from the group consisting of
hydrogen,

halogen,

10 alkyl of from one to six carbon atoms,

alkoxy of from one to six carbon atoms,

alkoyl of from one to seven carbon atoms,

phenyl, optionally substituted by

alkyl of from one to six carbon atoms,

15 alkoxy of from one to six carbon atoms, or

halogen,

NR^7R^8 where R^7 and R^8 are independently selected from,

hydrogen,

alkyl of from one to six carbon atoms,

20 or taken together with the nitrogen atom to which they

are attached form a saturated 5- or 6-membered
nitrogen-containing ring,

$-COOR^9$ where R^9 is independently selected from,

hydrogen, and alkyl of from one to six carbon atoms,

25 $-CONR^7R^8$ where R^7 and R^8 are as defined above, and

$-SO_2NR^7R^8$ where R^7 and R^8 are as defined above,

2- or 3-furyl,

- 2- or 3-thienyl,
2-, 4-, or 5-thiazolyl,
30 2-, 3-, or 4-pyridyl,
2-, or 4-pyrimidyl,
benzoyl, wherein the phenyl moiety is optionally substituted by
halogen,
alkyl of from one to six carbon atoms, or
35 alkoxy of from one to six carbon atoms,
phenoxy optionally substituted by
halogen,
alkyl of from one to six carbon atoms, or
alkoxy of from one to six carbon atoms,
40 phenylalkyloxy in which the alkyl portion contains from one to six
carbon atoms and the phenyl is optionally substituted with
halogen,
alkyl of from one to six carbon atoms, or
alkoxy of from one to six carbon atoms, or
45 phenylalkoyl in which the alkoyl portion contains from one to seven
carbon atoms and the phenyl moiety is optionally substituted by;
halogen,
alkyl of from one to six carbon atoms, or
alkoxy of from one to six carbon atoms;
50
- R²** is selected from the group consisting of
hydrogen,
alkyl of from one to six carbon atoms;
-(CH₂)_pCOOR⁹, where p is 0 or an integer of from 1 to 4 and R⁹ is as
55 defined above,
-(CH₂)_qNR⁷R⁸, where q is an integer of from 2 and 4 and R⁷ and R⁸
are as defined above,
-(CH₂)_pCOR⁹ where R⁹ is as defined above,
-(CH₂)_qOH,
60 -(CH₂)_pSO₂R⁹ where p and R⁹ are as defined above,
-(CH₂)_pSO₂NR⁷R⁸ where p, R⁷ and R⁸ are as defined above,

- 65 $-(CH_2)_pCONR^{10}R^{11}$, where p is as defined above and R^{10} and R^{11}
are independently selected from
hydrogen,
alkyl of from one to six carbon atoms,
70 $-(CH_2)_rCOOR^9$, where r is an integer of from 1 to 4 and R^9 is as
defined above,
 $-(CH_2)_rNR^7R^8$ where r , R^7 and R^8 are as defined above,
 $-(CH_2)_rOH$,
 $-(CH_2)_rSO_2R^9$ where r and R^9 are as defined above, and
 $-(CH_2)_rSO_2NR^7R^8$ where r , R^7 and R^8 are as defined above,
75 $-(CH_2)_pCN$ where p is as defined above;
 $-(CH_2)_p-1H\text{-tetrazol-5-yl}$ where p is as defined above;
 $-CONHNH_2$, or;
 $-(CH_2)_r\text{-phenyl}$, where r is as defined above and the phenyl moiety is
optionally substituted by
80 halogen,
alkyl of from one to six carbon atoms, or
alkoxy of from one to six carbon atoms;

85 R^3 , R^4 , and R^5 are independently selected from hydrogen or alkyl of from one
to six carbon atoms;

X is selected from the group consisting of S , SO , SO_2 , O , and CH_2 ;

Y is selected from the groups consisting of
90 N ,
 N^+-R^{12} where R^{12} is an alkyl group of from one to six carbon atoms,
 $N^+ \rightarrow O^-$,
 N^+-OR^{12} where R^{12} is as defined above,
 $N^+-NR^7R^8$ where R^7 and R^8 are as defined above,
95 $N^+-NHCONR^7R^8$ where R^7 and R^8 are as defined above,
 $N^+-NHCOR^9$ where R^9 is as defined above,
 $N^+-CR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above,
 $N^+-OCR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined above,
 $N^+-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above,
100 $N^+-O-CR^7R^8OCONR^7R^8$ where R^7 and R^8 are as defined above; and

A is selected from the group consisting of

O,
NOR¹⁰,
NOCOR¹⁰,
NNR⁷R⁸,

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where where R⁷, R⁸ and R¹⁰ are as defined above.

2. A compound as defined by Claim 1 or a pharmaceutically acceptable salt thereof wherein

R¹ is phenyl, optionally substituted by

5

alkyl of from one to six carbon atoms,
alkoxy of from one to six carbon atoms, or
halogen,

R² is selected from the group consisting of

10

hydrogen,
alkyl of from one to six carbon atoms;
-(CH₂)_pCOOR⁹, where p and R⁹ are as defined therein,
-(CH₂)_qNR⁷R⁸, where q, R⁷ and R⁸ are as defined therein,
-(CH₂)_pCOR⁹ where p and R⁹ is as defined therein,
15 -(CH₂)_qOH where q is as defined therein,
-(CH₂)_pSO₂R⁷ where p and R⁷ are as defined therein,
-(CH₂)_pSO₂NR⁷R⁸ where p, R⁷ and R⁸ are as defined therein,
-(CH₂)_pCONR¹⁰R¹¹, where p, R¹⁰ and R¹¹ are as defined therein,
-(CH₂)_rCN,

20

-(CH₂)_r-1H-tetrazol-5-yl where r is as defined therein,
-CONHNH₂, or,
-(CH₂)_r-phenyl, where r is as defined therein and the phenyl moiety is
optionally substituted by

25

halogen,
alkyl of from one to six carbon atoms, or
alkoxy of from one to six carbon atoms;

R³, R⁴, and R⁵ are hydrogen;

30 X is S;

Y is selected from the group consisting of

N,

$N^+ \rightarrow O^-$,

35 $N^+-CR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined therein,
and

$N^+-OCR^7R^8OCOR^{12}$ where R^7 , R^8 and R^{12} are as defined therein,
and

40 A is selected from the groups consisting of

O, or

NOH.

3. A compound as defined by Claim 2 or a pharmaceutically acceptable salt thereof wherein R^1 is phenyl or 4-fluorophenyl and R^2 is selected from the group consisting of $CONH_2$, $CONHCH_3$, and $CON(CH_3)_2$.

4. A compound as defined by Claim 1 is selected from the group consisting of:

3-(pyridin-3-yl)-7-(indol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

5 3-(pyridin-3-yl)-7-(5-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

10 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-5-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

15 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-7-phenylmethoxyindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(1-*tert*-butyloxycarbonylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-(6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 20 3-(Pyridin-3-yl)-7-[1-(morpholin-4-ylcarbonyl)indol-3-yl]carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-yl)carbonyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
2-oxide-3-(pyridin-3-yl)-7-(1-*tert*-butoxycarbonylindol-3-ylcarbonyl)-
25 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
2-oxide-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole;
3-(pyridin-3-yl)-7-(1-*N,N*-diisopropylcarbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
30 1,1-dimethyl-3-(pyridin-3-yl)-7-(indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(1-carbomethoxycarbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
1,1-dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
35 3-(pyridin-3-yl)-7-(1-*N*-methyl-*N*-phenylcarbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
40 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
2-oxide-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
1,1-dimethyl-3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
45 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
1,1-dimethyl-3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
50 3-(pyridin-3-yl)-7-(1-carbophenoxy-6-phenylmethoxyindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
55

- 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-6-(4-fluorophenyl)indol-3-yl-
carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 60 1,1-dimethyl-3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-
6-(4-methoxyphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-methylpyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 65 3-(1-oxide-pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylindol-3-yl-
carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 1,1-dimethyl-3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 70 3-(pyridin-3-yl)-7-(1-*N*-methylcarbamoyl-6-phenylmethoxyindol-3-yl-
carbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[6-(4-methoxyphenyl)indol-3-yl]carbonyl-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 75 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-pyrid-3-ylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo-
1,2-*c*]thiazole;
- 80 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-pyrid-4-ylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N*-methylcarbamoyl-6-(4-methoxyphenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoylindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 85 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-methoxyphenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-carbomethoxyethyl)-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 90 3-(pyridin-3-yl)-7-(6-chloroindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3,4,5-trimethoxyphenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 3-(pyridin-3-yl)-7-[1-(2-carboxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 95 3-(pyridin-3-yl)-7-[1-(2-sulfamylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-methanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-ylcarbonyl)-
100 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride;
- 3-(pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-phenylindol-3-
ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole hydrochloride;
- 105 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3-aminophenyl)indol-3-
ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-*tert*-butoxycarbonylaminoethyl)-6-(4-fluorophenyl)-
110 indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-pyridin-3-yl)-7-(1-methyl-6-phenylmethoxyindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 115 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylsulfamyl-6-(4-fluorophenyl)indol-
3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-[1-*N*-(2-hydroxyethyl)carbamoyl-6-(4-fluorophenyl)indol-
120 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(6-bromoindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-bromoindol-3-ylcarbonyl)-
1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-3-ylcarbonyl)-
125 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-oxide-Pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-chloroindol-
3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 3-(1-amino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-
indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

- 130 3-(pyridin-3-yl)-7-[1-(2-methanesulfonylaminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-hydrazinocarbonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole Hydrochloride;
- 135 3-(pyridin-3-yl)-7-[1-ethanesulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-(2-hydroxyethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 140 3-(1-oxide-pyridin-3-yl)-7-[1-phenylsulfonyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-pyrimid-2-yl)indol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(1-oxide-pyridin-3-yl)-7-[1-(2-*N,N*-dimethylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 145 3-(pyridin-3-yl)-7-[1-carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(1-carbamoylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 150 3-(1-pyrid-3-ylamino-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(1-oxide-pyridin-3-yl)-7-[1-(2-aminosulfonylethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(3-aminosulfonylphenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 155 3-(pyridin-3-yl)-7-[1-(2-*N*-methylcarbamoylmethyl)-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 160 3-(pyridin-3-yl)-7-[6-(4-fluorophenyl)indol-3-ylcarbonyloxime]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(pyridin-3-yl)-7-[1-(*N*-methyl-*N*-(dimethylaminoethyl))carbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
- 165 3-(pyridin-3-yl)-7-[1-*N*-carboxymethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
3-(1-methyl-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)-

- indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-thiazol-2-yl)indol-3-yl-
 carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 170 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-
 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(2-aminopyrimid-5-yl)indol-3-
 yl)carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 175 3-(1-oxide-pyridin-3-yl)-7-[1-(2-aminoethyl)-6-(4-fluorophenyl)indol-
 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
 6-(4-hydrazinylcarbonylphenyl)indol-3-ylcarbonyl]-
 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(1-acetoxymethylpyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-
 180 6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N*-methyl-*N*-hydroxymethylcarbamoyl-
 6-(4-fluorophenyl)indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-cyanomethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 185 3-(pyridin-3-yl)-7-[1-carbamoylmethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-carboxymethyl-6-(4-fluorophenyl)indol-3-ylcarbonyl]-
 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-(1*H*-tetrazol-5-ylmethyl)-6-(4-fluorophenyl)indol-
 190 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(2,4(1*H*,3*H*)-pyrimidinedion-
 5-yl)indol-3-yl)carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-6-(4-fluorophenyl)indol-
 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 195 3-(pyridin-3-yl)-7-[1-*N*-sulfoethylcarbamoyl-~~6~~-(4-fluorophenyl)indol-
 3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-thiophen-2-yl)indol-3-yl-
 carbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 3-(pyridin-3-yl)-7-(1-*N,N*-dimethylcarbamoyl-6-(4-hydroxymethyl)-
 200 phenylindol-3-ylcarbonyl)-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
 2-oxide-3-(1-oxide-pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-
 fluorophenyl)indole-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;

3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylhydrazone]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
205 3-(pyridin-3-yl)-7-[1-*N*-(2-(4-imidazolyl)ethyl)carbamoyl-6-(4-fluorophenyl)-indol-3-ylcarbonyl]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole; and
3-(pyridin-3-yl)-7-[1-*N,N*-dimethylcarbamoyl-6-(4-fluorophenyl)indol-3-ylcarbonylsemicarbazide]-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole;
or a pharmaceutically acceptable salt thereof.

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5. A pharmaceutical composition useful for inhibiting PAF in a mammal in need of such treatment comprising a PAF-inhibitive effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.
6. A method of inhibiting PAF activity in a mammal in need of such treatment comprising administering a PAF-inhibitive effective amount of a compound as defined by Claim 1.
7. A method of treating PAF-mediated disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound as defined by Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/05890

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/44/ C07D 513/04, 498/04, 487/04

US CL : 546/270, 273; 514/338, 339

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/270, 273; 514/338, 339

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

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

CAS on line, structural search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A. 327417 (Rajoharison) 90 Aug. 1989 see abstract	1-7
Y	297987 (Rajoharison) 04 Jan. 1989 see abstract	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

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

Date of the actual completion of the international search

31 AUGUST 1992

Date of mailing of the international search report

Name and mailing address of the ISA/
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/05890

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

- I. Claims 1-7 wherein both R^1, R^2 contain no additional heterocyclic rings
- II. Claims 1-7 wherein R^1 contains heterocyclic(s), R^2 contains no additional heterocyclic ring.
- III. Claims 1-7 wherein R^1 contains non-heterocyclic; R^2 contains additional heterocyclic ring.
- IV. Claims 1-7 wherein both R^1, R^2 contain additional heterocyclic ring(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-7

Remark on Protest

☐
☐

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

No protest accompanied the payment of additional search fees.