

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 199741466 B2**
(10) Patent No. **733226**

(54) Title
Non-peptide bombesin receptor antagonists

(51)⁶ International Patent Classification(s)
C07D 401/12 C07D 213/56
A61K 031/395 C07D 213/89
C07D 209/20 C07D 405/12
C07D 213/40 C07D 417/12

(21) Application No: **199741466**

(22) Application Date: **1997 .08 .06**

(87) WIPO No: **WO98/07718**

(30) Priority Data

| (31) Number | (32) Date | (33) Country |
|------------------|---------------------|--------------|
| 60/024323 | 1996 .08 .22 | US |

(43) Publication Date : **1998 .03 .06**

(43) Publication Journal Date : **1998 .05 .07**

(44) Accepted Journal Date : **2001 .05 .10**

(71) Applicant(s)
Warner-Lambert Company

(72) Inventor(s)
David Christopher Horwell; Martyn Clive Pritchard

(74) Agent/Attorney
BALDWIN SHELSTON WATERS, Level 21, 60 Margaret Street, SYDNEY NSW 2000

(56) Related Art
US 5200408
EP 415413
WO 94/04494

OPI DATE 06/03/98 APPLN. ID 41466/97
 AOIP DATE 07/05/98 PCT NUMBER PCT/US97/13871



AU9741466

(PCT)

| | | |
|---|--|--|
| (51) International Patent Classification ⁶ : C07D 401/12, A61K 31/395, C07D 209/20, 213/89, 213/40, 213/56, 405/12, 417/12 | | (11) International Publication Number: WO 98/07718 (43) International Publication Date: 26 February 1998 (26.02.98) |
| (21) International Application Number: PCT/US97/13871 (22) International Filing Date: 6 August 1997 (06.08.97) (30) Priority Data: 60/024,323 22 August 1996 (22.08.96) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HORWELL, David, Christopher [GB/GB]; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). PRITCHARD, Martyn, Clive [GB/GB]; The Maples, 9 Bury Close, St. Ives, Huntingdon, Cambridgeshire PE17 4WB (GB). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. | | (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. |
| (54) Title: NON-PEPTIDE BOMBESIN RECEPTOR ANTAGONISTS (57) Abstract <p>Compounds of Formula (I) or a pharmaceutically acceptable salt thereof wherein Ar is phenyl or pyridyl unsubstituted or substituted. Ar¹ can be independently selected from Ar and can also include pyridyl-N-oxide, indolyl, imidazole, and pyridyl; R³ can be independently selected from Ar or is hydrogen, hydroxy, NMe₂, N-methyl-pyrrole, imidazole, tetrazole, thiazole (a), (b), (c) or (d), wherein Ar² is phenyl or pyridyl. The compounds of the instant invention are novel compounds which antagonize the bombesin receptors in mammals and are therefore effective in treating and/or preventing depression, psychoses, seasonal affective disorders, cancer, feeding disorders, gastrointestinal disorders, inflammatory bowel disease, sleep disorders, and memory impairment.</p> | | |
| <div style="text-align: center;"> <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="text-align: center;"> <p>(a)</p> </div> <div style="text-align: center;"> <p>(b)</p> </div> <div style="text-align: center;"> <p>(c)</p> </div> </div> <div style="text-align: center; margin-top: 20px;"> <p>(d)</p> </div> | | |

NON-PEPTIDE BOMBESIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

Bombesin is a 14-amino acid peptide originally isolated from the skin of the European frog *Bombina bombina* (Anastasi A., et al., Experientia, 1971;27:166). It belongs to a class of peptides which share structural homology in their C-terminal decapeptide region (Dutta A.S., *Small Peptides; Chemistry, Biology, and Clinical Studies*, Chapter 2, pp 66-82). At present, two mammalian bombesin-like peptides have been identified (Battey J., et al., TINS, 1991;14:524), the decapeptide neuromedin B (NMB) and a 23-residue amino acid, gastrin-releasing peptide (GRP). Bombesin-like immunoreactivity detected in mammalian brain (Braun M., et al., Life. Sci., 1978;23:2721) and GI tract (Walsh J.H., et al., Fed. Proc. Fed. Am. Soc. Exp. Biol., 1979;38:2315) together with the more recent studies measuring mRNA levels in rat brain (Battey J., et al., TINS, 1991;14:524), point to the widespread distribution of both NMB and GRP in mammalian peripheral and central nervous systems.

NMB and GRP are believed to mediate a variety of biological actions via acting upon the corresponding bombesin receptors including their action as autocrine growth factors in human small cell lung carcinoma and other cancers (Taylor J.E., et al., Ann. N.Y. Acad. Sci., 1988;547:350; Rozengurt E., *Ibid.*, 277; Cuttitta F., et al., Nature, 1985;316:823; Kozacko M.F., et al., Proc. Natl. Acad. Sci. USA, 1996;93:2953), secretion of other neuropeptides and hormones (Ghatei M.A., et al., J. Clin. Endocrinol. Metab., 1982;54:980), contraction of smooth muscle (Erspamer V., et al., Pure Appl. Chem., 1973;35:463), behavioral effects (Kulkosky P.J., et al., Physiol. Behav., 1982;28:505; Gmerek D.E., et al., Peptides, 1983;4:907; Cowan A., Ann. N.Y. Acad. Sci., 1988;547:204), thermoregulation (Brown M.R., et al., Ann. N.Y. Acad. Sci., 1988;547:174), effects on satiety (Kirkham T.C., et al., Pharma. Biochem. Behav., 1995;52:101 and Ladenheim E.E., et al., Eur. J. Pharmacol., 1994;271:R7), regulation of circadian rhythms (Albers H., et al., J. Neurosci., 1991;11:846),

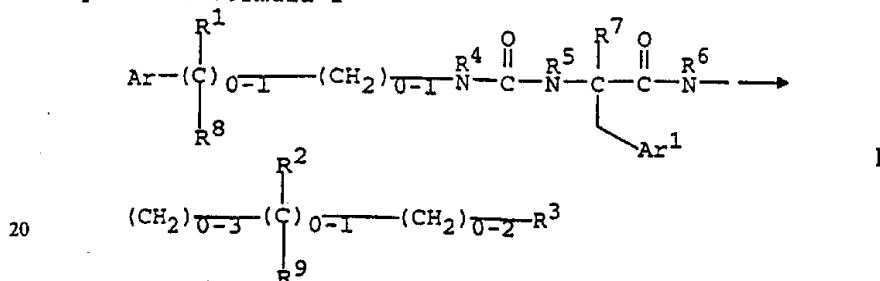
regulation of gastric acid secretion (Walsh J.H., Ann. Rev. Physiol., 1988;50:41) and gastrointestinal motility (see Lebacqz-Verheyden A., et al., in Handbook of Experimental Pharmacology, 1990;95 (Part II) and references therein), effects on locomotor activity and nociception (Pert A., et al., Brain Res., 1980;193:209),
 5 effects on memory (Flood J.F., et al., Brain Res., 1988;460:314), and interaction with 5HT-containing neurones (Pinnock R.D., et al., Brain Res., 1994;653:199 and Pinnock R.D., et al., J. Physiol., 1991;440:55).

Accordingly, compounds capable of antagonizing the effects of NMB and/or GRP at bombesin receptors will be useful in treating or preventing a variety
 10 of disorders including depression, psychoses, seasonal affective disorders, cancer, feeding disorders, gastrointestinal disorders including colitis, Crohn's disease and inflammatory bowel disease, sleeping disorders, and memory impairment.

SUMMARY OF THE INVENTION

This invention is for compounds which are bombesin receptor antagonists.
 15 The compounds have proved to be antagonists of bombesin receptors.

According to a first aspect, the invention provides a compound of Formula I



or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl or pyridyl unsubstituted or substituted by from 1 to
 3 substituents selected from alkyl, halogen, alkoxy, nitro, amino, NH_2CH_2 -,
 cyano, CF_3 , -NHCONH_2 , and CO_2R^1 ;



R^1 is hydrogen or straight, branched, or cyclic alkyl of from 1 to 7 carbon atoms;

R^8 is hydrogen or forms a ring with R^1 of from 3 to 7 atoms;

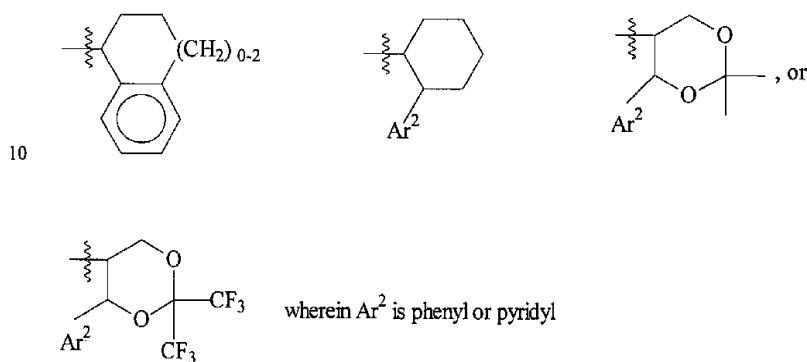
R^2 is hydrogen or straight, branched, or cyclic alkyl of from 1 to 8 carbon atoms;

R^9 is hydrogen or forms a ring of from 3 to 7 carbon atoms with R^2 ;

5 Ar^1 can be independently selected from Ar and can also include pyridyl-N-oxide, indolyl, imidazole, and pyridyl;

R^4 , R^5 , R^6 and R^7 are each independently selected from hydrogen and methyl;

R^3 can be independently selected from Ar or is hydrogen, hydroxy, NMe_2 , N-methyl-pyrrole,



with the proviso that when Ar^1 is phenyl, said phenyl is substituted;

15 $-[CR^1(R^8)]_{0-1}-(CH_2)_{0-1}-$ is not $-(CH_2)_{1-2}-$; and $-(CH_2)_{0-3}-[CR^2(R^9)]_{0-1}-(CH_2)_{0-2}-$ is not $-(CH_2)_{1-6}-$.

Preferably R^2 is hydrogen or straight, branched or cyclic alkyl of from 1 to 8 carbon atoms which can also contain 1 to 2 oxygen or nitrogen atoms.

Preferably R^9 is hydrogen or forms a ring of from 3 to 7 carbon atoms with R^2 which may contain an oxygen or nitrogen atom.

20 R^3 may also be selected from imidazole, tetrazole or thiazole.



According to a second aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the first aspect in combination with a pharmaceutically acceptable carrier.

According to a third aspect, the present invention provides a method of
5 antagonizing the effects of neuromedin B and/or gastrin-releasing peptide at bombesin receptors which comprises administering a compound according to the first aspect to a patient.

According to a fourth aspect, the present invention provides a method of treating depression in a patient in need of said treatment comprising administering a
10 therapeutically effective amount of a compound according to the first aspect.

According to a fifth aspect, the present invention provides a method of treating seasonal affective disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect.

According to a sixth aspect, the present invention provides a method of treating
15 feeding disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect.

According to a seventh aspect, the present invention provides a method of treating gastrointestinal disorders in a patient in need of said treatment comprising administering
20 a therapeutically effective amount of a compound according to the first aspect.

According to an eighth aspect, the present invention provides a method of treating sleeping disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect.



According to a ninth aspect, the present invention provides a method of treating memory impairment in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect.

According to a tenth aspect, the present invention provides a method of treating
5 cancer in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect

According to an eleventh aspect, the present invention provides a method of treating small cell lung carcinoma in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first
10 aspect.

According to a twelfth aspect, the present invention provides a method of treating psychoses in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to the first aspect.

According to a thirteenth aspect, the present invention provides use of a compound
15 according to the first aspect for the manufacture of a medicament for antagonizing the effects of neuromedin B and/or gastrin releasing peptide at bombesin receptors.

According to a fourteenth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of depression.

20 According to a fifteenth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of seasonal affective disorders.



According to a sixteenth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of feeding disorders.

According to a seventeenth aspect, the present invention provides use of a
5 compound according to the first aspect for the manufacture of a medicament for the treatment of gastrointestinal disorders

According to an eighteenth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of sleeping disorders.

10 According to a nineteenth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of memory impairment.

According to a twentieth aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of
15 cancer.

According to a twenty-first aspect, the present invention provides use of a compound according to the first aspect for the manufacture of a medicament for the treatment of small cell lung carcinoma.

According to a twenty-second aspect, the present invention provides use of a
20 compound according to the first aspect for the manufacture of a medicament for the treatment of psychoses.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an



inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

DETAILED DESCRIPTION

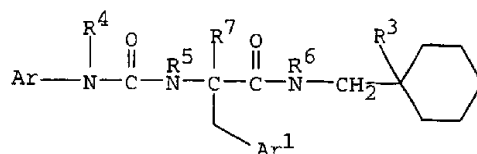
The compounds of the invention are those of Formula I above.

5 Preferred compounds are those of Formula I

20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95



-4-



wherein

Ar is phenyl unsubstituted or substituted with 1 or 2 substituents selected from isopropyl, chloro, nitro, and cyano;

5 R⁴, R⁵, and R⁶ are hydrogen;

R⁷ is methyl or hydrogen;

R³ is 2-pyridyl or hydroxy; and

Ar¹ is indolyl, pyridyl, pyridyl-N-oxide, and imidazol.

Other preferred compounds are those of Formula I wherein

10 Ar is unsubstituted phenyl;

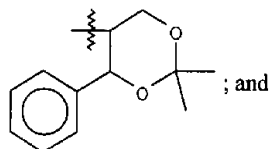
R¹ is cyclopentyl or tert-butyl;

R⁴ and R⁵ are hydrogen;

R⁷ is methyl;

R⁶ is hydrogen;

15 R³ is phenyl with two isopropyl substituents, unsubstituted phenyl, or



Ar¹ is indolyl.

Other preferred compounds are those of Formula I wherein

Ar is 2,6-diisopropyl-phenyl, 4-nitro-phenyl, and 4-cyano-phenyl;

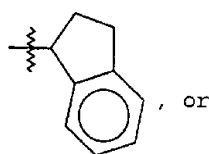
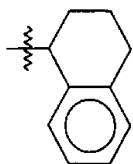
20 R⁴, R⁵, and R⁶ are hydrogen;

R⁷ is methyl;

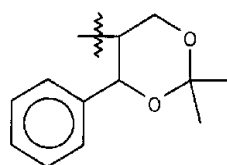
R² is hydrogen or cyclohexyl; and

-5-

R³ is hydroxyl,
pyridyl,



, or



More preferred compounds are selected from

- 5 N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-N-methyl-propionamide;
- 10 N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-1-methyl-ureido]-3-(1H-indol-3-yl)-propionamide;
2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-(1-oxy-pyridin-2-yl)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-pyridin-2-yl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 15 2-[3-(2-tert-Butyl-phenyl)-ureido]-N-cyclohexylmethyl-3-(1H-indol-3-yl)-2-methyl-propionamide;

- N-Cyclohexylmethyl-2-[3-(2,6-dichloro-phenyl)ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- N-Cyclohexylmethyl-2-[3-(2,6-dimethoxy-phenyl)ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 5 N-Cyclohexylmethyl-2-[3-(2,6-dimethylamino-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- [1-(Cyclohexylmethyl-carbamoyl)-2-(1H-indol-3-yl)-1-methyl-ethyl]-carbamic acid 4-nitro-benzyl ester;
- N-Cyclohexylmethyl-2-[3-(2,2-dimethyl-1-phenyl)propyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 10 {2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-carbamic acid 3-nitro-benzyl ester;
- N-(2,2-Dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(1H-indol-3-yl)-2-methyl-2-[3-(1-phenyl-cyclopentylmethyl)-ureido]-propionamide;
- 15 (S)-N-(2,6-Diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1H-indol-3-yl)-propionamide;
- (R)-N-(2,6-Diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1H-indol-3-yl)-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-(2,2-dimethyl-4-phenyl-[1,3]dioxan-4-yl)-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 20 N-Cyclohexyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- N-(2-Cyclohexyl-ethyl)-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 25 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(3-methyl-butyl)-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(3-phenyl-propyl)-propionamide;
- 30 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-propionamide;

-7-

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-cyclohexyl)-propionamide;

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-indan-1-yl-3-(1H-indol-3-yl)-2-methyl-propionamide;

5 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-(1-hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-propionamide;

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

10 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)-propionamide.

The compounds of the invention include solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the compounds of Formula I.

15 Pharmaceutical compounds of compounds of the invention are also covered by the instant invention.

Method of using the compounds of the instant invention are antagonizing the effect of neuromedin B and/or gastrin-releasing peptide at bombesin receptors. Other treatments are depressing seasonal affective disorders, feeding disorders, gastrointestinal disorders, sleep disorders, memory impairment, psychoses
20 treatment, and cancer treatment, for example, treatment of small cell lung cancers.

The compounds of the invention are those for Formula I and the pharmaceutically salts thereof. All stereoisomers of the compounds are included in the scope of the invention.

25 Prodrugs of the above are also contemplated such as would occur to one skilled in the art, see Bundgaard, et al., *Acta Pharm. Suec.*, 1987;24:233-246.

The alkyl groups contemplated by the invention include straight, branched, or cyclic carbon chains of from 1 to 8 carbon atoms except where specifically stated otherwise. Representative groups are methyl ethyl, propyl, isopropyl, n-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, 2-methylhexyl, n-pentyl,
30 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like.

The cycloalkyl groups contemplated by the invention comprise those having 3 to 7 carbon atoms. They may be substituted with from 1 to 3 groups selected from halogens, nitro, alkyl, and alkoxy.

5 The alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from 1 to 6 carbon atoms unless otherwise stated. Representative groups are methoxyl, ethoxy, propoxy, i-propoxy, t-butoxy, and hexoxy.

The term "halogen" is intended to include fluorine, chlorine, bromine, and iodine.

10 The term "Ar" is intended to include substituted or unsubstituted phenyl. The substituents include one or more substituents such as halogens, nitro, alkyl, alkoxy, and others as specified or as would occur to one skilled in the art.

The term "amine" is free amino, alkylated amines, and acylated amines.

15 The compounds of the instant invention are highly selective antagonists of bombesin receptors.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

20 A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with 25 the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous 30 mixture is then poured into convenient sized molds and allowed to cool and solidify.

The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

5 The compounds of the present invention can have multiple chiral centers in the above Formula I depending on their structures. In particular, the compounds of the present invention may exist as diastereomers, mixtures of diastereomers, or as the mixed or the individual optical enantiomers. The present invention
10 contemplates all such forms of the compounds. The mixtures of diastereomers are typically obtained as a result of the reactions described more fully below. Individual diastereomers may be separated from mixtures of the diastereomers by conventional techniques such as column chromatography or repetitive
15 recrystallizations. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active compound, followed by separation by chromatography or recrystallization and
 reconversion to the nonsalt form.

 Where it is appropriate to form a salt, the pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate,
20 estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate
 (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate,
25 stearate, subacetate, succinate, sulfate, tannate, tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.

 Cyclodextrin is one suitable inclusion in a pharmaceutical preparation.

30 The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

-10-

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

The compounds of the invention have been evaluated in receptor binding assays which measure the affinity of the novel compounds in a cloned human NMB-preferring receptor (BB₁) assay and in a cloned human GRP-preferring receptor (BB₂) assay.

Protocol for Binding Assays

CHO-K1 cells stably expressing cloned human NMB and GRP receptors were routinely grown in Ham's F12 culture medium supplemented with 10% foetal calf serum and 2 mM glutamine. For binding experiments, cells were harvested by trypsinization, and stored frozen at -70°C in Ham's F12 culture medium containing 5% DMSO until required. On the day of use, cells were thawed rapidly, diluted

-11-

with an excess of culture medium, and centrifuged for 5 minutes at 2000 g. Cells were resuspended in 50 mM Tris-HCl assay buffer (pH 7.4 at 21°C, containing 0.02% BSA, 40 µg/mL bacitracin, 2 µg/mL chymostatin, 4 µg/mL leupeptin, and 2 µM phosphoramidon), counted, and polytroned (setting 5, 10 sec) before
5 centrifuging for 10 minutes at 28,000 g. The final pellet was resuspended in assay buffer to a final cell concentration of 1.5×10^5 /mL. For binding assays, 200 µL aliquots of membranes were incubated with [125 I][Tyr 4]bombesin (<0.1 nM) in the presence and absence of test compounds (final assay volume 250 µL) for 60 minutes and 90 minutes for NMB and GRP receptors, respectively. Nonspecific
10 binding was defined by 1 µM bombesin. Assays were terminated by rapid filtration under vacuum onto Whatman GF/C filters presoaked in 0.2% PEI for >2 hours, and washed 50 mM Tris-HCl (pH 6.9 at 21°C; 6 × 1 mL). Radioactivity bound was determined using a gamma counter. See Table 1.

The compounds of the invention have been tested in *in vitro* functional assays using cloned human NMB-preferring receptors expressed in CHO cells.

Protocols for functional assays:

1. Measurement of intracellular calcium levels

Culture of Chinese hamster ovary cells

Chinese hamster ovary cells were routinely grown as monolayers in Ham's
20 F12 nutrient mixture supplemented with 10% FBS and 2 mM glutamine, and maintained at 37°C under 5% CO $_2$. Cells were passaged every 3 to 4 days. At each passaging, cells were seeded at a density of 3 to 6 million per 175 cm 2 flask. For the imaging experiments, cells were plated out onto glass coverslips at a density of 5 to 10,000/cm 2 and usually used within 2 to 3 days after plating.

[Ca $^{2+}$] Studies in single cells

Plated cells were incubated with 2 µM Fura-2-AM for between 45 and 120 minutes at 25°C to 29°C. This procedure loaded the cells with the dye which was hydrolysed to the free acid form inside the intact cells. Single coverslips were then mounted in a chamber on top of an inverted fluorescence microscope and
30 perfused with a Krebs-Hepes assay buffer (composition in mM: NaCl 118,

-12-

KCl 4.7, MgSO₄ 1.2, CaCl₂ 1.2, KH₂PO₄ 1.2, Hepes 10, glucose 11, pH 7.2 at 37°C) {332}.

Measurements of $[Ca^{2+}]_i$ in individual cells were made from the fluorescence ratio (excitations 340/380 nM, emission >510 nM for Fura-2) using a specially designed filter wheel assembly, CCD camera or photomultiplier tubes, and specially designed suites of software (MAGICAL OR phocal, Applied Imaging, Sunderland, UK) which samples emission following excitation at different wavelengths at regular intervals. The $[Ca^{2+}]_i$ could be calculated from a calibration curve using the equation $[Ca^{2+}] = K_d \cdot \beta \cdot (R - R_{min}) / (R_{max} - R)$ where R_{max} , R_{min} , and R were, respectively, the maximum ratio, minimum ratio, and measured ratio at lower λ /upper λ . R_{max} (14.5), R_{min} (0.75), and β (8.51) were determined from free standing solutions of 2 mM and zero $[Ca^{2+}]_o$ (+1 mM EGTA) in Hepes buffer solution as previously described {458, 457}. These values did not vary significantly from day to day. The data was displayed as ratio values of emission after excitation at the lower λ and upper λ (ie, 340/380 nM) due to the uncertainties in calculating cytosolic $[Ca^{2+}]$ from a calibration curve determined in free standing solutions. The relative concentration of Fura-2 inside cells over the course of an experiment was monitored by measuring emission after excitation at the dye's isobestic point (360 nM).

2. Measurement of extracellular acidification (CYTOSENSOR)

The Cytosensor Microphysiometer (Molecular Devices Corp., California, USA) has been demonstrated to measure the activity of isolated cells in terms of their rate of production of hydrogen ions. This acidification rate is detected as a change in potential across a silicon light addressable sensor, during periods of media cessation (McConnell, et al., 1992).

CHO-NMB Cells seeded on polycarbonate microporous capsule cups were placed in sensor chambers at 37°C inside the microphysiometer, and maintained by a flow of nonbuffering Ham's F12 nutrient media (growth media without NaHCO₃, pH 7.3-7.4) at approximately 120 μ L/min. The flow was halted for 22 seconds at

-13-

the end of each 2 minute repeated cycle, and the rate of acidification (μ volts/sec) measured for 15 seconds during that period.

Agonists were introduced sequentially every 28 to 30 minutes to the perfusing media, 20 seconds before flow-off periods, and removed after two rate
5 measurements via the automatic valve-switch.

The effects of various antagonists were determined after continuous perfusion 30 minutes prior to, and throughout the application of agonists. All agents were applied at the working pH of the media.

TABLE 1. Human NMB and GRP Receptor Binding Affinities

| Example No. | NMB K _i (nM) | GRP K _i (nM) |
|----------------|----------------------------|----------------------------|
| 11 | 103 | 1A |
| 7 | 487 | 1A |
| 24 | 413 | 1A |
| 10 | 758 | 1460 |
| 19 | 3 | 762 |
| 22 | 35 | 589 |
| 20 | 33 | 1A |
| 21 | 20 | 2550 |
| 23 | 16 | 5360 |
| 17 | 3310 | 2940 |
| 12 | 0.7 | 60 |
| 14 | 0.15 | 19 |
| 16 | 3 | 140 |
| 15 | 2 | 165 |
| 13 | 0.3 | 38 |
| 8 | 3 | 450 |
| 9 | 3.3 | 1130 |
| 18 | 25 | 1A |
| 4 | 215 | 1A |
| 5 | 942 | 1A |
| 25 | 95 | 1A |
| 2 | 14 | 1A |
| 6 | 783 | 1A |
| 1 | 5 | 1A |
| 3 | 130 | 1A |
| 26 | 0.25 | 29 |
| 27 | 0.15 | 1.0 |
| 28 | 0.81 | 79 |
| 29 | 10 | 1A |
| 31 | 0.17 | 21 |
| 32 | 0.17 | 20 |

* 1A is defined as those compounds which bind with lower than 10 micromolar affinity at the receptor.

TABLE 2. In Vitro Functional Activity of Compounds at NMB-Preferring Receptor (BB,1)

| Example No. | [Ca ²⁺] _i Mobilization | Acidification Response |
|-------------|---|------------------------|
| | KE (nM) | appKB |
| 2 | -- | 54.3 (2.5-152.4) |
| 1 | 18 (10-33) | 7.6 (5.3-110) |
| 14 | 1.2 | 1.0 |

General synthetic schemes for compounds of the invention follow.

DESCRIPTION OF SYNTHETIC SCHEMES

Scheme I describes the synthesis of C-terminal derivatives

- 5 Examples 1 through 6. Intermediate I is prepared by the addition of 2,6-diisopropyl phenyl isocyanate to α -methyl Trp in DMF at 100°C. Coupling of Intermediate I to a selection of amines using HBTU and DIPEA in DMF furnished Examples 1 through 6.

- 10 Scheme II highlights the synthesis of Example 7. Addition of 2,6-diisopropyl phenyl isocyanate to (RS)-tryptophan in DMF at 100°C provided Intermediate IV. This was then coupled to N-methyl cyclohexyl methyl amine using HBTU and DIPEA in DMF to give Example 7.

- 15 In Scheme III the intermediate acid V is prepared following the addition of p-nitrophenylisocyanate to (S)- α -methyl tryptophan in DMF at 60°C. Subsequent coupling of the intermediate acid V to cyclohexyl methyl amine and cyclohexan-1-ol methyl amine using HBTU and DIPEA in DMF yielded Examples 8 and 9, respectively.

Scheme IV outlines the preparation of Example 10. Initial addition of 2,6-diisopropyl phenyl isocyanate to (RS)-N-methyl tryptophan in DMF at 50°C

furnished the intermediate acid VI which was subsequently coupled to cyclohexyl methyl amine to provide Example 10.

In Scheme V the intermediate acid VII is prepared following the addition of Boc_2O to (S)- α -methyl tryptophan in dioxan/water in the presence of NaHCO_3 .

5 Coupling of this intermediate to either cyclohexyl methyl amine or 1-(2-pyridyl) 1-aminomethyl cyclohexane (Intermediate II) in the presence of either HBTU, DIPEA, or DCC,PFP yielded the required Intermediate VIII. Deprotection of the Boc group using TFA in CH_2Cl_2 followed by coupling of the revealed amine to a selection of isocyanates in THF provided Examples 11 through 17.

10 Scheme VI describes the preparation of Example 18. Intermediate X is generated by adding Boc_2O in dioxan/water in the presence of NaHCO_3 to (S)- α -methyl tryptophan. Coupling of the free carboxylic acid in Intermediate X to 2,6-diisopropyl phenyl amine using HBTU and DIPEA in DMF yielded Intermediate XI. Subsequent removal of the Boc protecting group using TFA in
15 CH_2Cl_2 followed by reaction of the revealed amine with (RS)- α -t-butyl benzyl isocyanate in THF furnished Example 18.

In Scheme VII the intermediate acid XIII is prepared via the addition of 2,6-diisopropyl phenyl isocyanate to the required (RS)- α -methyl amino acid in DMF at 60°C. This intermediate is then coupled to 1-(2-pyridyl)-1-aminomethyl
20 cyclohexane (Intermediate II) using HBTU and DIPEA in DMF to yield Examples 19 through 21. Catalytic hydrogenation of Example 19 furnished Example 22.

Scheme VIII outlines the preparation of Example 23. (RS)-N-trityl-histidine was reacted with 2,6-diisopropyl-phenylisocyanate in DMF at 60°C to provide
25 Intermediate XIV. This acid was then coupled to 1-(2-pyridyl)-1-aminomethyl cyclohexane (Intermediate II) using HBTU and DIPEA in DMF to give Intermediate XV which was subsequently reacted with formic acid in CH_2Cl_2 to provide Example 23.

The synthesis of Example 24 is outlined in Scheme IX. Reacting
30 p-nitrophenyl chloroformate with (RS)- α -methyl tryptophan methyl ester provided the reactive Intermediate XVI which was then added to 2,6-diisopropylphenyl-N-

-17-

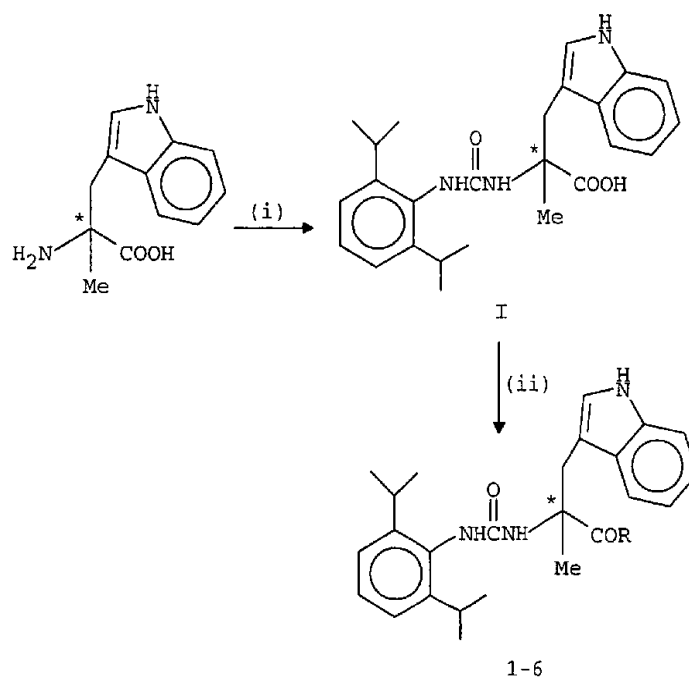
methyl amine in toluene to yield Intermediate XVII. Hydrolysis of the methyl ester using LiOH in MeOH/water gave Intermediate XVIII which was then coupled with cyclohexyl methyl amine using HBTU and DIPEA in DMF to give Example 24.

5 In Scheme X Intermediate XIX is prepared by adding the acetone of (S)-phenyl serinol to (RS)-N-Boc- α -methyl tryptophan using DCC and HOBT in CH_2Cl_2 . Subsequent removal of the N-Boc protecting group using HCl gas in Et_2O gave Intermediate XX which was then reacted with 2,6-diisopropyl phenyl isocyanate in EtOAc to give Example 25 after column chromatography.

10 Intermediate II was prepared after initial alkylation of pyridine-2-acetonitrile with 1,5-dibromopentane followed by reduction of the nitrile with Raney nickel.

Intermediate III was prepared by initial displacement of the alcohol in 2-phenyl cyclohexan-1-ol with azide via the use of DEAD, PPh_3 , and $(\text{PhO})_2\text{PON}_3$ in THF followed by catalytic reduction of the azide to give the amine
15 Intermediate III.

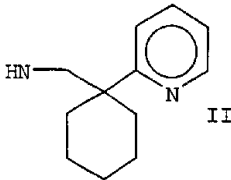
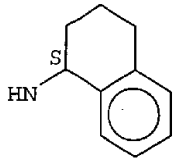
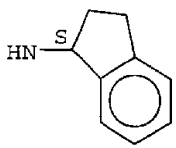
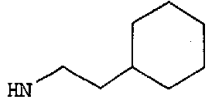
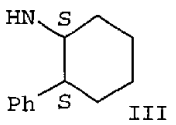
-18-
SCHEME 1



Reagents and Conditions:

- i) 2,6-diisopropylphenylisocyanate, triethylamine, DMF, 100°C ;
5 ii) HBTU, R, DIPEA, DMF, 20°C

Table for Scheme 1

| Example No. | * | R |
|-------------|----|--|
| 1 | S |  |
| 2 | R |  |
| 3 | R |  |
| 4 | RS |  |
| 5 | RS | NHPH |
| 6 | R |  |

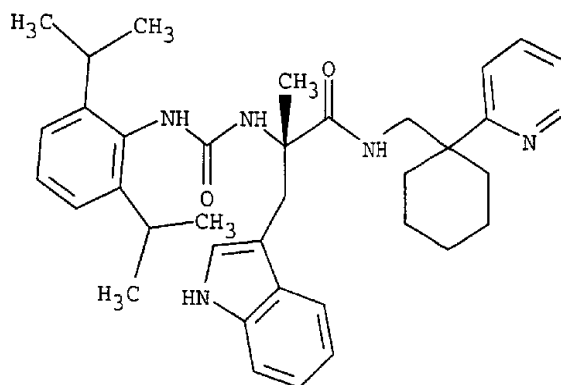
Synthesis of Examples 1-6Step 1

To a stirred solution of α -methyl-tryptophan (1.0 g, 4.6 mmol) in DMF (50 mL) was added 2,6-diisopropyl phenyl isocyanate (1.0 g, 5 mmol) followed by triethylamine (1.4 g, 14 mmol), and the mixture was heated to 100°C for 1 hour. The reaction mixture was allowed to cool to room temperature and was taken up in EtOAc, washed with 1N HCl, brine, and dried (MgSO₄). The solvents were removed *in vacuo*, and the residue was triturated with ether to yield intermediate I as a white solid (1.38 g, 71%).

¹H NMR (DMSO): δ 1.15 (12H, br, 4 \times CH₃(ⁱPr)), 1.46 (3H, s, α CH₃), 3.26 (3H, br, 2 \times CH(ⁱPr), CHH indole), 3.41 (1H, d, 14.4 Hz, CHH indole), 6.32 (1H, br s, urea NH), 6.96-7.39 (7H, br m, 3 \times CH (Ph), indole H-2, H-5, H-6, H-7), 7.56 (2H, br, indole H-4, benzylic urea NH), 10.96 (1H, br, indole NH), 12.59 (1H, br, acid OH);

IR (film): 3357, 2959, 1704, 1657, 1620, 1526, and 1456 cm⁻¹; MS m/e (CI) 422 (M⁺ + H) (4%) 204 (100%); Analysis C₂₅H₃₁N₃O₃•0.25 H₂O, C, H, N; mp 194-195°C.

EXAMPLE 1



-21-

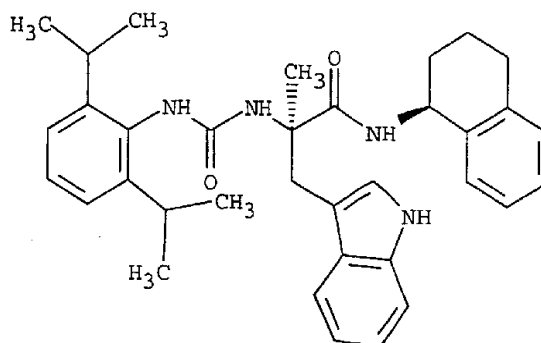
2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-
2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

To a stirred solution of the acid (I) (674 mg, 1.6 mmol) in DMF (80 mL) was added 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uranium
 5 hexafluorophosphate (HBTU) (607 mg, 1.6 mmol) followed by diisopropyl ethyl amine (620 mg, 4.8 mmol), and the mixture was stirred at room temperature for 5 minutes. Amine II (304 mg, 1.6 mmol) was added to the solution which was stirred for a further 2 hours. The reaction mixture was taken up in EtOAc and washed with NaHCO₃ (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The
 10 residue was purified on reverse phase silica eluting with a gradient of MeOH/H₂O 50% to 100% to give Example 1 as a white solid (696 mg, 73%).
¹H NMR (CDCl₃): δ 0.75 and 0.88 (6H, 2 × br d, (CH₃)₂CH), 1.03 (6H, br d, (CH₃)₂CH), 1.22-1.64 (8H, m, cyclohexyl), 1.64 (3H, s, αCH₃), 2.09-2.13 (2H, m, cyclohexyl), 2.97-3.04 (3H, m, (CH₃)₂CH × 2, CHH indole), 3.22 (1H, d,
 15 14.65 Hz, CHH indole), 3.38-3.39 (2H, m, CNHCH₂), 4.94 (1H, br s,

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{PhNHCNH} \end{array}$$

 20 PhNHCNH), 5.44 (1H, br s, PhNH), 6.34 (1H, brs, NH amide), 6.93-7.00 (2H, m, 2ArH), 7.03-7.11 (4H, m, 4ArH), 7.22 (1H, d, 8.06 Hz, ArH), 7.26-7.31 (2H, m, 2ArH), 7.36 (1H, d, 8.06 Hz, ArH), 7.633 and 7.63 (1H, dt, 7.60 Hz, ArH), 7.73 (1H, br s, indole NH), 8.54 (1H, d, 3.17 Hz, ArH);
 IR (film): 3291.0, 2955.0, 2870.0, 1652.0, 1532.0, 1457.0, and 742.0 cm⁻¹; MS
 25 m/e (APCI): 594.7 (M⁺ + H); Analysis C₃₇H₄₇N₅O₂, C, H, N; mp 116-117°C;
 HPLC R.T. = 12.88, C₁₈ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

EXAMPLE 2



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-

2-methyl-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-propionamide

5 Example 2 was prepared as for Scheme 1 using 1,2,3,4-tetrahydro-1-naphthyl amine(s).

Example 2 was isolated in 24% yield.

^1H NMR (CDCl_3): δ 0.43-0.52 (3H, br d, CH_3CH), 0.90-0.94 (3H, br d, CH_3CH),
0.98 and 1.07 (6H, 2 \times d, 6.59 and 6.11 Hz, $(\text{CH}_3)_2\text{CH}$), 1.70 (3H, s, αCH_3),
10 1.78-1.84 (3H, m, $\text{CHCHHCH}_2\text{tetralin}$), 1.87-2.04 (1H, m, $\text{CH}_2\text{CHHtetralin}$),
2.69-2.91 (3H, m, $(\text{CH}_3)_2\text{CH}$, PhCH_2), 2.89 (1H, d, 14.65 Hz, CHH indole),
3.06-3.15 (1H, m, $(\text{CH}_3)_2\text{CH}$), 3.47 (1H, d, 14.40 Hz, CHH indole), 4.75 (1H, br s,

15 PhNHC(=O)NH), 5.01-5.06 (1H, m, CHNCH), 5.30 (1H, br s, PhNHHC(=O)NH), 6.28 (1H, br s, NH amide), 6.63 (1H, br d, 7.57 Hz, ArH), 6.71 (1H, br d, 7.81 Hz, ArH), 6.91 (1H, t, 7.82 Hz, ArH), 6.98 (1H, t, 7.32 Hz, ArH), 7.04 (2H, t, 6.84 Hz, ArH), 7.09-7.16 (2H, m, 2 ArH), 7.22-7.37 (3H, m, 3 ArH), 7.39 (1H, d, 8.3 Hz, ArH), 7.77 (1H, br s, indole NH);

20 IR (film): 3291.0, 2962.0, 1674.0, 1651.6, 1506.0, 1456.0, and 737.0 cm^{-1} ; MS m/e (APCI) 551.5 ($\text{M}+\text{H}^+$);

-23-

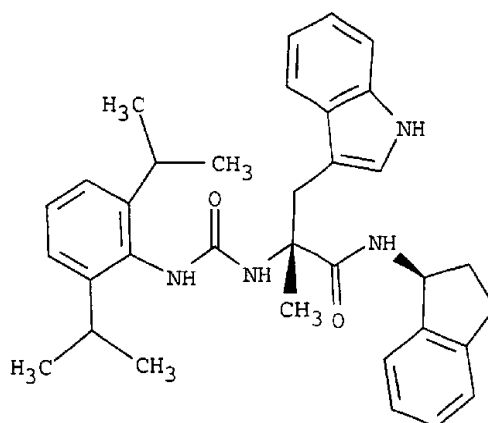
Analysis $C_{35}H_{42}N_4O_2$, C, H, N; $\alpha^D = -45.33$ (MeOH, $c = 0.075$ g, 100 mL^{-1});

mp $210-212^\circ\text{C}$; HPLC R.T. = 17.90, C^{18} reverse phase, 40% to 100%

MeCN:TFA/ H_2O :TFA.

EXAMPLE 3

5



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-indan-1-yl-3-(1H-indol-3-yl)-2-methyl-propionamide

Example 3 was prepared as for Scheme 1 using S-(+)-l-aminoindone.

Example 3 was isolated in 40.5% yield.

10 ^1H NMR (CDCl_3): δ 0.55 (3H, br s, CH_3CH), 0.94 (3H, br d, 5.62 Hz, CH_3CH), 0.99 (3H, br d, 6.35 Hz, CH_3CH), 1.07 (3H, br d, 6.10 Hz, CH_3CH), 1.70 (3H, s,

15 αCH_3), 1.71-1.86 (1H, m, CNHCHCHH), 2.53-2.61 (1H, m, CNHCHCHH), 2.78-2.97 (4H, m, CHH indole, PhCH_2 , $(\text{CH}_3)_2\text{CH}$), 3.01-3.20 (1H, Br m,

$(\text{CH}_3)_2\text{CH}$), 3.47 (1H, d, 14.40 Hz, CHH indole), 4.77 (1H, br s, NHCNH),

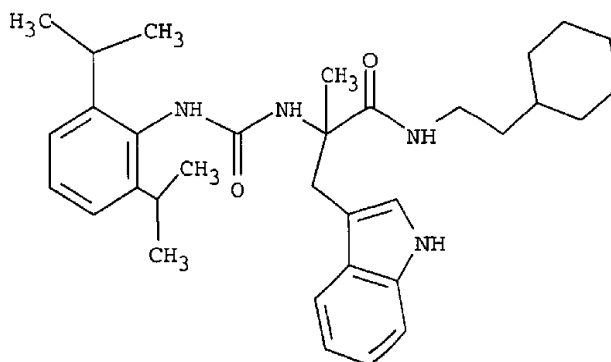
-24-

5.36 (1H, q, 7.57 Hz, CNHCH), 5.58 (1H, s, NHCHNH), 6.30 (1H, br s, amide nH), 6.60 (1H, br d, 6.59 Hz, ArH), 6.65 (1H, br d, 8.06 Hz, ArH), 6.94-7.06 (3H, m, 3ArH), 7.11-7.20 (4H, m, 4ArH), 7.26-7.34 (2H, m, 2ArH), 7.38 (1H, d, 7.32 Hz, ArH), 7.82 (1H, br s, indole NH);

IR (film): 3354.0, 1668.0, 1506.0, and 1060.0 cm^{-1} ;

MS m/e (APCI) 537.7 ($\text{M} + \text{H}^+$); Analysis $\text{C}_{34}\text{H}_{40}\text{N}_4\text{O}_2$, C, H, N; $\alpha^D = -30.29^\circ$ (MeOH, c = 0.175 g, 100 mL^{-1} ; mp 228-230°C; HPLC R.T. = 16.96, C^{18} reverse phase, 40% to 100% MeCN:TFA/ H_2O :TFA.

EXAMPLE 4



15 N-(2-Cyclohexyl-ethyl)-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide

Example 4 was prepared as for Scheme 1 using cyclohexyl ethyl amine.

Example 4 was isolated in 54% yield.

^1H NMR ($\text{DMSO}-d_6$): δ 0.50-1.73 (28H, br, αCH_3 + cyclohexyl + $2 \times (\text{CH}_3)_2\text{CH}$ + CH_2 cyclohexyl), 2.92-3.30 (5H, br, CH_2N + $2 \times (\text{CH}_3)_2\text{CH}$ + CHH indole),

-25-

3.50 (1H, br d, CHH indole), 6.42 (1H, br s, PhNHCNH), 6.83-7.38 7H, br m,

5

3 ArH + 4 indole H), 7.52 (1H, d, 8.0 z, indole H), 7.71 2H, br, PhNHC + amide NH), 10.90 (1H, br, indole NH);

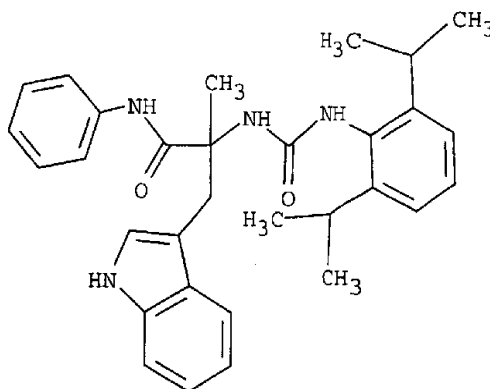
IR (film): 3289.0, 2924.0, 1668.0, 1652.0, 1520.0, 1456.0, and 740.0 cm⁻¹; MS

m/e (CI) 531.8 (M⁺ + H); Analysis C₃₃H₄₆N₄O₂•0.2 H₂O, C, H, N;

10

mp 113-116°C.

EXAMPLE 5



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-phenyl-propionamide

15

Example 5 was prepared as for Scheme 1 using phenylamine.

Example 5 was isolated in 69% yield.

¹H NMR (DMSO-d₆): δ 1.11 (12H, br, 2 × (CH₃)₂CH), 1.47 (3H, br s, αCH₃),

3.29 (2H, br, 2 × (CH₃)₂CH), 3.45 (2H, br, CH₂ indole), 6.43 (1H, br s,

20

PhNHCNH), 6.90-7.39 (10H, br m, 6ArH + 4 indole H), 7.50-.71 (4H, br,

-26-

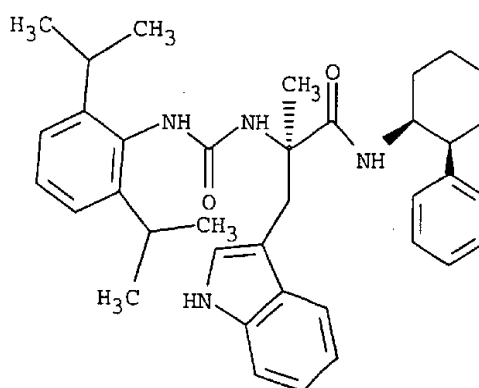
$$\text{O}$$

$$\parallel$$

$$\text{2ArH} + \text{indole H} + \text{PhNH}\text{C}\text{NH}$$
 9.70 (1H, br s, amide NH), 10.98 (1H, br, indole NH);

5 IR (film): 3278.0, 2927.0, 1673.0, 1599.0, 1519.0, 1499.0; MS m/e (CI) 497.6 ($\text{M}^+ + \text{H}$); Analysis $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_2 \cdot 0.5 \text{H}_2\text{O}$, C, H, N; mp 121-124°C.

EXAMPLE 6



10 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-cyclohexyl)-propionamide

Example 6 was prepared as for Scheme 1 using Intermediate III.

Yield (78 mg, 53%).

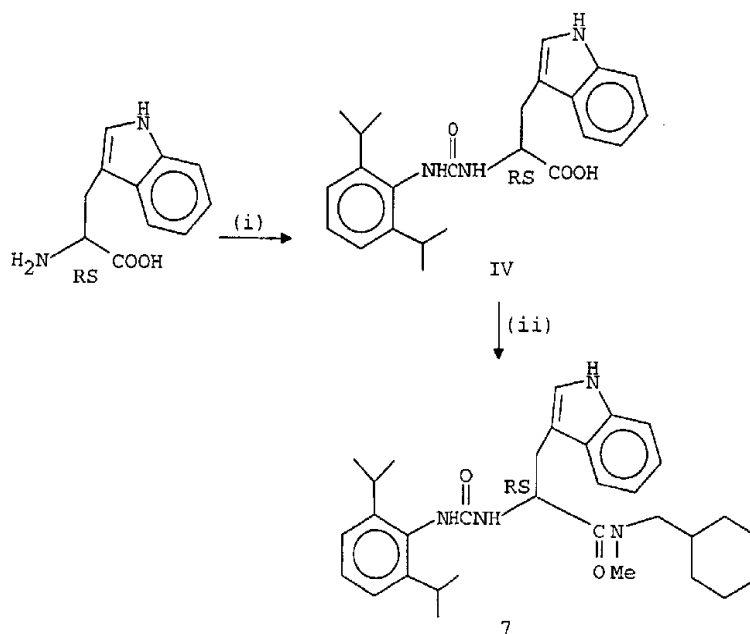
^1H NMR (CDCl_3): 0.85-2.04 (20H, m, $4 \times \text{CU}_2$), 1.36 (3H, s, $\alpha\text{-CU}_3$), 2.79 (1H, d, CHH), 2.92-3.10 (3H, m, CHH , $2 \times \text{CU}(\text{CU}_3)_2$), 4.46-4.51 (2H, m, NHCH , Ph CU), 5.63 (1H, s, CONH), 6.14 (1H, s, NHCO), 6.91-7.28 (13H, m, aromatic), 7.70 (1H, s, NH), 7.92 (1H, bs, CONH);

15 IR (film): 3286, 3061, 2928, 2867, 1674, 1662, 1496, 906, and 734; MS m/e M^+ 580, 405, 377; HPLC 97.6%, R.T. = 16.55, 60% to 100% acetonitrile in water

(— TFA); $[\alpha]_{\text{D}}^{22} + 67.5^\circ$ ($c = 0.57$, acetone).

-27-

SCHEME 2



Reagents and Conditions:

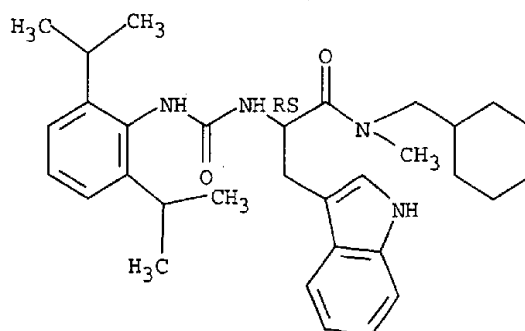
- i) 2,6-Diisopropyl phenyl isocyanate, triethylamine, DMF, 100°C
 5 ii) HBTU, DIPEA, DMF, 20°C, N-methyl cyclohexyl methyl amine

Synthesis of Example 7Step 1

- To a stirred solution of tryptophan (203 mg, 1.0 mmol) and triethylamine (9 mL, 65 mol) in dioxan (50 mL) was added diisopropyl phenyl isocyanate (203 mg, 1.0 mmol), and the mixture was refluxed for 3 hours. The reaction mixture was allowed to cool to room temperature and was taken up in EtOAc and washed with 1N HCl (aq), brine, and dried (MgSO₄). The solvents were removed *in vacuo* and the residue was triturated with ether to yield IV as a white solid (191 mg, 47%).
 10
 15 IR (film): 2962.0, 1614.0, and 1456.0 cm⁻¹; MS m/e (CI) 408 (M + H).

-28-

EXAMPLE 7







N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-N-methyl-propionamide





5 Example 7 was isolated in 75% yield.

To a stirred solution of the acid IV (122 mg, 0.3 mmol), HBTU (114 mg, 0.3 mmol), and diisopropyl ethyl amine (116 mg, 0.9 mmol) in DMF (50 mL) which had been stirred for 5 minutes was added N-methyl cyclohexyl methyl amine (76.2 mg, 0.6 mmol). The mixture was stirred for 2 hours and then taken up
 10 in EtOAc (150 mL) and washed with NaHCO₃ (aq), 1N HCl (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on normal phase silica eluting with a gradient of heptane to 6:4 heptane:EtOAc to yield 7 (116.3 mg, 75%).

¹H NMR (CDCl₃): δ 0.51-1.07 (6H, m, cyclohexyl), 1.14 and 1.16 (12H, 2 × d,
 15 6.83 Hz, [(CH₃)₂CH] × 2), 1.23-1.60 (5H, m, cyclohexyl), 2.53-2.89 (2H, m,

[(CH₃)₂CH] × 2), 2.57 and 2.67 (3H, 2 × s, , 3.01-3.26 (4H, m,

20  indole and N(Me), 5.16-5.20 (1H, m, NHCN)CH, 5.22-5.27 (1H, m,

 αH), 5.72 (1H, m, NHCN)H), 6.98-7.02 (1H, m, Ar)H), 7.08-7.19 (4H, m, 4ArH),

-29-

7.26-7.34 (2H, m, 2ArH), 7.69 (1H, d, 8.06 Hz, ArH), 7.95 (1H, br s, indole NH);

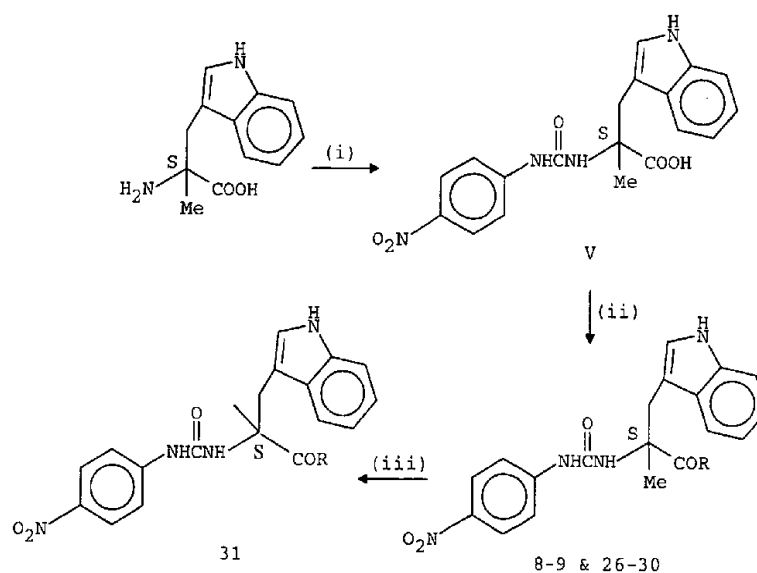
IR (film): 3291.0, 2925.0, 1615.0, 1538.0, 1213.0, and 740.0 cm^{-1} ; MS m/e (CI)

518 (M + H); Analysis $\text{C}_{32}\text{H}_{45}\text{N}_4\text{O}_2$, C, H, N; mp 179-181°C; HPLC

R.T. = 18.09, C_{18} reverse phase, 10% to 80% MeCN:TFA/ H_2O :TFA.

-30-

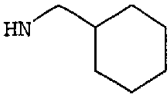
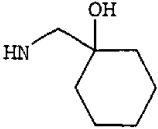
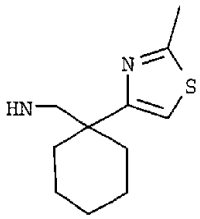
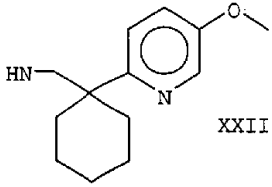
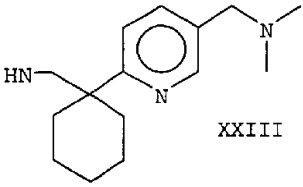
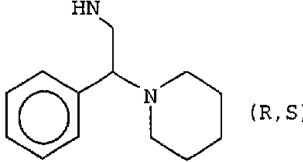
SCHEME 3



Reagents and Conditions:

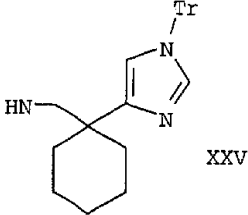
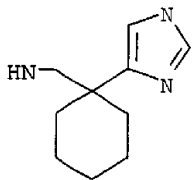
- i) p-nitrophenyl isocyanate, pyridine, DMF, 60°C
5 ii) HBTU, R, DIPEA, DMF, 20°C
iii) 2N HCl, MeOH, Reflux

Table for Scheme 3

| Example No. | R |
|-------------|---|
| 8 |  |
| 9 |  |
| 26 |  XXI |
| 27 |  XXII |
| 28 |  XXIII |
| 29 |  XXIV |

-32-

Table for Scheme 3 (cont)

| Example No. | R |
|-------------|--|
| 30 |  |
| 31 |  |

Synthesis of Examples 8 and 9, 26 through 30Step 1

To a mixture of (S)- α -Me tryptophan (2.51 g, 11.5 mmol) in DMF (100 mL) was added p-nitro phenyl isocyanate (1.89 g, 11.5 mmol) followed by pyridine (1 mL), and the reaction mixture was heated to 60°C for 30 minutes. The solvent was removed *in vacuo*, and the residue was taken up in 1N NaHCO₃ (aq) and extracted with ether. The aqueous layer was acidified with 5N HCl (aq) to pH 1 and re-extracted with EtOAc, dried (MgSO₄), and concentrated *in vacuo* to give V as a yellow solid (4.07 g, 96.1%).

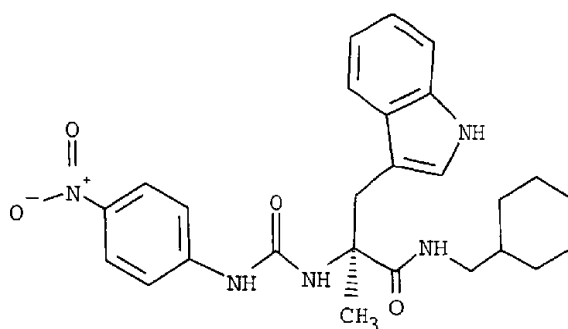
¹H NMR (DMSO): δ 1.55 (3H, s, α -CH₃), 3.31 (1H, d, obscured by water peak,

CHH indole), 3.48 (1H, d, 14.40 Hz, CHH indole), 6.57 (1H, s, NHCNH),
 6.82 (1H, t, 7.81 Hz, indole H5), 6.99 (1H, t, 7.32 Hz, indole H6), 7.04 (1H, d, 2.2 Hz, indole H2), 7.30 (1H, d, 8.3 Hz, indole H7), 7.49 (1H, d, 8.06 Hz, indole H4), 7.62 (2H, d, 9.04 Hz, 2 \times p-NO₂Ph ArH), 8.16 (2H, d, 9.03 Hz,

-33-

O
||
2 × P-NO₂ ArH, 9.45 (1H, s, NH_{CNH}), 10.89 (1H, s, indole NH).

EXAMPLE 8



5

N-Cyclohexylmethyl-3-(1H-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide

Example 8 was isolated in 54.4% yield.

To a solution of the acid V (150 mg, 0.4 mmol), HBTU (155 mg, 0.4 mmol), and diisopropyl ethyl amine (158 mg, 1.2 mmol) in DMF (100 mL) which had been stirred for 5 minutes was added cyclohexyl methyl amine (250 mg, 2.17 mmol), and the reaction mixture was stirred for 2 hours. The mixture was taken up in EtOAc and washed with 1N HCl (aq), 1N NaHCO₃ (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on silica eluting with 1:1 heptane:EtOAc to EtOAc to give a yellow solid which was washed with EtOAc to yield pure 8 (104 mg, 54.4%).

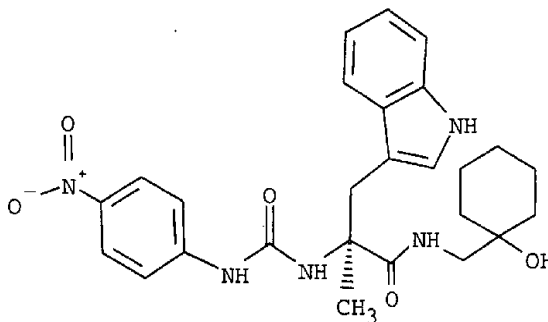
¹H NMR (DMSO): δ 0.78-0.86 (2H, m, cyclohexyl), 1.06-1.20 (3H, m, cyclohexyl), 1.40-1.49 (1H, m, cyclohexyl), 1.57 (3H, s, αCH₃), 1.56-1.63 (5H, m, cyclohexyl), 2.82-2.89 (1H, m, CNHCHH), 2.95-3.01 (1H, m, CNHCHH), 3.34 (1H, d, 14.89 Hz, CHH indole), 3.58 (1H, d, 14.65 Hz, CHH indole),

20

-34-

- 6.66 (1H, s, PhNHCNH), 6.81 (1H, t, 7.57 Hz, indole H5), 6.94 (1H, s, indole H2),
 6.98 (1H, t, 7.33 Hz, indole H6), 7.27 (1H, d, 8.06 Hz, indole H7), 7.48 (1H, d,
 5 8.06 Hz, indole H4), 7.62 (2H, d, 9.3 Hz, 2-p-NO₂Ph ArH), 7.99 (1H,
 NH), 5.62 Hz, CNH), 8.15 (2H, d, 9.03 Hz, 2 \times pNO₂Ph ArH), 9.60 (1H, s,
 10 NHCNH), 10.81 (1H, s, indole NH);
 IR (film): 3345.0, 2924.0, 2852.0, 1695.0, 1644.0, 1557.0, 1505.0, 1456.0, 1329.0,
 1302.0, 1231.0, 1112.0, and 741.0 cm⁻¹; MS m/e (APCI) 478.6 (M + H⁺);
 Analysis C₂₆H₃₁N₅O₄•0.35 H₂O, C, H, N; mp 129-131 then 208-225°C; HPLC
 15 R.T. = 13.52, C₁₈ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

EXAMPLE 9



N-(1-Hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide

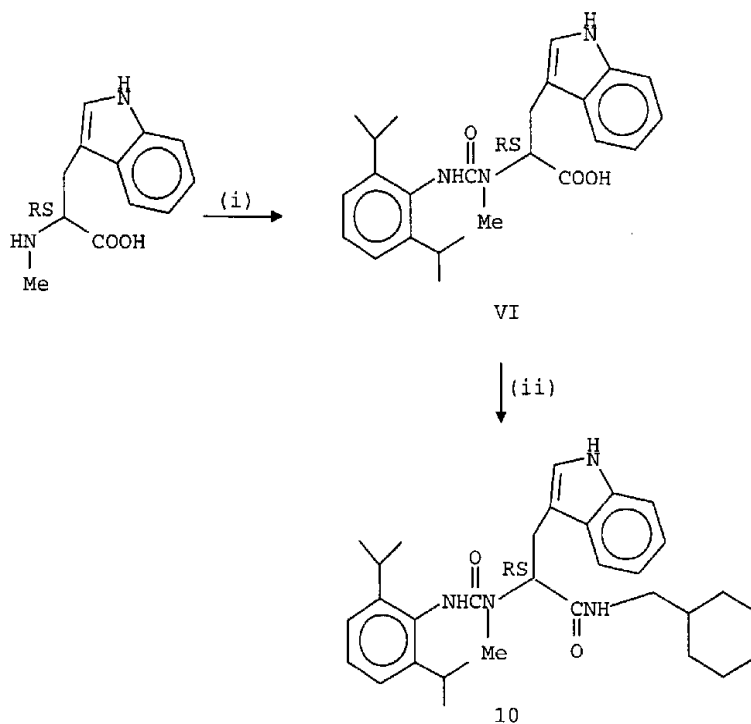
- 20 Example 9 was prepared as for Scheme 3 using 1-amino methyl-1-cyclohexanol.
 Example 9 was isolated in 59% yield.

¹H NMR (DMSO): δ 1.13-1.57 (8H, m, cyclohexyl), 1.42 (3H, s, αCH_3),

-35-

2.07-2.12 (2H, m, cyclohexyl), 2.98 (1H, dd, 13.19 and 5.13 Hz, CNHCHH),
 5 3.27 (1H, dd, 12.94 and 6.84 Hz, CNHCHH), 3.41 and 3.37 (2H, 2 × d, 14.90 Hz,
 CHH indole), 6.54 (1H, s, NHCNH), 6.81 (1H, t, 7.57 Hz, indole H5), 6.93 (1H,
 10 s, indole H2), 6.98 (1H, t, 7.57 Hz, indole H6), 7.10 (1H, t, 7.33 Hz, ArH),
 7.15-7.21 (3H, m, 2 ArH + NHCNH), 7.27-7.30 (3H, m, 3 ArH), 7.44 (1H, d,
 8.06 Hz, indole H7), 7.66 (2H, d, 9.28 Hz, 2 × p $\text{NO}_2\text{Ph ArH}$), 8.18 (2H, d,
 15 9.28 Hz, 2p $\text{NO}_2\text{Ph ArH}$), 9.52 (1H, s, CNH), 10.81 (1H, s, indole NH).
 IR (film): 3323.0, 1698.3, 1645.0, 1615.2, 1558.5, and 1505.0 cm^{-1} ; MS m/e
 (APCI) 554.5 ($\text{M} + \text{H}^+$); Analysis $\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}_5$, C, H, N; mp 182-184°C; HPLC
 20 R.T. = 10.53, C^{18} reverse phase, 40% to 100% MeCN:TFA/ H_2O :TFA.

SCHEME 4



Reagents and Conditions:

- i) 2,6-Diisopropylphenylisocyanate, triethylamine, DMF, 50°C
- 5 ii) HBTU, cyclohexylmethylamine, DIPEA, DMF

Synthesis of Example 10Step 1

- To a suspension of N-methyl (RS) tryptophan (500 mg, 2.3 mmol) in DMF (30 mL) was added 2,6-diisopropyl phenyl isocyanate (0.54 mL, 2.53 mmol), and triethyl amine (697 mg, 6.9 mmol), and the reaction mixture was heated to 50°C and stirred for 30 minutes. The mixture was allowed to cool to room temperature
- 10

-37-

before being taken up in EtOAc and washed with 1N HCl, brine, dried (MgSO₄), and concentrated *in vacuo* to give VI (966 mg, 100%).

¹H NMR (CDCl₃): δ 1.15 (6H, d, 6.84 Hz, (CH₃)₂CH), 1.25 (6H, d, 6.84 Hz, (CH₃)₂CH), 2.94 (3H, s, N-me), 2.88-3.05 (2H, 2 × m, [(CH₃)₂CH]₂),

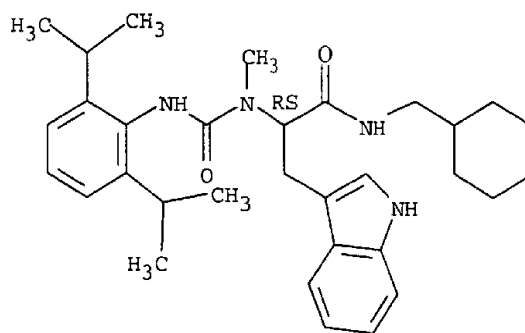
5

3.45-3.47 (2H, m, CHH indole), 4.97 (1H, t, 8.06 Hz, αH), 5.81 (1H, s, NH_C), 7.10-7.20 (5H, m, 5ArH), 7.22 (1H, t, 7.1 Hz, ArH), 7.26-7.30 (1H, m, ArH), 7.38 (1H, d, 8.06 Hz, ArH), 7.66 (1H, d, J = 7.82 Hz, ArH), 8.17 (1H, s, indole NH);

10

IR (film): 3320.8, 2963.0, 2291.5, 1716.0, 1652.0, 1507.0, 1466.8, and 743.0 cm⁻¹; MS m/e (ES) 420.7 (M - H⁺) 421.7 (M⁺).

EXAMPLE 10



15 N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-1-methyl-ureido]-3-(1H-indol-3-yl)-propionamide

Example 10 was isolated in 32.6% yield.

To a solution of the acid VI (211 mg, 0.5 mmol) in DMF (50 mL) was added HBTU (189.6 mg, 0.5 mmol), diisopropyl ethyl amine (194 mg, 1.5 mmol), and the mixture was stirred for 10 minutes. Cyclohexyl methyl amine (80 mg, 0.7 mmol) was then added to the reaction mixture and this was stirred for a further 5 hours. The mixture was taken up in EtOAc and washed with 1N HCl (aq),

20

-38-

NaHCO₃ (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on normal phase silica eluting with a gradient of heptane to 6:4 heptane:EtOAc to give a solid which was washed with ether to yield pure 10 (84.2 mg, 32.6%).

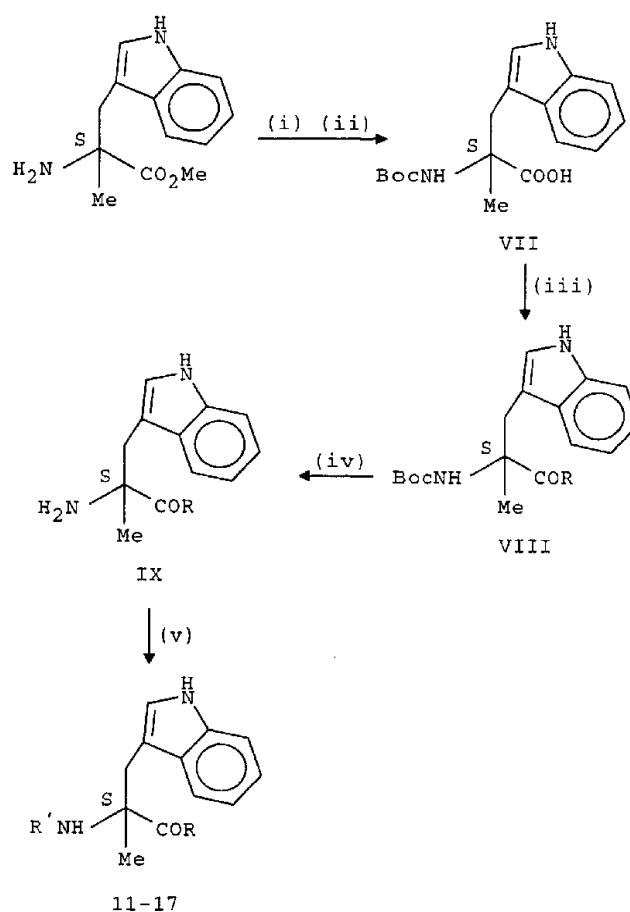
5 ¹H NMR (CDCl₃): δ 0.82-0.91 (2H, m, cyclohexyl), 1.10-1.20 (8H, m, cyclohexyl), 1.14 (12H, d, 6.84 Hz, [(CH₃)₂CH] × 2), 1.38-1.43 (1H, m,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{CNHCH}_2\text{CH} \end{array}$, 1.58-1.70 (2H, m, [(CH₃)₂CH] × 2), 3.03 (3H, s, N-CH₃),

10 $\begin{array}{c} \text{O} \\ \parallel \\ \text{CNHCH}_2\text{CH} \end{array}$, 3.08 (2H, t, 6.35 Hz, CNHCH₂), 3.30 (1H, dd, 9.77 and 15.87 Hz, CHH indole), 3.36 (1H, dd, 6.10 and 15.87 Hz, CHH indole), 5.29-5.33 (1H, m, αH), 5.65 (1H, s, PhNH₂C), 6.50 (1H, bt, amide NH), 7.08 (1H, d, 2.2 Hz, indole H₂),

15 $\begin{array}{c} \parallel \\ \text{O} \end{array}$
7.10-7.20 (3H, m, 3ArH), 7.20 (1H, t, 7.10 Hz, ArH), 7.22-7.26 (1H, m, ArH), 7.37 (1H, d, 8.3 Hz, ArH), 7.67 (1H, d, 7.57 Hz, 1ArH), 7.97 (1H, s, indole NH);
IR (film): 3323.0, 2925.0, 1668.2, 1645.0, and 1506.0 cm⁻¹; MS m/e (APCI)
20 515.9 (M⁺), 517.7 (M + H⁺); Analysis C₃₂H₄₄N₄O₂, C, H, N; mp 183-185.5°C;
HPLC R.T. = 18.41, C₁₈ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

SCHEME 5



Reagents and Conditions:

- i) Boc_2O , NaHCO_3 , dioxan
- 5 ii) LiOH , THF, MeOH
- iii) HBTU, R, DIPEA, DMF or DCC, PFP, R, EtOAc
- iv) TFA, DCM
- v) RNCO , THF

Table for Scheme 5

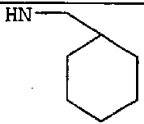
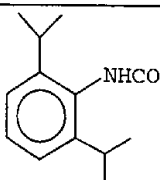
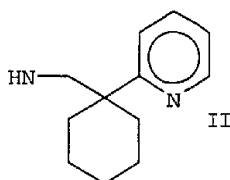
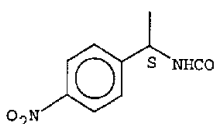
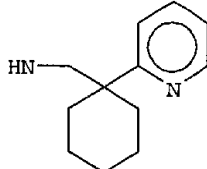
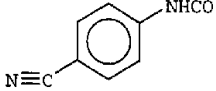
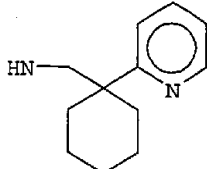
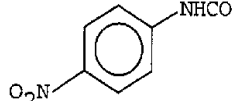
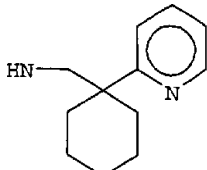
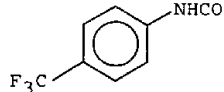
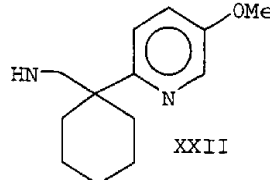
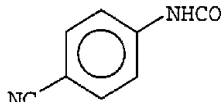
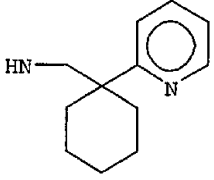
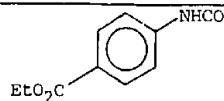
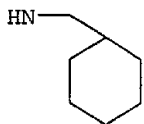
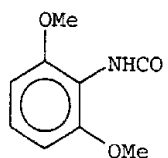
| Example No. | R | R' |
|-------------|---|--|
| 11 |  |  |
| 12 |  II |  |
| 13 |  |  |
| 14 |  |  |
| 15 |  |  |
| 32 |  XXII |  |

Table for Scheme 5 (cont)

| Example No. | R | R' |
|------------------------------|---|---|
| 16 |  |  |
| 17 (R,S-stereo-chemistry) |  |  |

Synthesis of Examples 12-16

Step 1 as for Examples 11 and 17.

Step 2

- 5 To a solution of the acid VII (2.067 g, 6.5 mmol), HBTU (2.47 g, 6.5 mmol), and diisopropyl ethyl amine (2.52 g, 19.5 mmol) in DMF (130 mL) which had been stirred ~5 minutes was added the amine II (1.24 g, 6.5 mmol), and stirring was continued for a further 2 hours. The reaction mixture was taken up in EtOAc and washed with NaHCO₃ (aq), 1N HCl (aq), dried (MgSO₄), and
- 10 concentrated *in vacuo*. The residue was purified on reverse phase silica eluting with 77% MeOH/H₂O to obtain pure VIII (R = II) (2.17 g, 68%).

¹H NMR (CDCl₃): δ 1.27-1.63 (8H, m, cyclohexyl), 1.40 (9H, s, (CH₃)₃C), 1.52 (3H, s, αCH₃), 2.0-2.13 (2H, m, cyclohexyl), 3.31 (1H, d, 14.65 Hz,

- 15 CHH indole), 3.29-3.50 (3H, m, CHH indole and CNHCH₂), 5.05-5.15 (1H, br s, CHH indole), 6.93 (1H, s, indole H2), 7.0-7.12 (2H, m, 2ArH), 7.16 (1H, t, 8.06 Hz, CNH), 6.93 (1H, s, indole H2), 7.0-7.12 (2H, m, 2ArH), 7.16 (1H, t, 8.06 Hz,

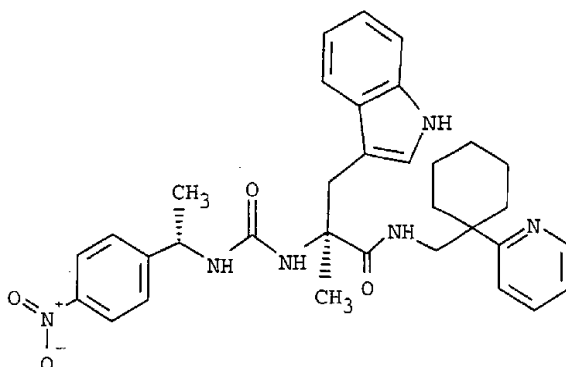
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{NHC} \end{array}$$
 ArH), 7.10-7.22 (1H, m, NHC), 7.31 (2H, t, 7.81 Hz, 2ArH), 7.52 (1H, d, 7.57 Hz, ArH), 7.63 (1H, t, 7.81 Hz, ArH), 7.99 (1H, br s, indole NH), 8.50 (1H, d, 3.66 Hz, pyridyl H);
 5 IR (film): 3333.0, 2928.0, 1652.0, 1471.0, and 1163.0 cm^{-1} ; MS m/e (APCI) 491.6 ($\text{M} + \text{H}^+$); Analysis $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_3$, C, H, N; mp: 78.5-79.5°C; HPLC R.T. = 8.47 and 8.73, C^{18} reverse phase, 40% to 100% MeCN:TFA/ H_2O :TFA.

Step 3

10 VIII (R = II) (473 mg, 0.96 mmol) was dissolved in formic acid (30 mL) and stirred for 5 hours. The mixture was basified with dilute sodium hydroxide solution to pH 14 and extracted with EtOAc, dried (MgSO_4), and concentrated *in vacuo* to give IX (R = II) (300 mg, 80%).
 ^1H NMR (CDCl_3): δ 1.27-1.63 (8H, m, cyclohexyl), 1.32 (3H, s, αCH_3),
 15 2.0-2.2 (2H, 2 \times m, cyclohexyl), 2.79 (1H, d, 14.65 Hz, indole CHH), 3.35 (1H, d, 14.65 Hz, indole CHH), 3.36 (1H, dd, 6.35 Hz, 13.18 Hz, CNHCHH), 3.42 (1H, dd, 6.10 and 13.18 Hz, CHHNHC), 7.00 (1H, d, 2.44 Hz, indole H2), 7.03-7.19 (4H, m, 4ArH), 7.35 (1H, d, 8.06 Hz, ArH), 7.52 (1H, td, 1.95 and 7.57 Hz, ArH), 7.59 (1H, d, 7.82 Hz, ArH), 7.60-7.68 (1H, br t, CNH), 8.02 (1H, 20 br s, indole NH), 8.51-8.58 (1H, m, pyridyl H); MS m/e (ES) 391.7 ($\text{M} + \text{H}^+$).

-43-

EXAMPLE 12



3-(1H-Indol-3-yl)-2-methyl-2-{3-[1-(4-nitro-phenyl)-ethyl]-ureido}-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

5 Example 12 was isolated in 39% yield.

To a solution of the amine IX (R = II) (100 mg, 0.26 mmol) in THF (100 mL) was added 4-nitro- α -methyl benzyl isocyanate (180 mg, 0.94 mmol), and the solution was stirred for 4 hours at room temperature. The reaction mixture was taken up in EtOAc and washed (H₂O), dried (MgSO₄), and concentrated
 10 *in vacuo*. The residue was taken up in EtOAc and crystallized to yield 12 (58.6 mg, 39%).

¹H NMR (DMSO): δ 1.08-1.48 (8H, m, cyclohexyl), 1.24 (3H, s, α -CH₃), 1.33 (3H, d, 7.08 Hz, PNO₂PhCHCH₃), 2.03-2.18 (2H, m, cyclohexyl), 3.07 (1H,

15 dd , 5.62 and 12.94 Hz, CNHCHH), 3.21-3.15 (2H, m, CHH indole and
 CNHCHH), 3.34-3.29 (1H, d, obscured by water peak CHH indole), 4.90 (1H, m,
 20 CHCH₃), 5.93 (1H, s, CHNHCHNH), 6.77 (1H, d, 7.32 Hz, ArH), 6.86-6.90 (2H,

-44-

m, 1ArH, and CNH), 7.01 (1H, t, 7.32 Hz, ArH), 7.13-7.16 (1H, m, ArH),

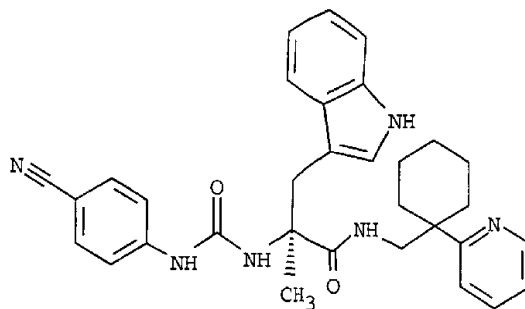
5

7.27-7.30 (2H, m, 2ArH), 7.36-7.40 (2H, m, CNH and ArH), 7.55 (2H, d, 8.79 Hz, 2 × p-NO₂Ph ArH), 7.64 (1H, td, 1.95 and 7.81 Hz, ArH), 8.16 (2H, d, 8.54 Hz, 2 × p-NO₂Ph ArH), 8.50 (1H, d, 2.93 Hz, pyridyl H), 10.85 (1H, s, indole NH);

10

IR (film): 3340.0, 2923.6, 1642.0, 1520.0, 1345.6, and 1107.0 cm⁻¹; MS m/e (APCI) 583.6 (M + H⁺); Analysis C₃₃H₃₈N₆O₄, C, H, N; mp 202-203.5°C; HPLC R.T. = 9.38 and 9.77, C₁₈ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA;

EXAMPLE 13



15

2-[3-(4-Cyano-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

Example 13 was prepared as for Scheme 5 using Intermediate II and 4-cyano phenyl isocyanate.

Example 13 was isolated in 37% yield.

20

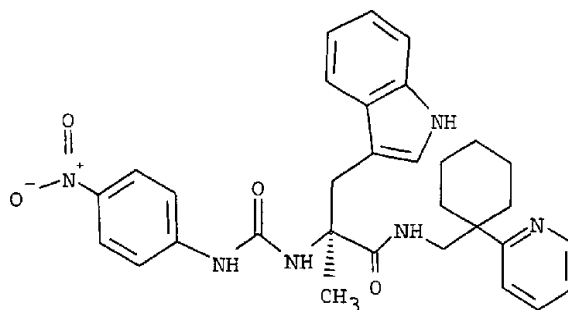
¹H NMR (DMSO): δ 1.13-1.55 (8H, m, cyclohexyl), 1.41 (3H, s, αCH₃),

2.16-2.23 (2H, m, cyclohexyl), 3.09 (1H, dd, 5.37 and 12.94 Hz, CNHCHH),

-45-

3.28-3.39 (3H, m obscured by water peak, CNHC $\overline{\text{H}}$ H and indole C $\overline{\text{H}}$ H), 6.44 (1H, s, NHCN $\overline{\text{H}}$), 6.81 (1H, t, 7.32 Hz, indole H5), 6.92 (1H, d, 2.20 Hz, indole H2), 6.98 (1H, t, 7.08 Hz, indole H6), 7.07-7.10 (1H, m, Ar $\overline{\text{H}}$), 7.28 (2H, t, 8.06 Hz, 2Ar $\overline{\text{H}}$), 7.41 (1H, d, 8.06 Hz, indole H7), 7.44-7.52 (3H, m, 2Ar $\overline{\text{H}}$ and CN $\overline{\text{H}}$), 7.56 (2H, d, 8.79 Hz, 2 \times pNO₂Ph Ar $\overline{\text{H}}$), 7.68 (2H, d, 8.79 Hz, 2 \times pNO₂Ph Ar $\overline{\text{H}}$), 8.47-8.49 (1H, m, pyridyl $\overline{\text{H}}$), 9.22 (1H, s, CN $\overline{\text{H}}$), 10.81 (1H, s, indole NH); IR (film): 3352.0, 2934.2, 1652.0, 1532.0, and 1113.0 cm⁻¹; MS m/e (APCI): 535.5 (M + H⁺); Analysis C₃₂H₃₄N₆O₂, C, H, N; mp 234.5-237°C; HPLC R.T. = 6.75 and 7.02, C¹⁸ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA;

EXAMPLE 14



20 3-(1H-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-N-(1-pyridin-2-yl)-cyclohexylmethyl)-propionamide

Example 14 was isolated in 63.3% yield.

Example 14 was prepared as for Scheme 5 using Intermediate II and 4-nitrophenyl isocyanate.

-46-

^1H NMR (DMSO): δ 1.11-1.55 (8H, m, cyclohexyl), 1.44 (3H, s, αCH_3),

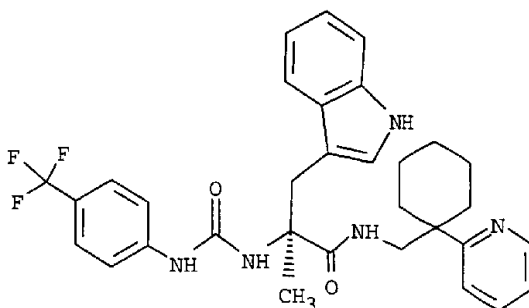
2.18-2.25 (2H, m, cyclohexyl), 3.09 (1H, dd, 5.37 and 13.18 Hz, CNHCCH_2),

3.29-3.38 (3H, m, CHH indole and CNHCCH_2), 6.54 (1H, s, NHCNH), 6.81 (1H, t, 8.06 Hz, indole H5), 6.93 (1H, s, indole H2), 6.98 (1H, t, 7.08 Hz, indole H6), 7.07-7.10 (1H, m, ArH), 7.28 (2H, t, 9.03 Hz, 2 ArH), 7.42 (1H, d, 7.81 Hz, indole H7), 7.49-7.60 (2H, m, amide NH and 1 ArH), 7.62 (2H, d, 9.28 Hz, 2 \times p- NO_2Ph ArH), 8.16 (2H, d, 9.28 Hz, 2 \times p- NO_2Ph ArH), 8.48-8.50 (1H, m, pyridyl H),

9.49 1H, s, Ph NHCNH), 10.81 (1H, s, indole NH);

IR (film): 3363.0, 2934.2, 1644.2, 1454.1, 1433.0, and 1046.0 cm^{-1} ; MS m/e (APCI): 555.5 ($\text{M} + \text{H}^+$); Analysis $\text{C}_{31}\text{H}_{34}\text{N}_6\text{O}_4$, C, H, N; mp 215-219°C; HPLC R.T. = 8.79, C^{18} reverse phase, 40% to 100% MeCN:TFA/ H_2O :TFA.

EXAMPLE 15



3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-
2-[3-(4-trifluoromethyl-phenyl)-ureido]-propionamide

Example 15 was isolated in 20% yield.

-47-

Example 15 was prepared as for Scheme 5 using Intermediate II and 4-trifluoromethylphenylisocyanate.

¹H NMR (DMSO): δ 1.12-1.55 (8H, m, cyclohexyl), 1.40 (3H, s, αCH₃), 2.18-2.26 (2H, m, cyclohexyl), 3.08 (1H, dd, 5.37 and 12.94 Hz, CNHC₁H),

5



3.27-3.36 (3H, obscured by water peak, CH₁H indole and CNHC₂H), 6.38 (1H, s,

10



NHCN₁H), 6.81 (1H, t, 7.81 Hz, indole H5), 6.93 (1H, d, 2.2 Hz, indole H2), 6.98 (1H, t, 7.57 Hz, indole H6), 7.07-7.10 (1H, m, ArH), 7.29 (2H, t, 9.03 Hz,

15



2ArH), 7.42 (1H, d, 8.06 Hz, indole H7), 7.46-7.51 (2H, m, ArH and NHC₃H),



7.59 (4H, s, 4 × ArH), 8.48 8.49 (1H, m, pyridyl H), 9.13 (1H, s, NHC₄H), 10.83 (1H, br s, indole NH);

20

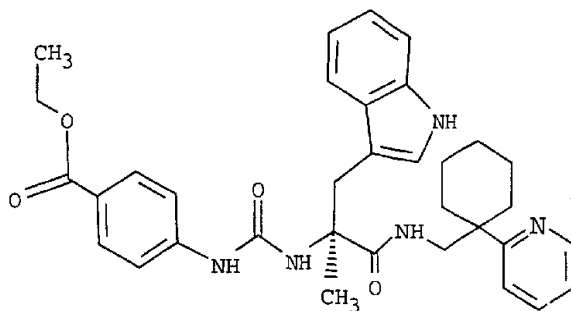
IR (film): 3360.0, 2934.2, 1651.9, 1559.3, 1440.3, 1334.6, and 1070.0 cm⁻¹; MS

m/e (APCI): 578.5 (M + H⁺); Analysis C₃₂H₃₄N₅O₂F₃, C, H, N; HPLC

R.T. = 10.99, C₁₈ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

-48-

EXAMPLE 16



4-(3-(2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-
carbamoyl]-ethyl)-ureido)-benzoic acid ethyl ester

- 5 Example 16 was prepared as for Scheme 5 using Intermediate II and ethyl-4-isocyanatobenzoate.

Example 16 was isolated in 55% yield.

¹H NMR (CDCl₃): δ 1.26-1.61 (8H, m, cyclohexyl), 1.39 (3H, t, 7.08 Hz, CH₃CH₂O), 1.70 (3H, s, αCH₃), 2.03-2.1 (2H, m, cyclohexyl), 3.18 (1H, dd,

10 ¹H NMR (CDCl₃): δ 1.26-1.61 (8H, m, cyclohexyl), 1.39 (3H, t, 7.08 Hz, CH₃CH₂O), 1.70 (3H, s, αCH₃), 2.03-2.1 (2H, m, cyclohexyl), 3.18 (1H, dd,

15 4.15 and 13.18 Hz, CNHCHH), 3.30 (1H, d, 14.65 Hz, CHH indole), 3.51 (1H, dd,

5.86 and 12.94 Hz, CNHCHH), 3.53 (1H, d, 14.65 Hz, indole CHH), 4.35 (1H, q^t, 7.08 Hz, CH₃CH₂O), 5.83 (1H, s, NHCNH), 6.85 (1H, d, 2.44 Hz, ArH),

20 6.98 (1H, t, 7.81 Hz, ArH), 7.02-7.07 (2H, m, ArH and NH₂C), 7.11 (1H, t,

7.08 Hz, ArH), 7.24-7.33 (4H, m, 4ArH), 7.41-7.45 (2H, m, ArH and NH₂C), 7.59 (1H, td, 7.57 and 1.95 Hz, ArH), 7.90 (2H, d, 8.79 Hz, 2ArH), 7.95 (1H, br s, indole NH), 8.44-8.45 (1H, m, pyridyl H);

IR (film): 3342.0, 2931.0, 1645.0, 1538.0, 1279.0, 1174.0, and 1107.0 cm^{-1} ; MS m/e (APCI) 582.5 ($M + H^+$); Analysis $\text{C}_{34}\text{H}_{39}\text{N}_5\text{O}_4$, C, H, N; mp 117-120°C; HPLC R.T. = 9.58, C^{18} reverse phase, 40% to 100% MeCN:TFA/ H_2O :TFA.

Synthesis of Examples 11 and 17

5 Step 1

To a stirring solution of (S)- α -methyl tryptophan methyl ester (5.0 g, 22 mmol) in dioxan (50 mL) water (50 mL) was added NaHCO_3 (3.0 g, 36 mmol) followed by di-*t*-butyl dicarbonate (5.0 g, 23 mmol). Stirring was continued for 18 hours at ambient temperature. The mixture was acidified (HCl, 200 mL, 2N aq, cautiously at first) and the products extracted (EtOAc, 300 mL). The organic phase was dried (MgSO_4) and evaporated to dryness *in vacuo* (60°C). The residual brown oil was purified by flash column chromatography (silica gel, eluant 40% EtOAc/60% heptane). Recovered 7.0 g (99%) of the protected ester as a pale yellow oil, which was not fully characterized. To a stirring solution of this ester 10 (7.0 g, 21 mmol) in MeOH (60 mL)/THF (60 mL) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.5 g, 35 mmol) in water (20 mL). Stirring was continued for 18 hours at ambient temperature. The mixture was acidified (HCl, 200 mL, 2N aq) and the products extracted (EtOAc, 2 \times 150 mL). The combined organics were dried (MgSO_4) and evaporated to dryness *in vacuo* (60°C). Recovered (VII) 6.8 g (99%) 15 as a pale yellow oil. This was not fully characterized.

IR (film): 1702 and 1694 cm^{-1} .

Step 2

To a stirring solution of (VII) (0.5 g, 1.6 mmol) in EtOAc (30 mL) was added N,N-dicyclohexyl carbodiimide (0.5 g, 2.4 mmol) and pentafluorophenol 25 (0.4 g, 2.2 mmol). Stirring was continued for 30 minutes at ambient temperature, then the white precipitate was removed by filtration. To the filtrate was added, with stirring, aminomethyl cyclohexane (0.4 mL, 0.3 g, 3.0 mmol). Stirring was continued for 30 minutes at ambient temperature, then the reaction mixture was

-50-

washed with HCl (50 mL, 2N aq), dried (MgSO₄), and evaporated to dryness
in vacuo (60°C). The residue was purified by flash column chromatography (silica
 gel, eluant 80% EtOAc/heptane) followed by reverse phase column
 chromatography (74% MeOH/26% H₂O). This gave (VIII) (R = CH₂ cyclohexyl)
 5 as a white foam (0.54 g, 83%).

¹H NMR (DMSO-d₆): δ 0.83 (2H, br, cyclohexyl), 1.08-1.72 (21H, m, α-CH₃ +
 (CH₃)₃O + cyclohexyl), 2.78-3.02 (2H, br, CH₂-N), 3.18 (1H, br, CHH indole),

10 3.31 (obscured, CHH indole), 6.40 (1H, br s, OCNH), 6.92 (1H, t, 7.6 Hz,
 indole H), 6.96 (1H, s, indole H), 7.03 (1H, t, 7.6 Hz, indole H), 7.31 (1H, d,
 8.0 Hz, indole H), 7.48 (1H, d, 7.6 Hz, indole H), 7.61 (1H, br, amide NH),
 10.85 (1H, br, indole NH);

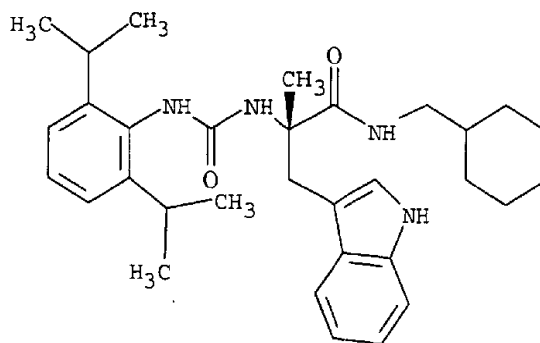
IR (film): 3322, 2922, 1698, 1652, 1519, 1490, and 1455 cm⁻¹; MS m/e (CI)
 15 414 (M⁺ + H);, mp 82-85°C; Analysis C₂₄H₃₅N₃O₃·0.1 H₂O, C, H, N; ;

$\alpha \frac{20}{D} = -29^\circ$ (c = 0.5, MeOH).

Step 3

To a solution of (VIII) (0.14 g, 0.34 mmol) in CH₂Cl₂ (30 mL) was added
 trifluoroacetic acid (0.1 mL, 1.3 mmol), and the reaction was warmed to reflux for
 20 30 minutes, then allowed to cool to ambient temperature. The mixture was taken
 up in EtOAc (100 mL) and washed (Na₂CO₃, 2N aq, 100 mL), dried (MgSO₄),
 and evaporated to dryness *in vacuo* (60°C). Recovered (IX) as a yellow oil
 (109 mg, 103%). This was to fully characterized.

EXAMPLE 11



N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide

5 Example 11 was isolated in 74% yield.

To a stirring solution of (IX) (109 mg, 0.34 mmol) in THF (40 mL) was added 2,6-diisopropyl phenyl isocyanate (0.15 g, 0.7 mmol), and the reaction was heated to reflux for 30 minutes, then allowed to cool to ambient temperature.

Volatiles were removed *in vacuo* (60°C), and the residue was purified by flash column chromatography (silica gel, eluant 50% EtOAc/50% heptane) followed by reverse phase column chromatography (63% acetonitrile/37% water). Recovered Example 11 as a white solid (132 mg, 74%), mp 229-231°C.

¹H NMR (DMSO-d₆): δ 0.50-1.70 (26H, br m, αCH₃ + 2 × (CH₃)₂CH + cyclohexyl), 2.88 (2H, br, CH₂N), 3.10-3.60 (4H, br, 2 × (CH₃)₂CH +

15 CHH indole), 6.45 (1H, br, PhNHCNH), 6.94 (1H, br, indole CH), 7.00-7.80

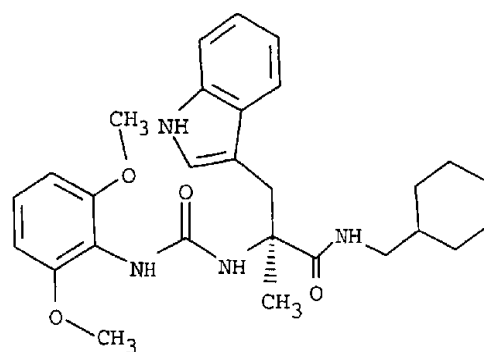
20 (9H, br m, 4 × indole CH + PhNHCNH + amide NH + 3 × aromatic CH), 10.90 (1H, br s, indole NH);

IR (film): 3287, 2925, 1668, and 1519 cm⁻¹;

MS m/e (CI) 517 ($M^+ + H$); Analysis $C_{32}H_{44}N_4O_2$, C, H, N; mp 229-231°C;

$\alpha \frac{20}{D} = 2^\circ$ (c = 0.25, MeOH).

EXAMPLE 17



5 N-Cyclohexylmethyl-2-[3-(2,6-dimethoxy-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide

Example 17 was prepared as for Scheme 5 using cyclohexylmethylamine and 2,6-dimethoxy phenylisocyanate.

Example 17 was isolated as a white amorphous solid (70 mg).

10 1H NMR ($CDCl_3$): δ 0.90 (2H, m), 1.20 (3H, m), 1.30 (2H, m), 1.40 (1H, m), 1.65 (3H, s), 1.70 (2H, m), 2.90 (1H, m), 3.05 and 3.45 (2H, ABq, J = 15 Hz), 3.20 (1H, m), 3.58 (6H, s), 5.20 (1H, s), 5.70 (1H, s), 6.45 (2H, m), 6.82 (1H, s), 6.90 (1H, br s), 7.00 (1H, br s), 7.15 (2H, m), 7.30 (1H, d, J = 6 Hz), 7.45 (1H, d, J = 6 Hz), 8.10 (1H, br s);

15 IR ($CDCl_3$, film): 3306, 3050, 2924, 1668, 1652, 1594, and 1258 cm^{-1} ;

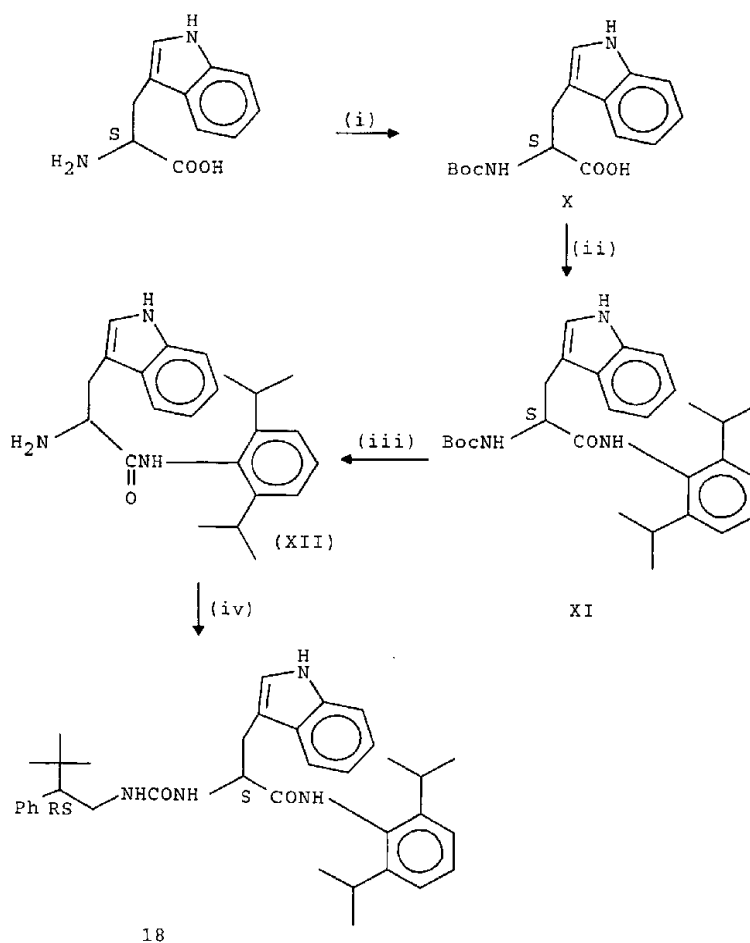
Analysis calculated for $C_{28}H_{36}N_4O_4$:

C, 68.27; H, 7.37; N, 11.37.

Found: C, 68.21; H, 7.55; N, 11.01.

-53-

SCHEME 6



Reagents and Conditions:

- i) Boc_2O , 10% Na_2CO_3 , dioxan
- 5 ii) HBTU, 2,6-diisopropylphenylamine, DIPEA, DMF
- iii) TFA, DCM
- iv) α -t-butyl benzyl isocyanate, THF

Synthesis of Example 18Step 1

To a solution of (S)-tryptophan (5.1 g, 25 mmol) in 10% Na₂CO₃ (aq) (61 mL) and dioxan (150 mL) was added di tertiary butyl dicarbonate (5.67 g, 26 mmol), and the mixture was stirred for 18 hours. The solvent was removed *in vacuo*, and the residue was taken up in water and EtOAc. The mixture was acidified to pH 2-3 and extracted with EtOAc, dried (MgSO₄), and concentrated *in vacuo* to yield X as a white foam (7.6 g, 100%).

¹H NMR (CDCl₃): δ 1.43 (9H, s, C(CH₃)₃), 3.32 (2H, m, CH₂ indole), 4.66 (1H, m, αCH), 5.06 (1H, m, NH), 7.02 (1H, s, ArH), 7.10 (1H, t, ArH), 7.20 (1H, t, ArH), 7.35 (1H, d, 8 Hz, ArH), 7.60 (1H, d, 7.6 Hz, ArH), 8.14 (1H, br s, NH indole).

Step 2

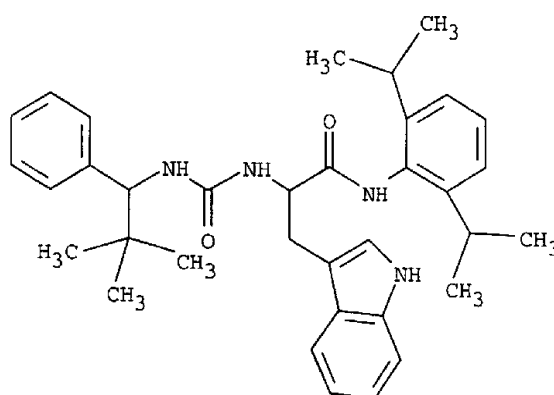
To a mixture of the acid X (3.04 g, 10 mmol), HBTU (3.79 g, 10 mmol), and diisopropyl ethyl amine (3.77 g, 30 mmol) in DMF (100 mL) which had been stirred for 20 minutes was added diisopropyl aniline, and the mixture was stirred for a further 18 hours. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc and washed with ammonium chloride saturated solution, brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on normal phase silica with 2.5% MeOH in DCM to yield XI (1.39 g, 30%).

¹H NMR (CDCl₃): δ 0.98-1.06 (12H, m, [(CH₃)₂CH]₂), 1.46 (9H, s, C(CH₃)₃), 2.7 (2H, m, [CH(CH₃)₂]₂), 3.34 (2H, dd, 3.6 and 8 Hz, CH₂ indole), 4.70 (1H, m, αH), 5.20 (1H, br s, CNH), 7.09-7.27 (7H, m, 6ArH + CNH), 7.39 (1H, d, 8.0 Hz, ArH), 7.75 (1H, d, 8.0 Hz, ArH), 8.10 (1H, s, indole NH); IR (film): 3289.0, 2966.0, 1694.9, 1668.0, 1505.0, 1366.0, 1250.0, 1167.0, 910.0, and 739.0 cm⁻¹; MS m/e (Fab) 464 (M + H⁺); Analysis C₂₈H₃₇N₃O₃, C, H, N; mp 98-100°C.

Step 3

XI (1.0 g, 2.2 mmol) was dissolved in formic acid (30 mL) and stirred for 5 hours. The mixture was basified with dilute sodium hydroxide solution to pH 14 and extracted with EtOAc, dried (MgSO₄), and concentrated *in vacuo* to give XII (745 mg, 95%) as a crude yield which was used without further purification in the next step.

EXAMPLE 18



10 N-(2,6-Diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1H-indol-3-yl)-propionamide

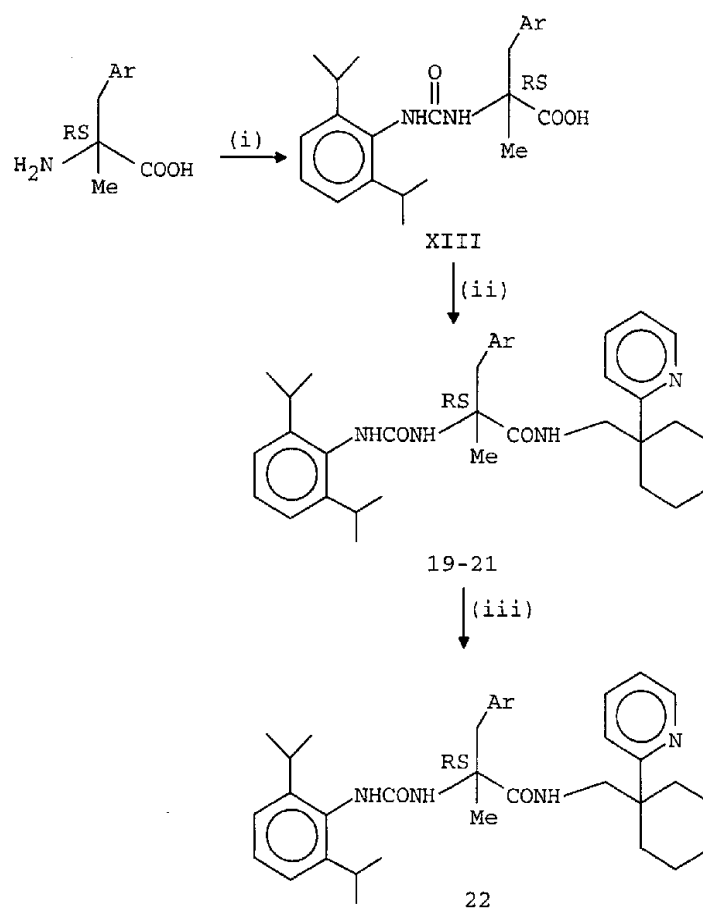
To a solution of the amine XII (51.0 g, 0.14 mmol) in THF (50 mL) was added α -t-butyl benzyl isocyanate (27 mg, 0.14 mmol), and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography using 1:1 EtOAc/heptane as eluant to yield 18 as a white solid (>7 mg, >10%).

¹H NMR (CDCl₃): δ 0.81 and 0.85 (9H, 2 \times s, t-butyl), 0.93 (6H, d, 7.20 Hz, (CH₃)₂CH), 1.02 (6H, d, 6.8 Hz, (CH₃)₂CH), 2.58-2.68 (2H, m, [(CH₃)₂CH]₂), 3.2-3.7 (2H, m, CH₂ indole), 4.40-4.50 (1H, m, α H), 4.8-5.5 (3H, m,

-56-

$\begin{array}{c} \text{O} \\ \parallel \\ \text{CNH} \times 2 \text{ and PhCH}(\text{CH}_3)_3, \end{array}$ 6.7-6.8 (1H, m, CNH), 7.0-7.26 (11H, m, 11ArH),
7.4 and 7.44 (1H, 2 \times d, ArH), 7.65-7.75 (1H, m, 1ArH), 7.85 and 7.05 (1H,
5 2 \times br s, indole NH); IR (film): 3387.7, 3296.8, 1653.8, 1663.3, and 1552.8 cm^{-1} ;
Analysis $\text{C}_{35}\text{H}_{44}\text{N}_4\text{O}_2$, C, H, N; mp 160-161°C.

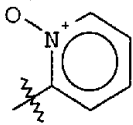
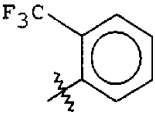
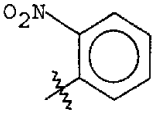
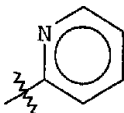
SCHEME 7



Reagents and Conditions:

- 5 i) 2,6-diisopropyl phenyl isocyanate, DMF, 60°C
 ii) Intermediate II, HBTU, DIPEA, DMF
 iii) Pd/C, H₂, EtOH

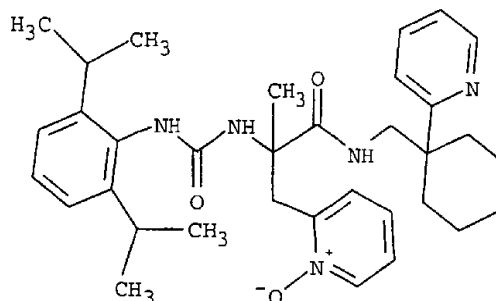
Table for Scheme 7

| Example No. | Ar |
|-------------|--|
| 19 |  |
| 20 |  |
| 21 |  |
| 22 |  |

Synthesis of Example 19Step 1

- 5 To a suspension of the racemic amino acid (500 mg) in THF (10 mL) was added NEt₃ (244 mg) followed by the isocyanate (250 mg). The reaction mixture was refluxed for 4 days, evaporated to dryness, and the residue partitioned between EtOAc and 0.1 M HCl to yield the crude acid XIII (Ar = 2-pyridine-N-oxide) as a yellow gum (405 mg). The compound was taken without purification onto the next step.

EXAMPLE 19



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-(1-oxo-pyridin-2-yl)-
N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

5 To a solution of the acid XIII (Ar = 2-pyridine-N-oxide) (200 mg), HBTU (198 mg) and Intermediate II (100 mg) in DMF (3 mL) was added DIPEA (135 mg). The reaction mixture was stirred at room temperature for 2 days, evaporated to dryness, and the residue partitioned between EtOAc/H₂O to yield the crude product as a yellow gum. This was then purified by column chromatography
10 to yield Example 19 as a white amorphous solid (195 mg).

¹H NMR (CDCl₃): δ 0.95 (2H, br s), 1.05 (2H, br s), 1.20-1.60 (8H, m), 1.70 (3H, br s), 2.20 (2H, m), 3.10-3.50 (4H, m), 5.50 (1H, s), 7.00-7.20 (5H, m), 7.40 (3H, m), 7.60 (2H, m), 7.80 (1H, br s), 8.60 (1H, s);

IR (CDCl₃, film): 3253, 3050, 2931, 1667, 1661, 1531, and 1441 cm⁻¹;

15 Analysis for C₃₄H₄₅N₅O₃•0.5 CH₂Cl₂:

Calculated: C, 67.47; H, 7.55; N, 11.40.

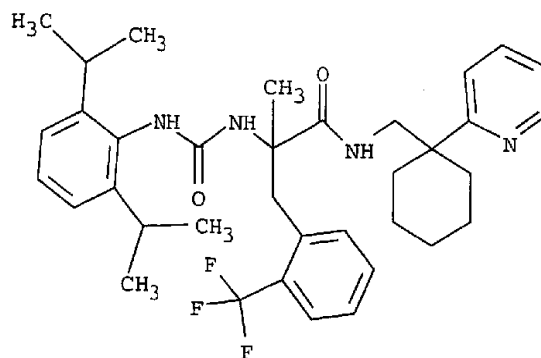
Found: C, 67.89; H, 7.58; N, 11.63.

Synthesis of Example 20

Step 1

20 As for Step 1 in synthesis of Example 19, yield of XIII (Ar = 2-trifluoromethyl phenyl) was 280 mg. Used without purification in the next step.

EXAMPLE 20



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-3-(2-trifluoromethyl-phenyl)-propionamide

5 As for Step 2 in synthesis of Example 19, yield of Example 20 was 100 mg (amorphous solid).

¹H NMR (CDCl₃): δ 0.90 (2H, br s), 1.10 (12H, br s), 1.30-1.60 (8H, m), 1.55 (3H, s), 2.00 (2H, m), 3.10 (1H, br s), 3.30-3.50 (3H, m), 5.10 (1H, s), 5.50 (1H, s), 7.10-7.30 (9H, m), 7.50 (1H, d, J = 8 Hz), 7.65 (1H, t, J = 7 Hz), 8.50 (1H, d, J = 2 Hz);

10 IR (CDCl₃, film): 3334, 3050, 2932, 1668, 1651, 1538, and 1311 cm⁻¹;

Analysis for C₃₆H₄₅F₃N₄O₂:

Calculated: C, 69.43; H, 7.28; N, 8.99.

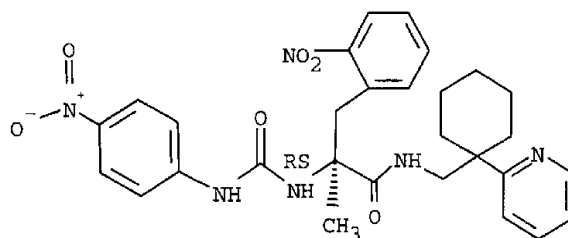
Found: C, 69.43; H, 7.38; N, 8.70.

15 Synthesis of Example 21

Step 1

As for Step 1 in synthesis of Example 19, yield of XIII (Ar = 2-nitrophenyl) was 450 mg. Used without purification in the next step.

EXAMPLE 21



2-Methyl-3-(2-nitro-phenyl)-2-[3-(4-nitro-phenyl)-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

5 As for Step 2 in synthesis of Example 19, yield of Example 21 was 80 mg (amorphous white solid).

¹H NMR (CDCl₃): δ 0.90 (2H, br s), 1.10 (12H, br s), 1.30-1.50 (8H, m),
1.60 (3H, s), 2.10 (2H, m), 3.10 (1H, m), 3.30-3.60 (3H, m), 5.50 (2H, br s),
7.10 (4H, m), 7.30 (3H, m), 7.35 (2H, d, J = 8 Hz), 7.65 (2H, m), 8.60 (1H, d,
10 J = 2 Hz);

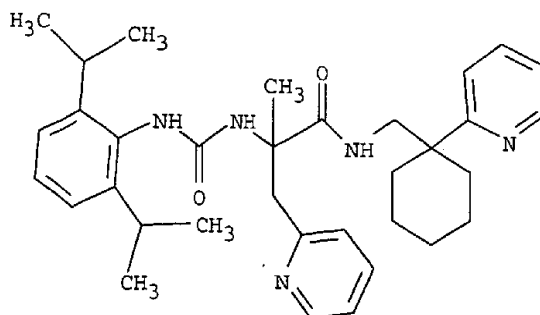
IR (CDCl₃, film): 3335, 3050, 2931, 1667, 1651, 1527, and 1351 cm⁻¹;

Analysis for C₃₅H₄₅N₅O₄•0.2 heptane:

Calculated: C, 70.53; H, 7.84; N, 11.30.

Found: C, 70.92; H, 7.91; N, 11.06.

EXAMPLE 22



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-pyridin-2-yl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

5 To a solution of the N-oxide 19 (153 mg, 0.27 mmol) in ethanol (50 mL) was added 10% Palladium on Carbon, and the reaction mixture was shaken on a Parr hydrogenation apparatus under 55 psi of hydrogen at 35°C for 20 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was purified on normal phase silica eluting with a gradient of
10 heptane to 1:1 heptane:EtOAc to yield 22 (24.9 mg, 16.7%).

¹H NMR (CDCl₃): δ 0.99-1.05 (6H, m, (CH₃)₂CH), 1.05-1.20 (6H, m, (CH₃)₂CH), 1.31-1.69 (8H, m, cyclohexyl), 1.56 (3H, s, αCH₃), 2.12-2.21 (2H, m, cyclohexyl), 2.72-2.75 (1H, m, (CH₃)CH), 3.10-3.20 (3H, m, pyridyl CH₂,

15 (CH₃)₂CH), 3.40 (1H, dd, 13.43 and 5.86 Hz, CNHCHH), 3.53 (1H, dd, 13.43,

6.35 Hz, CNHCHH), 5.46 (1H, s, PhNHCNH), 6.92 (1H, br t, 5.13 Hz,

20 CNH-amide), 7.08-7.12 3H, m, 3ArH), 7.22-7.26 (2H, br s, PhNHCNH, ArH), 7.27-7.48 (4H, m, 4ArH), 7.62-7.66 (2H, m, 2ArH), 8.60-8.62 (1H, m, ArH);

IR (film): 3278.0, 2929.0, 1668.0, 1590.0, 1520.0, 1471.0, and 1208.0 cm^{-1} ; MS

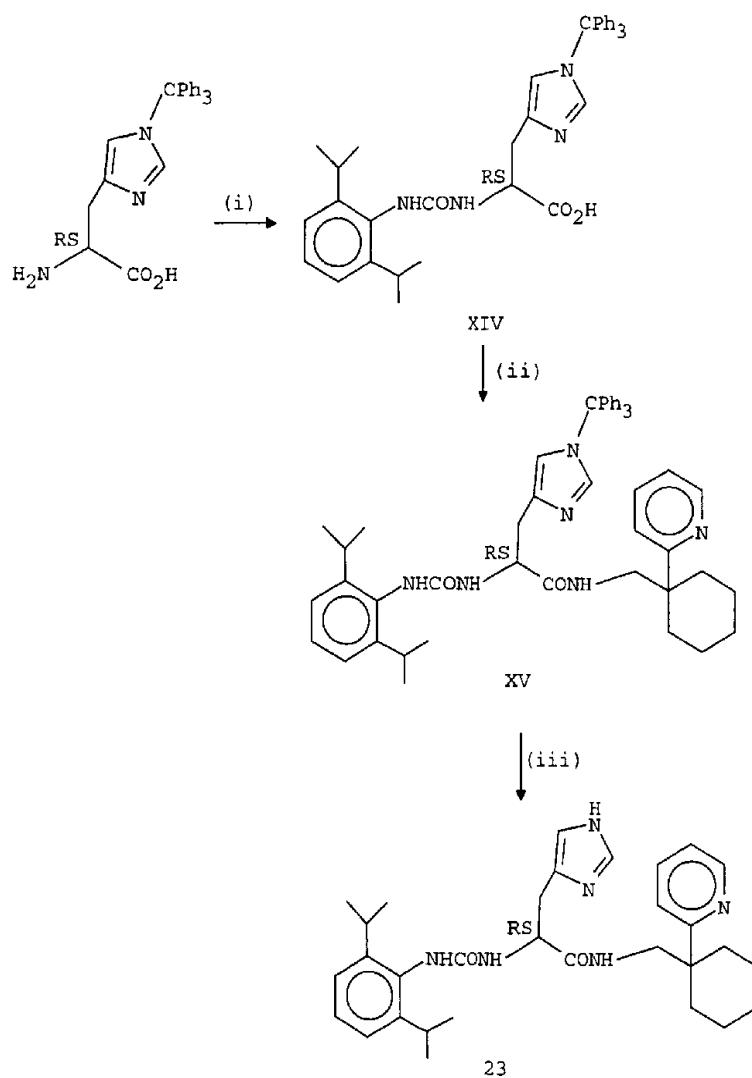
m/e (APCI) 556.0 ($\text{M} + \text{H}^+$); Analysis $\text{C}_{34}\text{H}_{45}\text{N}_5\text{O}_2 \cdot 0.25 \text{H}_2\text{O}$, C, H, N;

mp 185-186°C; HPLC R.T. = 6.16, C^{18} reverse phase, 40% to 100%

MeCN:TFA/ H_2O :TFA.

-64-

SCHEME 8



Reagents and Conditions:

- 5 i) 2,6-Diisopropyl phenyl isocyanate, DMF, 60°C
 ii) Intermediate II, HBTU, DIPEA, DMF
 iii) Formic acid, DCM

Synthesis of Example 23Step 1

To a mixture of N-trityl histidine (0.99 g, 2.5 mmol) in THF (70 mL) and DMF (20 mL) was added pyridine (396 mg, 5 mmol) followed by diisopropyl phenyl isocyanate (1.02 g, 5 mmol), and the mixture was refluxed for 1.5 hours. The reaction mixture was allowed to cool to room temperature before being taken up in EtOAc and washed with 1N HCl (aq), dried (MgSO₄), and concentrated *in vacuo*. The residue was used crude for the next step (2.20 g, 100%) XIV.

Step 2

To a solution of the acid XIV (500 mg, 0.81 mmol) in DMF (50 mL) was added HBTU (309 mg, 0.81 mmol) and diisopropyl ethyl amine (316 mg, 2.43 mmol), and the mixture was stirred for 5 minutes. The amine II (155 mg, 0.81 mmol) was then added to the reaction mixture which was then stirred for a further 2 hours. The mixture was taken up in EtOAc and washed with NaHCO₃ (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on normal phase silica eluting with a gradient of heptane:EtOAc 1:1 to EtOAc and then repurified on reverse phase silica eluting with MeOH to yield pure XV (120 mg, 7.8%).

¹H NMR (CDCl₃): δ 0.90-1.64 (20H, 4 × m, [(CH₃)₂CH]₂ and cyclohexyl -8H), 2.05-2.18 (2H, m, cyclohexyl), 2.60-2.70 (1H, m, (CH₃)₂CH), 2.96 (1H, dd,

14.65 and 4.39 Hz, indole CH), 3.35 (1H, dd, 5.86 and 13.19 Hz, CNHCH),

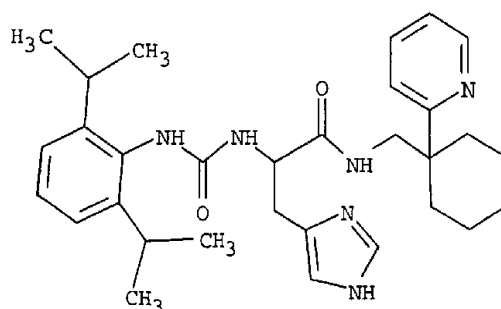
3.45 (1H, dd, 6.35 and 13.43 Hz, CNHCH), 3.0-3.25 (2H, m, CH indole and

(CH₃)₂CH), 4.47 (1H, m, 5.58-5.65 (1H, m, CNH), 6.05-6.15 (1H, m, CNH),

-66-

6.5 (1H, s, $\text{PhNH}\overset{\text{O}}{\parallel}\text{CNH}$), 6.85-7.04 (1H, m, 1ArH), 7.03 (8H, t, 1.46 Hz, 8ArH),
 7.11 (2H, d, 7.82 Hz, 2ArH), 7.20-7.38 (14H, m, 14ArH), 7.57 (1H, td, 1.71 and
 5 7.81 Hz, ArH), 8.53 (1H, d, 3.17 Hz, pyridyl H).

EXAMPLE 23



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-imidazol-4-yl)-N-(1-pyridin-2-yl-
 cyclohexylmethyl)-propionamide

10 A mixture of XV (120 mg, 0.15 mmol) in formic acid (5 mL) and DCM
 (50 mL) was stirred at room temperature for 24 hours. The solvents were removed
in vacuo, and the residue was taken up in water (50 mL) and washed with EtOAc.
 The aqueous layer was concentrated *in vacuo* at below 40°C, and the residue was
 taken up in DCM and ether and concentrated *in vacuo* to obtain 23 as a solid
 15 (57.8 mg, 65.4%).

^1H NMR (DMSO): δ 1.05-1.60 (8H, m, cyclohexyl), 1.06 (12H, d, 6.84 Hz,

20 $[(\text{CH}_3)_2\text{CH}]_2$), 2.10-2.13 (2H, m, cyclohexyl), 2.67-2.72 (1H, m, CNHCHH),
 2.80-2.98 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.0-3.16 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.18-3.21 (1H, m,
 CNHCHH), 3.31-3.41 (2H, obscured by water peak, CHH imidazole),

-67-

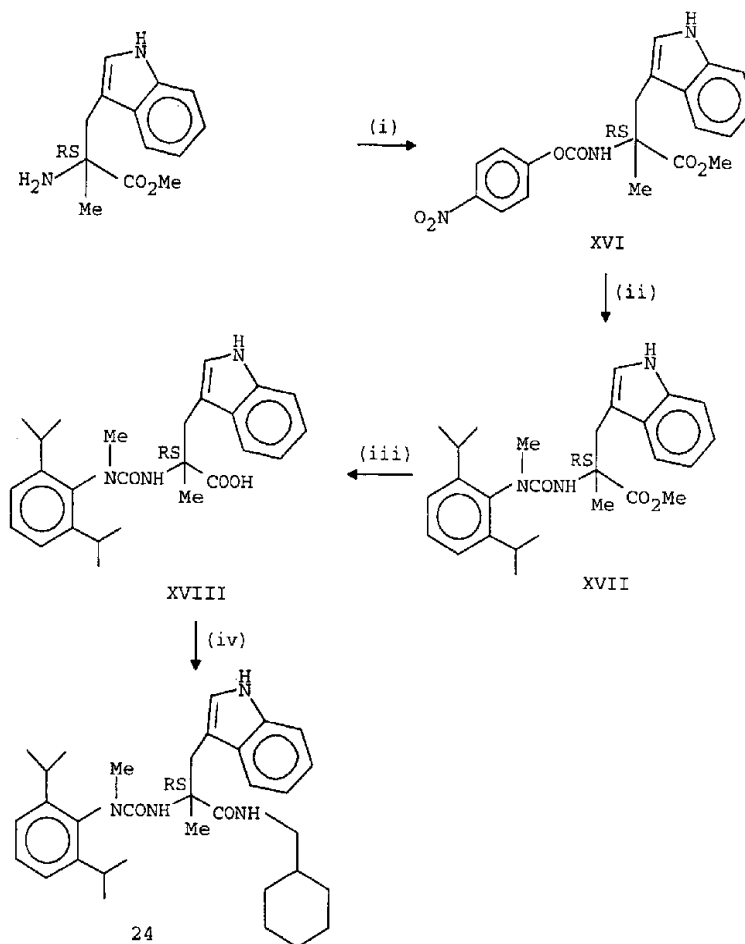
4.384.42 (1H, m, aH), 6.43 (1H, br s, CNH), 6.77 (1H, br s, CNH), 7.08 (2H, d, 7.32 Hz, 2ArH), 7.18-7.21 (2H, m, 2ArH), 7.34 (1H, d, 8.06 Hz, 1ArH),

5

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{7.52-7.69 (2H, m \times 2, CNH, 1ArH)}, 7.71 (1\text{H, t, } 7.81 \text{ Hz, 1ArH)}, 8.56 (1\text{H, d, } \\ 4.15 \text{ Hz, ArH)}, 12.00 (1\text{h, br s, indole NH}); \end{array}$$
 IR (film): 3291.0, 2929.0, 1733.0, 1645.0, 1589.0, 1539.0, 1471.0, 1362.0, and
 10
 1238.0 cm^{-1} ; MS m/e (E1+) 530 (M^+) 531 ($\text{M} + \text{H}^+$);
 Analysis for $\text{C}_{31}\text{H}_{42}\text{N}_6\text{O}_2 \cdot 0.7 \text{ HCOOH}$; mp 114-116°C; HPLC R.T. = 17.045 and
 17.36, C^{18} reverse phase 10% to 80% MeCN:TFA/ H_2O :TFA.

-68-

SCHEME 9



Reagents and Conditions:

- i) P-nitrophenyl chloroformate, NEt_3 , THF
- 5 ii) 2,6-Diisopropyl phenyl N methyl amine, NEt_3 , toluene, Δ
- iii) LiOH , H_2O , MeOH , Δ
- iv) HBTU, cyclohexyl methyl amine, DIPEA, DMF

Synthesis of Example 24Step 1

To a cooled (0°C) solution of α -Me (R,S) tryptophan methyl ester (2 g, 8.6 mmol) in dry THF (100 mL) was added dropwise p-nitro phenyl chloroformate (1.74 g, 8.6 mmol) followed by triethyl amine (1.2 mL, 8.6 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 2 hours. The solution was then taken up in EtOAc and washed with 1N HCl (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified on normal phase silica with a gradient of heptane to 7:3 heptane/EtOAc as eluent to yield XVI (1.85 g, 54%) which was used without further purification in the next step.

Step 2

To a solution of the carbamate XVI (318 mg, 0.8 mmol) in toluene (60 mL) was added N-methyl diisopropyl aniline (XX) (153 mg, 0.8 mmol) followed by triethyl amine (1 mL), and the mixture was refluxed for 9 hours. The mixture was taken up in EtOAc and washed with 1N HCl (aq), brine, NaHCO₃ (aq), dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by normal phase chromatography eluting with a gradient of heptane to 6:4 heptane/EtOAc to yield pure XVII (213 mg, 59.2%).

¹H NMR (CDCl₃): δ 0.77, 0.86, 1.10, 1.14 (12H, 4 \times d, 6.84, 6.59, 7.08, 6.84 Hz, respectively, [(CH₃)₂CH]₂), 1.68 (3H, s, α -CH₃), 2.86 (1H, qⁿ, 6.84 Hz, (CH₃)₂CH), 2.98 (1H, qⁿ, 6.84 Hz, (CH₃)₂CH), 3.03 (1H, d, 14.40 Hz, CHH indole), 3.08 (3H, s, N-CH₃), 3.13 (1H, d, 14.40 Hz, CHH indole), 3.63 (3H, s, CO₂CH₃), 4.68

¹³C NMR (CDCl₃): δ 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 21.0, 21.1, 21.2, 21.3, 21.4, 21.5, 21.6, 21.7, 21.8, 21.9, 22.0, 22.1, 22.2, 22.3, 22.4, 22.5, 22.6, 22.7, 22.8, 22.9, 23.0, 23.1, 23.2, 23.3, 23.4, 23.5, 23.6, 23.7, 23.8, 23.9, 24.0, 24.1, 24.2, 24.3, 24.4, 24.5, 24.6, 24.7, 24.8, 24.9, 25.0, 25.1, 25.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 25.9, 26.0, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, 28.0, 28.1, 28.2, 28.3, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4, 31.5, 31.6, 31.7, 31.8, 31.9, 32.0, 32.1, 32.2, 32.3, 32.4, 32.5, 32.6, 32.7, 32.8, 32.9, 33.0, 33.1, 33.2, 33.3, 33.4, 33.5, 33.6, 33.7, 33.8, 33.9, 34.0, 34.1, 34.2, 34.3, 34.4, 34.5, 34.6, 34.7, 34.8, 34.9, 35.0, 35.1, 35.2, 35.3, 35.4, 35.5, 35.6, 35.7, 35.8, 35.9, 36.0, 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, 36.9, 37.0, 37.1, 37.2, 37.3, 37.4, 37.5, 37.6, 37.7, 37.8, 37.9, 38.0, 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, 39.0, 39.1, 39.2, 39.3, 39.4, 39.5, 39.6, 39.7, 39.8, 39.9, 40.0, 40.1, 40.2, 40.3, 40.4, 40.5, 40.6, 40.7, 40.8, 40.9, 41.0, 41.1, 41.2, 41.3, 41.4, 41.5, 41.6, 41.7, 41.8, 41.9, 42.0, 42.1, 42.2, 42.3, 42.4, 42.5, 42.6, 42.7, 42.8, 42.9, 43.0, 43.1, 43.2, 43.3, 43.4, 43.5, 43.6, 43.7, 43.8, 43.9, 44.0, 44.1, 44.2, 44.3, 44.4, 44.5, 44.6, 44.7, 44.8, 44.9, 45.0, 45.1, 45.2, 45.3, 45.4, 45.5, 45.6, 45.7, 45.8, 45.9, 46.0, 46.1, 46.2, 46.3, 46.4, 46.5, 46.6, 46.7, 46.8, 46.9, 47.0, 47.1, 47.2, 47.3, 47.4, 47.5, 47.6, 47.7, 47.8, 47.9, 48.0, 48.1, 48.2, 48.3, 48.4, 48.5, 48.6, 48.7, 48.8, 48.9, 49.0, 49.1, 49.2, 49.3, 49.4, 49.5, 49.6, 49.7, 49.8, 49.9, 50.0, 50.1, 50.2, 50.3, 50.4, 50.5, 50.6, 50.7, 50.8, 50.9, 51.0, 51.1, 51.2, 51.3, 51.4, 51.5, 51.6, 51.7, 51.8, 51.9, 52.0, 52.1, 52.2, 52.3, 52.4, 52.5, 52.6, 52.7, 52.8, 52.9, 53.0, 53.1, 53.2, 53.3, 53.4, 53.5, 53.6, 53.7, 53.8, 53.9, 54.0, 54.1, 54.2, 54.3, 54.4, 54.5, 54.6, 54.7, 54.8, 54.9, 55.0, 55.1, 55.2, 55.3, 55.4, 55.5, 55.6, 55.7, 55.8, 55.9, 56.0, 56.1, 56.2, 56.3, 56.4, 56.5, 56.6, 56.7, 56.8, 56.9, 57.0, 57.1, 57.2, 57.3, 57.4, 57.5, 57.6, 57.7, 57.8, 57.9, 58.0, 58.1, 58.2, 58.3, 58.4, 58.5, 58.6, 58.7, 58.8, 58.9, 59.0, 59.1, 59.2, 59.3, 59.4, 59.5, 59.6, 59.7, 59.8, 59.9, 60.0, 60.1, 60.2, 60.3, 60.4, 60.5, 60.6, 60.7, 60.8, 60.9, 61.0, 61.1, 61.2, 61.3, 61.4, 61.5, 61.6, 61.7, 61.8, 61.9, 62.0, 62.1, 62.2, 62.3, 62.4, 62.5, 62.6, 62.7, 62.8, 62.9, 63.0, 63.1, 63.2, 63.3, 63.4, 63.5, 63.6, 63.7, 63.8, 63.9, 64.0, 64.1, 64.2, 64.3, 64.4, 64.5, 64.6, 64.7, 64.8, 64.9, 65.0, 65.1, 65.2, 65.3, 65.4, 65.5, 65.6, 65.7, 65.8, 65.9, 66.0, 66.1, 66.2, 66.3, 66.4, 66.5, 66.6, 66.7, 66.8, 66.9, 67.0, 67.1, 67.2, 67.3, 67.4, 67.5, 67.6, 67.7, 67.8, 67.9, 68.0, 68.1, 68.2, 68.3, 68.4, 68.5, 68.6, 68.7, 68.8, 68.9, 69.0, 69.1, 69.2, 69.3, 69.4, 69.5, 69.6, 69.7, 69.8, 69.9, 70.0, 70.1, 70.2, 70.3, 70.4, 70.5, 70.6, 70.7, 70.8, 70.9, 71.0, 71.1, 71.2, 71.3, 71.4, 71.5, 71.6, 71.7, 71.8, 71.9, 72.0, 72.1, 72.2, 72.3, 72.4, 72.5, 72.6, 72.7, 72.8, 72.9, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6, 73.7, 73.8, 73.9, 74.0, 74.1, 74.2, 74.3, 74.4, 74.5, 74.6, 74.7, 74.8, 74.9, 75.0, 75.1, 75.2, 75.3, 75.4, 75.5, 75.6, 75.7, 75.8, 75.9, 76.0, 76.1, 76.2, 76.3, 76.4, 76.5, 76.6, 76.7, 76.8, 76.9, 77.0, 77.1, 77.2, 77.3, 77.4, 77.5, 77.6, 77.7, 77.8, 77.9, 78.0, 78.1, 78.2, 78.3, 78.4, 78.5, 78.6, 78.7, 78.8, 78.9, 79.0, 79.1, 79.2, 79.3, 79.4, 79.5, 79.6, 79.7, 79.8, 79.9, 80.0, 80.1, 80.2, 80.3, 80.4, 80.5, 80.6, 80.7, 80.8, 80.9, 81.0, 81.1, 81.2, 81.3, 81.4, 81.5, 81.6, 81.7, 81.8, 81.9, 82.0, 82.1, 82.2, 82.3, 82.4, 82.5, 82.6, 82.7, 82.8, 82.9, 83.0, 83.1, 83.2, 83.3, 83.4, 83.5, 83.6, 83.7, 83.8, 83.9, 84.0, 84.1, 84.2, 84.3, 84.4, 84.5, 84.6, 84.7, 84.8, 84.9, 85.0, 85.1, 85.2, 85.3, 85.4, 85.5, 85.6, 85.7, 85.8, 85.9, 86.0, 86.1, 86.2, 86.3, 86.4, 86.5, 86.6, 86.7, 86.8, 86.9, 87.0, 87.1, 87.2, 87.3, 87.4, 87.5, 87.6, 87.7, 87.8, 87.9, 88.0, 88.1, 88.2, 88.3, 88.4, 88.5, 88.6, 88.7, 88.8, 88.9, 89.0, 89.1, 89.2, 89.3, 89.4, 89.5, 89.6, 89.7, 89.8, 89.9, 90.0, 90.1, 90.2, 90.3, 90.4, 90.5, 90.6, 90.7, 90.8, 90.9, 91.0, 91.1, 91.2, 91.3, 91.4, 91.5, 91.6, 91.7, 91.8, 91.9, 92.0, 92.1, 92.2, 92.3, 92.4, 92.5, 92.6, 92.7, 92.8, 92.9, 93.0, 93.1, 93.2, 93.3, 93.4, 93.5, 93.6, 93.7, 93.8, 93.9, 94.0, 94.1, 94.2, 94.3, 94.4, 94.5, 94.6, 94.7, 94.8, 94.9, 95.0, 95.1, 95.2, 95.3, 95.4, 95.5, 95.6, 95.7, 95.8, 95.9, 96.0, 96.1, 96.2, 96.3, 96.4, 96.5, 96.6, 96.7, 96.8, 96.9, 97.0, 97.1, 97.2, 97.3, 97.4, 97.5, 97.6, 97.7, 97.8, 97.9, 98.0, 98.1, 98.2, 98.3, 98.4, 98.5, 98.6, 98.7, 98.8, 98.9, 99.0, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9, 100.0, 100.1, 100.2, 100.3, 100.4, 100.5, 100.6, 100.7, 100.8, 100.9, 101.0, 101.1, 101.2, 101.3, 101.4, 101.5, 101.6, 101.7, 101.8, 101.9, 102.0, 102.1, 102.2, 102.3, 102.4, 102.5, 102.6, 102.7, 102.8, 102.9, 103.0, 103.1, 103.2, 103.3, 103.4, 103.5, 103.6, 103.7, 103.8, 103.9, 104.0, 104.1, 104.2, 104.3, 104.4, 104.5, 104.6, 104.7, 104.8, 104.9, 105.0, 105.1, 105.2, 105.3, 105.4, 105.5, 105.6, 105.7, 105.8, 105.9, 106.0, 106.1, 106.2, 106.3, 106.4, 106.5, 106.6, 106.7, 106.8, 106.9, 107.0, 107.1, 107.2, 107.3, 107.4, 107.5, 107.6, 107.7, 107.8, 107.9, 108.0, 108.1, 108.2, 108.3, 108.4, 108.5, 108.6, 108.7, 108.8, 108.9, 109.0, 109.1, 109.2, 109.3, 109.4, 109.5, 109.6, 109.7, 109.8, 109.9, 110.0, 110.1, 110.2, 110.3, 110.4, 110.5, 110.6, 110.7, 110.8, 110.9, 111.0, 111.1, 111.2, 111.3, 111.4, 111.5, 111.6, 111.7, 111.8, 111.9, 112.0, 112.1, 112.2, 112.3, 112.4, 112.5, 112.6, 112.7, 112.8, 112.9, 113.0, 113.1, 113.2, 113.3, 113.4, 113.5, 113.6, 113.7, 113.8, 113.9, 114.0, 114.1, 114.2, 114.3, 114.4, 114.5, 114.6, 114.7, 114.8, 114.9, 115.0, 115.1, 115.2, 115.3, 115.4, 115.5, 115.6, 115.7, 115.8, 115.9, 116.0, 116.1, 116.2, 116.3, 116.4, 116.5, 116.6, 116.7, 116.8, 116.9, 117.0, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.8, 117.9, 118.0, 118.1, 118.2, 118.3, 118.4, 118.5, 118.6, 118.7, 118.8, 118.9, 119.0, 119.1, 119.2, 119.3, 119.4, 119.5, 119.6, 119.7, 119.8, 119.9, 120.0, 120.1, 120.2, 120.3, 120.4, 120.5, 120.6, 120.7, 120.8, 120.9, 121.0, 121.1, 121.2, 121.3, 121.4, 121.5, 121.6, 121.7, 121.8, 121.9, 122.0, 122.1, 122.2, 122.3, 122.4, 122.5, 122.6, 122.7, 122.8, 122.9, 123.0, 123.1, 123.2, 123.3, 123.4, 123.5, 123.6, 123.7, 123.8, 123.9, 124.0, 124.1, 124.2, 124.3, 124.4, 124.5, 124.6, 124.7, 124.8, 124.9, 125.0, 125.1, 125.2, 125.3, 125.4, 125.5, 125.6, 125.7, 125.8, 125.9, 126.0, 126.1, 126.2, 126.3, 126.4, 126.5, 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.1, 130.2, 130.3, 130.4, 130.5, 130.6, 130.7, 130.8, 130.9, 131.0, 131.1, 131.2, 131.3, 131.4, 131.5, 131.6, 131.7, 131.8, 131.9, 132.0, 132.1, 132.2, 132.3, 132.4, 132.5, 132.6, 132.7, 132.8, 132.9, 133.0, 133.1, 133.2, 133.3, 133.4, 133.5, 133.6, 133.7, 133.8, 133.9, 134.0, 134.1, 134.2, 134.3, 134.4, 134.5, 134.6, 134.7, 134.8, 134.9, 135.0, 135.1, 135.2, 135.3, 135.4, 135.5, 135.6, 135.7, 135.8, 135.9, 136.0, 136.1, 136.2, 136.3, 136.4, 136.5, 136.6, 136.7, 136.8, 136.9, 137.0, 137.1, 137.2, 137.3, 137.4, 137.5, 137.6, 137.7, 137.8, 137.9, 138.0, 138.1, 138.2, 138.3, 138.4, 138.5, 138.6, 138.7, 138.8, 138.9, 139.0, 139.1, 139.2, 139.3, 139.4, 139.5, 139.6, 139.7, 139.8, 139.9, 140.0, 140.1, 140.2, 140.3, 140.4, 140.5, 140.6, 140.7, 140.8, 140.9, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.7, 141.8, 141.9, 142.0, 142.1, 142.2, 142.3, 142.4, 142.5, 142.6, 142.7, 142.8, 142.9, 143.0, 143.1, 143.2, 143.3, 143.4, 143.5, 143.6, 143.7, 143.8, 143.9, 144.0, 144.1, 144.2, 144.3, 144.4, 144.5, 144.6, 144.7, 144.8, 144.9, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.7, 145.8, 145.9, 146.0, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.0, 147.1, 147.2, 147.3, 147.4, 147.5, 147.6, 147.7, 147.8, 147.9, 148.0, 148.1, 148.2, 148.3, 148.4, 148.5, 148.6, 148.7, 148.8, 148.9, 149.0, 149.1, 149.2, 149.3, 149.4, 149.5, 149.6, 149.7, 149.8, 149.9, 150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.6, 150.7, 150.8, 150.9, 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.7, 151.8, 151.9, 152.0, 152.1, 152.2, 152.3, 152.4, 152.5, 152.6, 152.7, 152.8, 152.9, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 154.2, 154.3, 154.4, 154.5, 154.6, 154.7, 154.8, 154.9, 155.0, 155.1, 155.2, 155.3, 155.4, 155.5, 155.6, 155.7, 155.8, 155.9, 156.0, 156.1, 156.2, 156.3, 156.4, 156.5, 156.6, 156.7, 156.8, 156.9, 157.0, 157.1, 157.2, 157.3, 157.4, 157.5, 157.6, 157.7, 157.8, 157.9, 158.0, 158.1, 158.2, 158.3, 158.4, 158.5, 158.6, 158.7, 158.8, 158.9, 159.0, 159.1, 159.2, 159.3, 159.4, 159.5, 159.6, 159.7, 159.8, 159.9, 160.0, 160.1, 160.2, 160.3, 160.4, 160.5, 160.6, 160.7, 160.8, 160.9, 161.0, 161.1, 161.2, 161.3, 161.4, 161.5, 161.6, 161.7, 161.8, 161.9, 162.0, 162.1, 162.2, 162.3, 162.4, 162.5, 162.6, 162.7, 162.8, 162.9, 163.0, 163.1, 163.2, 163.3, 163.4, 163.5, 163.6, 163.7, 163.8, 163.9, 164.0, 164.1, 164.2, 164.3, 164.4, 164.5, 164.6, 164.7, 164.8, 164.9, 165.0, 165.1, 165.2, 165.3, 165.4, 165.5, 165.6, 165.7, 165.8, 165.9, 166.0, 166.1, 166.2, 166.3, 166.4, 166.5, 166.6, 166.7, 166.8, 166.9, 167.0, 167.1, 167.2, 167.3, 167.4, 167.5, 167.6, 167.7, 167.8, 167.9, 168.0, 168.1, 168.2, 168.3, 168.4, 168.5, 168.6, 168.7, 168.8, 168.9, 169.0, 169.1, 169.2, 169.3, 169.4, 169.5, 169.6, 169.7, 169.8, 169.9, 170.0, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 170.8, 170.9, 171.0, 171.1, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172.0, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 173.0, 173.1, 173.2, 173.3, 173.4, 173.5, 173.6, 173.7, 173.8, 173.9, 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.7, 174.8, 174.9, 175.0, 175.1, 175.2, 175.3, 175.4, 175.5, 175.6, 175.7, 175.8, 175.9, 176.0, 176.1, 176.2, 176.3, 176.4, 176.5, 176.6, 176.7, 176.8, 176.9, 177.0, 177.1, 177.2, 177.3, 177.4, 177.5, 177.6, 177.7, 177.8, 177.9, 178.0, 178.1, 178.2, 178.3, 178.4, 178.5, 178.6, 178.7, 178.8, 178.9, 179.0, 179.1, 179.2, 179.3, 179.4, 179.5, 179.6, 179.7, 179.8, 179.9, 180.0, 180.1, 180.2, 180.3, 180.4, 180.5, 180.6, 180.7, 180.8, 180.9, 181.0, 181.1, 181.2, 181.3, 181.4, 181.5, 181.6, 181.7, 181.8, 181.9, 182.0, 182.1, 182.2, 182.3, 182.4, 182.5, 182.6, 182.7, 182.8, 182.9, 183.0, 183.1, 183.2, 183.3, 183.4, 183.5, 183.6, 183.7, 183.8, 183.9, 184.0, 184.1, 184.2, 184.3, 184.4, 184.5, 184.6, 184.7, 184.8, 184.9, 185.0, 185.1, 185.2, 185.3, 185.4, 185.5, 185.6, 185.7, 185.8, 185.9, 186.0, 186.1, 186.2, 186.3, 186.4, 186.5, 186.6, 186.7, 186.8, 186.9, 187.0, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187

Step 3

To a solution of the ester XVII (151.6 mg, 0.34 mmol) in THF (20 mL) was added lithium hydroxide (529 mg, 12.6 mmol) as a solution in water (30 mL) followed by methanol (10 mL), and the reaction mixture was refluxed for 7 hours.

5 The mixture was concentrated *in vacuo* to remove only the organic solvents, and the aqueous mixture remaining was extracted with ether. The aqueous layer was acidified to pH 1 with HCl (aq) and re-extracted with EtOAc, dried (MgSO₄), and concentrated *in vacuo* to yield pure acid XVIII (105 mg, 71%).

¹H NMR (CDCl₃): δ 0.69 (3H, d, 6.84 Hz, CH₃CH), 0.82 (3H, d, 6.84 Hz, CH₃CH), 1.09 (3H, d, 6.84 Hz, CH₃CH), 1.13 (3H, d, 6.84 Hz, CH₃CH), 1.65 (3H, s, αCH₃), 2.72 (1H, qⁿ, 7.08 Hz, (CH₃)₂CH), 2.79 (1H, qⁿ, 6.59 Hz, (CH₃)₂CH), 2.99 (1H, d, 14.89 Hz, indole CHH), 3.32 (1H, d, 14.89 Hz,

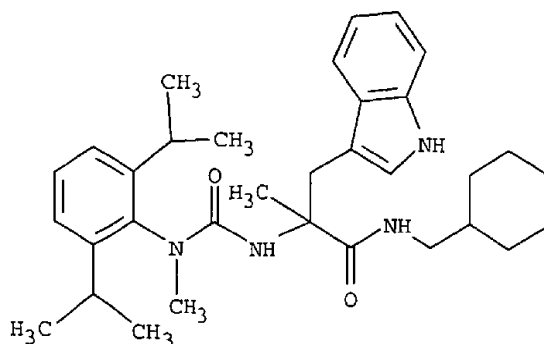
15 CHH indole), 3.10 (3H, s, N-CH₃), 4.72 (1H, s, NMeCNH), 6.46 (1H, d, 2.69 Hz, indole H2), 6.93 (1H, t, 7.08 Hz, indole H5), 6.99 (1H, t, 4.15 Hz, indole H6), 7.08-7.33 (5H, m, 5ArH), 7.79 (1H, br s, indole NH);

IR (film): 3383.0, 1634.0, 1505.0, and 1053.0 cm⁻¹;

MS m/e (APCI) 436.7 (M + H⁺).

20

EXAMPLE 24



N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-3-methyl-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide

To a solution of the acid XVIII (104 mg, 0.24 mmol), HBTU (91 mg, 0.24 mmol) and diisopropyl ethyl amine (93 mg, 0.72 mmol) which had been stirred for 10 minutes was added cyclohexyl methyl amine (54 mg, 0.48 mmol), and the mixture was stirred for an hour. The reaction mixture was taken up in EtOAc and washed with 1N HCl (aq), NaHCO₃ (aq), brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by normal phase chromatography eluting with a gradient of heptane to 1:1 heptane/EtOAc to yield pure 24 (56 mg, 45%), mp 214-216°C.

¹H NMR (CDCl₃): δ 0.68, 0.95, 1.11, 1.15 (12H, 4 × d, 7.08 Hz, [(CH₃)₂CH]₂), 0.82-0.93 (2H, m, cyclohexyl), 1.30-1.36 (2H, m, cyclohexyl), 1.56-1.66 (6H, m, cyclohexyl), 1.66 (3H, s, αCH₃), 2.76-2.83 (1H, m, (CH₃)₂CH), 2.78 (1H, d, 14.40 Hz, CHH indole), 2.90 (1H, qⁿ, 6.84 Hz, (CH₃)₂CH), 3.05 (2H, t, 6.10 Hz, CNHCH₂), 3.08 (3H, s, N-CH₃), 3.37 (1H, d, 14.65 Hz, CHH indole), 4.67 (1H, s,

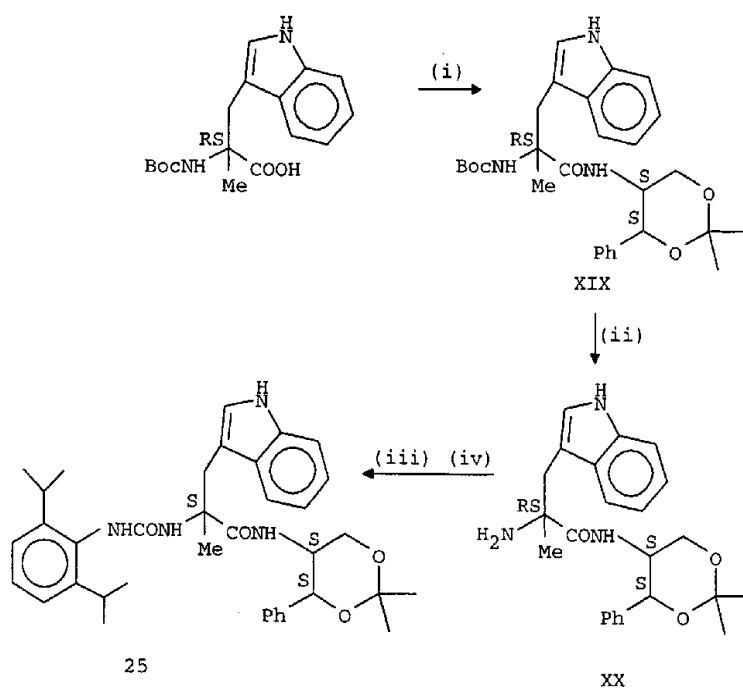
N(CH₃)CNH), 6.19 (1H, d, 2.4 Hz, ArH), 6.83 (1H, br t, CNHCH₂), 6.95 (1H, t, 7.81 Hz, ArH), 7.08 (2H, t, 7.57 Hz, 2ArH), 7.16 (1H, d, 7.57 Hz, ArH), 7.23 (1H, d, 8.3 Hz, ArH), 7.31-7.36 (2H, m, 2ArH), 7.73 (1H, br s, indole NH);

IR (film): 3307.0, 2925.0, 1625.0, 1505.0, 1339.0, and 739.0 cm⁻¹; MS m/e (APCI) 531.7 (M + H⁺);

Analysis for C₃₃H₄₆N₄O₂, C, H, N; mp 214-216°C; HPLC R.T. = 19.77,

C¹⁸ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

SCHEME 10



Reagents and Conditions:

- i) DCC, HOBT, amine, DCM
- 5 ii) HCl gas, Et₂O
- iii) 2,6-Diisopropyl phenyl isocyanate, EtOAc, Δ
- iv) Separate diastereoisomers by chromatography

Synthesis of Example 25Step 1

- 10 A solution of BOC(RS)-(α-methyl)tryptophan (3.00 g, 9.4 mmol),
(4S,5S)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (1.95 g, 9.4 mmol),
1-hydroxybenzotriazole hydrate (1.27 g, 9.4 mmol) in dichloromethane (100 mL)
was cooled to 0°C and stirred 5 minutes at which time dicyclohexylcarbodiimide

-73-

(1.94 g, 9.4 mmol) was added, and the reaction mixture was stirred 10 days at room temperature. The reaction mixture was concentrated to dryness, taken up in ethyl acetate, washed with 10% aqueous potassium carbonate, saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated to a yellow oil. The oil was filtered through silica gel using ethyl acetate as eluant. The product (Intermediate XIX) was obtained as a white foam, 4.70 g.

FAB mass spectrum $(M + H^+)^+ = 508.6$.

Analysis for $C_{29}H_{37}N_3O_5$ (507.63).

Step 2

Anhydrous hydrogen chloride gas was bubbled into a solution of the BOC-amide-acetonide (1.00 g, 2.0 mmol) (Intermediate XIX) for about 3 minutes. The reaction mixture was allowed to stand at room temperature for 3 hours and no starting material remained by tlc. The reaction mixture was concentrated *in vacuo* to a light tan solid. The solid was partitioned between 0.1N sodium hydroxide and ethyl acetate, the ethyl acetate was dried over magnesium sulfate, filtered, and concentrated to a white foam. The white foam was filtered through silica gel using ethyl acetate as eluant. The product (Intermediate XX) was obtained as a white solid, 0.33 g.

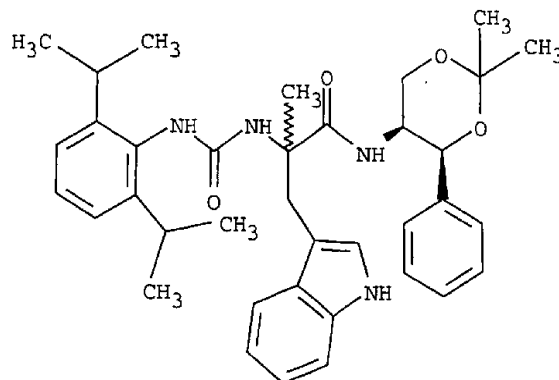
E1 mass spectrum $M^+ = 407$.

Parent molecular weight = 407.5.

Analysis calculated for $C_{24}H_{29}N_3O_3 \cdot 0.33 H_2O$, C, H, N.

A by-product of the reaction was the aminodiol 0.25 g. A larger run employing 3.4 g of the BOC-amide-acetonide yielded 2.18 g of the amino acetonide and 0.58 g of the aminodiol.

EXAMPLE 25



2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(1H-indol-3-yl)-2-methyl-propionamide

- 5 A solution of the amino acetonide (0.40 g, 0.98 mmol) (Intermediate XX) and 2,6-diisopropyl phenyl isocyanate (0.23 g, 1.13 mmol) in ethyl acetate (30 mL) was briefly heated to achieve solution. The reaction mixture was allowed to stand 2 days at room temperature and was then concentrated to a viscous oil. The oil was chromatographed on silica gel using ethyl acetate as eluant yielding 0.288 g of the
- 10 less polar product (Example 25).

FAB mass spectrum $(M + H^+)^+ = 611.2$.

Analysis for $C_{37}H_{46}N_4O_4 \cdot 0.33 C_4H_8O_2$, C, H, N.

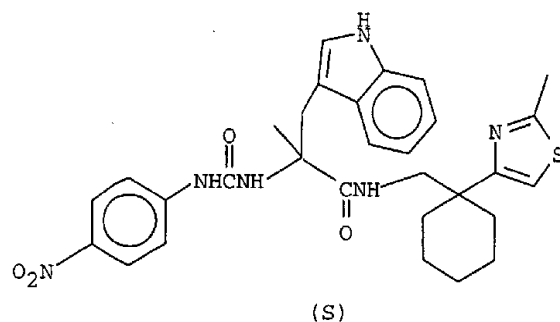
Parent molecular weight = 610.78.

Also obtained was 0.237 g of the more polar product.

- 15 FAB mass spectrum $(M + H^+)^+ = 611.2$.

-75-

EXAMPLE 26



Example 26 was prepared as for Scheme 3 using Intermediate XXI.

Example 26 was isolated in 24.5% yield.

- 5 ^1H NMR (DMSO): δ 1.12-1.55 (8H, mm, cyclohexyl), 1.47 (3H, s, $\alpha\text{-CH}_3$),
 1.96-2.03 (2H, m, cyclohexyl), 2.56 (3H, s, N = C- CH_3), 3.06 (1H, dd, $J = 5.37$
 and 13.19 Hz, CNHCHH), 3.27 (1H, dd, $J = 6.59$ and 13.18 Hz, CNHCHH), 3.40
 10 (2H, 2 \times d, $J = 15.62$ and 15.14 Hz, respectively, CHH indole), 6.56 (1H, s,
 $\text{NHCNH}\alpha\text{C}$), 6.81 (1H, t, $J = 7.81$ Hz, indole H-5), 6.95 (1H, d, $J = 2.20$ Hz,
 indole H-2), 6.98-7.00 (2H, m, indole H-6 and CH -5), 7.28 (1H, d, $J = 8.06$ Hz,
 15 ArH), 7.43 (1H, d, $J = 7.81$ Hz, ArH), 7.46 (1H, Bt, $J = 5.37$ Hz, CNHCH_2),
 7.63 (2H, d, $J = 9.28$ Hz, p- NO_2 $\text{ArH} \times 2$), 8.16 (2H, d, $J = 9.27$ Hz, p- NO_2
 20 $\text{ArH} \times 2$), 9.50 (1H, s, NHCNH), 10.83 (1H, s, indole NH);
 IR (film): 3342.0, 2933.4, 1704.3, 1645.0, 1555.9, 1505.0, 1456.4, 1329.0,
 1112.0 cm^{-1} ;
 MS m/e (ES) 573.05 (M^+), 575.08 ($\text{M}+\text{H}^+$);

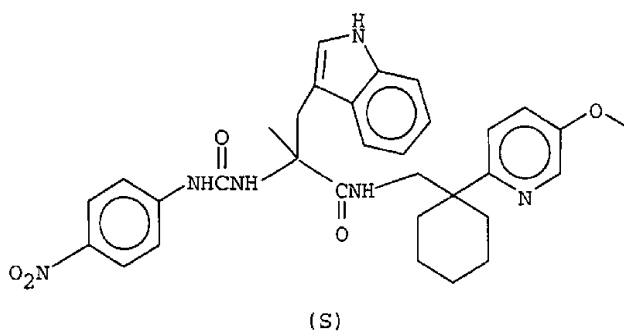
-76-

Analysis $C_{30}H_{34}N_6O_4S$: C,H,N;

mp 205-209°C;

HPLC R.T. = 10.85, C^{18} reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA.

EXAMPLE 27



Example 27 was prepared as for Scheme 3 using Intermediate XXII.

Example 27 was isolated in 26.2% yield.

 1H NMR (DMSO): δ 1.03-1.53 (8H, m, cyclohexyl), 1.44 (3H, s, α CH₃),2.10-2.20 (2H, m, cyclohexyl), 3.06 (1H, dd, $J = 5.13$ and 12.94 Hz, $CNHCHH$),3.28 (1H, dd, obscured by water peak, $CNHCHH$), 3.38 (2H, 2 \times d, $J = 15.14$ Hz,CHH indole), 3.68 (3H, s, OCH₃), 6.55 (1H, s, NHCNH α C), 6.81 (1H, t, $J = 7.08$ Hz indole H-5), 6.94 (1H, d, $J = 1.71$ Hz, indole H2), 6.98 (1H, t, $J = 7.08$ Hz,indole H6), 7.04 (1H, dd, $J = 2.93$ and 8.79 Hz, indole H7), 7.19 (1H, d, $J =$

8.79 Hz,

pyridyl H3), 7.23 (1H, d, $J = 8.3$ Hz, pyridyl H4), 7.41-7.45 (2H, m, $CNHCH_2$ and ArH), 7.62 (2H, d, $J = 9.28$ Hz, p-NO₂ ArH \times 2), 8.16 (2H, d, $J = 9.52$ Hz, p-NO₂

-77-

ArH \times 2), 8.17-8.19 (1H, m, ArH), 9.49 (1H, s, $\text{NH}\overset{\text{O}}{\parallel}\text{CNH}$), 10.82 (1H, s, indole NH);

5 IR (film): 3355.0, 2925.0, 1652.1, 1558.1, 1504.7, 1453.6, 1328.2, 1052.5 cm^{-1} ;

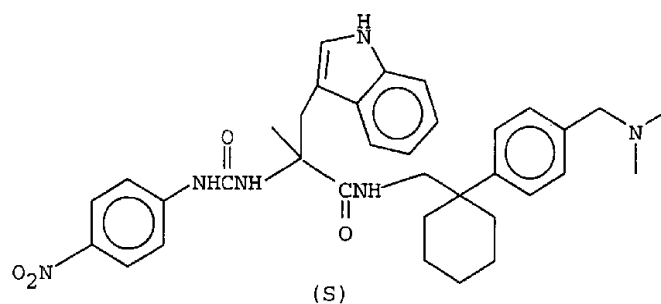
MS m/e (APCI) 584.1 (M), $(\text{M}+\text{H}^+) = 585.1$;

Analysis $\text{C}_{32}\text{H}_{36}\text{N}_6\text{O}_5 \cdot 0.3\text{H}_2\text{O}$: C, H, N;

mp 213-215°C;

10 HPLC R.T. = 9.81 and 10.40, C^{18} reverse phase, 40% to 100% MeCN:TFA/
H₂O:TFA.

EXAMPLE 28



Example 28 was prepared as for Scheme 3 using Intermediate XXIII.

Example 28 was isolated in 48% yield.

15 ^1H NMR (DMSO): δ 1.10-1.23 (3H, m, cyclohexyl), 1.37-1.60 (5H, m, cyclohexyl), 1.40 (3H, s, αCH_3), 1.98-2.08 (2H, m, cyclohexyl), 2.06 (6H, s,

NMe_2), 2.98 (1H, dd, $J = 5.62$ and 13.43 Hz, CNHCHH), 3.22 (2H, s,

20 ArCH₂NMe₂), 3.27 (1H, dd, $J = 7.08$ and 14.16 Hz, CNHCHH), 3.35 (1H, d, $J =$

-78-

14.65 Hz), CHH indole), 3.40 (1H, d, J = 14.65 Hz, CHH indole), 6.49 (1H, s,

5 $\begin{array}{c} \text{O} \\ \parallel \\ \text{NHCNH}\alpha\text{C} \end{array}$, 6.81 (1H, t, J = 7.81 Hz, indole H5), 6.93 (1H, d, J = 2.2 Hz, indole H-2), 6.98 (1H, t, J = 7.08 Hz, indole H6), 7.05 (2H, d, J = 8.06 Hz, 2 \times ArH), 7.16

10 $\begin{array}{c} \text{O} \\ \parallel \\ \text{CNHCH}_2 \end{array}$, 7.23 (2H, d, J = 8.30 Hz, 2 \times ArH), 7.27 (1H, d, J = 8.06 Hz, indole H7), 7.43 (1H, d, J = 7.81 Hz, indole H4), 7.64 (2H, d, J = 9.28 Hz, p-NO₂ ArH \times 2), 8.18 (1H, d, J = 9.28 Hz, 2 \times p-NO₂ ArH), 9.45 (1H, s,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{NHCNH} \end{array}$), 10.82 (1H, s, indole NH);

IR (film): 3339.0, 2930.8, 1705.3, 1651.2, 1599.0, 1505.0, 1329.0, 1112.0 (cm⁻¹);

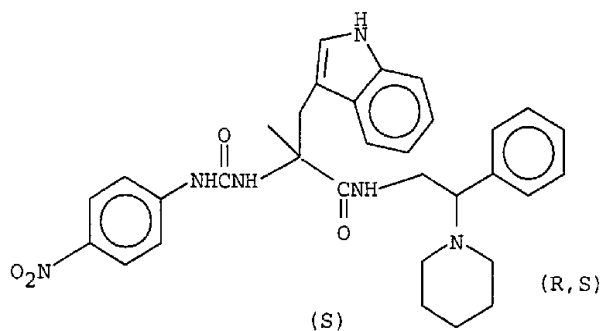
15 MS m/e (APCI) 611.2 (M+H⁺);

Analysis C₃₅H₄₂N₆O₄: C, H, N;

mp 200-202°C;

HPLC R.T. = 23.35, C¹⁸ reverse phase, 10% to 80% MeCN:TFA/H₂O:TFA.

EXAMPLE 29



Example 29 was prepared as for Scheme 3 using Intermediate XXIV.

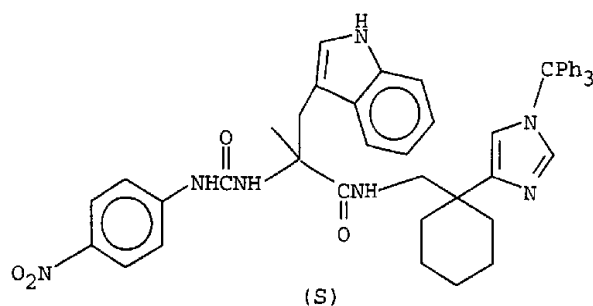
Example 29 was isolated in 70% yield.

-79-

- ¹H NMR (DMSO): δ 1.10-1.22 (2H, m, piperidino CH's), 1.24-1.42 (4H, m, piperidino CH's), 1.39 (1.5H, s, αMe), 1.43 (1.5H, s, αMe), 2.02-2.16 (2H, m, piperidino CH's), 2.21-2.30 (2H, m, piperidino CH's), 3.22-3.60 (5H, m, indole CH₃ and CONHCH₂CHN), 6.53 (0.5H, s, CONH), 6.57 (0.5H, s, CONH);
- 5 6.77-6.84 (1H, m, indole H₅), 6.95-7.04 (2H, m, indole H₆ and H₂), 7.12-7.32 (6H, m, indole H₇ and 5 × ArH's), 7.45 (1H, d, J = 8.1 Hz, indole H₄), 7.48-7.63 (1H, m, CONHCH₂), 7.62 (2H, d, J = 9.0 Hz ArHNO₂ ring), 8.14-8.17 (2H, m, ArHNO₂ ring), 9.49 (0.5H, s, CONH), 9.50 (0.5H, s, CONH), 10.84 (0.5H, s, indole NH), and 10.87 (0.5H, s, indole NH);
- 10 IR (film): 3336.0, 2934.0, 1710.0, 1657.0, 1506.0, 1329.0, 1229.0, 1112.0, and 851.0 cm⁻¹;
- MS m/e (ES+) 64.2 (20%), 205.2 (37%), 431.1 (12%), 569.2 (M+H⁺, 100%⁺); mp 133-137°C;
- HPLC R.T. = 10.57 and 10.77, C¹⁸ reverse phase, 40% to 100% MeCN:TFA/
- 15 H₂O:TFA.

-80-

EXAMPLE 30



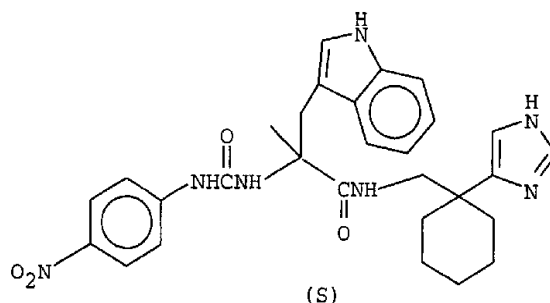
Example 30 was prepared as for Scheme 3 using Intermediate XXV.

Example 30 was isolated in 83% yield.

- 5 ^1H NMR (DMSO): δ 1.05-1.20 (3H, m, cyclohexyl CH), 1.30-1.42 (5H, m, cyclohexyl CH), 1.47 (3H, s, αCH_3), 1.70-1.90 (2H, m, cyclohexyl CH), 3.00-3.10 (1H, m, CHHNHCO), 3.20-3.28 (1H, m, CHHNHCO), 3.37 (1H, d, 14.4 Hz, CHH indole), 3.45 (1H, d, 14.4 Hz, CHH indole), 6.51 (1H, s, PhNHCONH or CH imidazole), 6.58 (1H, s, PhN, PhNHCONH or CH imidazole), 6.77-6.81 (1H, m, C5-H indole), 6.93-7.04 (8H, m, $6 \times \text{ArH}$, C6-H indole, C2-H indole), 7.19 (1H, s, imidazole CH), 7.27 (1H, d, 7.9 Hz, C7-H indole), 7.32-7.39 (9H, m, ArH), 7.42 (1H, d, 8.1 Hz C4-H indole), 7.56 (2H, d, 9.0 Hz, PhNO_2CH), 7.86 (1H, t, 5.4 Hz, NH amide), 8.07 (2H, d, 9.0 Hz, PhNO_2CH), 9.48 (1H, s, PhNHCO), 10.82 (1H, s, indole NH);
- 15 IR (film) 3335, 3060, 2932, 2855, 1704, 1645, 1599, 1557, 1505, 1446, 1330, 1303, 1230, 1176, 1113, 1039, 1011, 852, and 745 cm^{-1} ;
- MS m/e (APCI): 786.3 (M+H);
- mp 148-154°C;
- HPLC R.T. = 16.79, C¹⁸ reverse phase, 40% to 100% MeCN:TFA/H₂O:TFA over
- 20 20 minutes.

-81-

EXAMPLE 31



To a stirred solution of Example 30 (0.23 g, 0.29 mmol) in MeOH (50 mL) was added 2N HCl (2 mL). The reaction mixture was refluxed for 2 hours. The solution was neutralized using 1N NaOH and evaporated in vacuo. The residue was purified on reverse phase silica eluting with a gradient of MeOH/H₂O 0% to 100%. The product was eluted with 60% MeOH/H₂O to give Example 31 as a yellow solid (0.073 g, 44%).

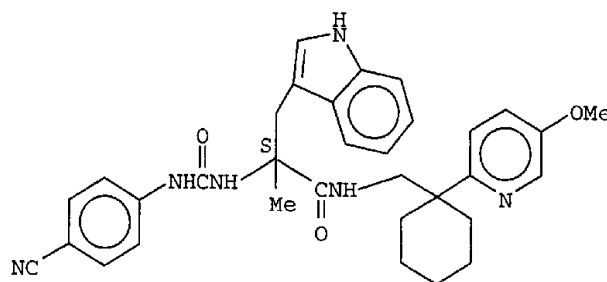
¹H NMR (DMSO + DCL/D₂O): δ 1.05-1.25 (3H, m, cyclohexyl CH), 1.35-1.55 (5H, m, cyclohexyl CH), 1.36 (3H, s, αCH₃), 1.90-2.00 (2H, m, cyclohexyl CH), 3.10 (1H, d, 13.2 Hz, CHH-indole or CHH-cyclohexyl), 3.23 (1H, d, 13.4 Hz, CHH indole or CHH-cyclohexyl), 3.28 (2H, s, CH₂-indole or CH₂-cyclohexyl), 6.78-6.80 (1H, m, indole C₅-H), 6.93-6.97 (1H, m, indole C₆-H), 7.01 (1H, s, ArH), 7.24-7.26 (2H, m, indole C₇-H, Ar-H), 7.40 (1H, d, J = 8.1 Hz, indole C₄-H), 7.59-7.61 (2H, m, PhNO₂ CH), 8.11-8.14 (2H, m, PhNO₂ CH), 9.05 (1H, d, 1.0 Hz, CH imidazole);

IR (film): 3356, 2935, 2859, 1699, 1652, 1597, 1557, 1505, 1458, 1331, 1303, 1232, 1208, 1195, 1177, 1112, 851, and 746 cm⁻¹;

MS m/e (ES⁺ high resolution), Measured (M+H)⁺ 544.2677, Expected (M+H)⁺ 544.2672, Deviation (ppm) +0.9; mp 150-152°C;

HPLC R.T. = 17.9 min, C¹⁸ reverse phase, 10% to 80% MeCN:TFA/H₂O:TFA over 20 minutes.

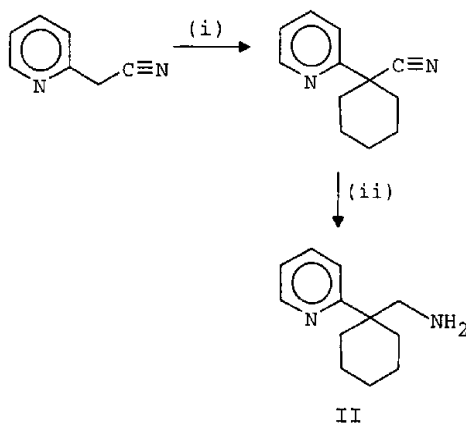
EXAMPLE 32



- 5 Example 32 was prepared as in Scheme 5 using Intermediate XXII; mp 110-115°C.
- ¹H NMR (DMSO): δ 1.05-1.25 (6H, m), 1.40 (3H, s), 1.40-1.50 (4H, m), 2.15 (2H, m), 3.05 and 3.25 (2H, Abq, J = 15 Hz), 3.70 (3H, s), 6.40 (1H, s), 6.80 (1H, t, J = 6 Hz), 6.95 (1H, s), 7.00 (1H, t, J = 6 Hz), 7.20 (1H, d, J = 7 Hz), 7.30 (1H, d, J = 7 Hz), 7.40 (2H, m), 7.57 (2H, d, J = 8 Hz), 7.70 (2H, d, J = 8 Hz), 8.20 (1H, s), 9.20 (1H, s), 10.80 (1H, s);
- 10 MS 565.11 (M+H).

-83-

PREPARATION OF INTERMEDIATE II



Reagents and Conditions:

- i) Sodium hydride, 1,5-dibromopentane, DMSO, Et₂O, 15°C
5 ii) Raney nickel, EtOH-NH₃, H₂, 50 psi, 40°C

PREPARATION OF INTERMEDIATES

Synthesis of Intermediate IIStep 1

- To a stirred suspension of sodium hydride (60% dispersed in oil) (4 g,
10 0.1 m) in DMSO (70 mL) under nitrogen at 15°C was added dropwise a solution of
2-pyridyl acetonitrile (6 g, 51 mmol) and 1,5-dibromopentane (6.81 mL, 51 mmol)
in ether (40 mL) and DMSO (10 mL) over 1 hour. The mixture was allowed to
warm to room temperature and stirred for a further 24 hours under nitrogen. The
reaction mixture was carefully quenched by the addition dropwise of isopropanol
15 (10 mL), followed by water (100 mL) 10 minutes later. The reaction solution was
taken up in EtOAc and washed with water. The aqueous layer was re-extracted
with EtOAc, and the two organic layers were combined, dried (MgSO₄), and
concentrated *in vacuo*. The residue was purified on silica with a gradient of

heptane to 9:1 heptane/EtOAc to give 1-cyano-1-(2-pyridyl) cyclohexane (6.77 g, 72%).

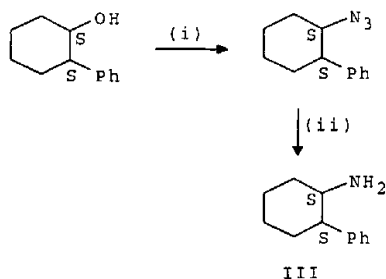
^1H NMR (CDCl_3): δ 1.77-2.17 (10H, 2 \times m, cyclohexyl), 7.20-7.27 (1H, m, pyridyl H), 7.60-7.62 (1H, m, pyridyl H), 7.70-7.73 (1H, m, pyridyl H), 8.4-8.42 (1H, m, pyridyl H).

Intermediate II

Raney nickel (8 g) was washed with water to obtain pH 7 and then washed with ethanol to remove water (ensuring the catalyst was moist at all times). The Raney nickel was taken up in ethanolic ammonia (100 mL) and 1-cyano-1-(2-pyridyl) cyclohexane (6.7 g, 0.036 m) was added to the mixture which was then shaken on a Parr hydrogenation apparatus under 50 psi of hydrogen at 40°C for 22 hours. The reaction mixture was filtered through Celite and concentrated *in vacuo* to give pure II as a clear oil (6.89 g, 100%).

^1H NMR: δ 1.20-1.65 (10H, m, cyclohexyl), 2.20-2.36 (2H, m, CH_2NH_2), 2.70-2.90 (2H, br s, NH_2), 7.00-7.20 (1H, m, ArH), 7.3-7.4 (1H, m, ArH), 7.6-7.73 (1H, m, ArH), 8.6-8.7 (1H, m, ArH).

PREPARATION OF INTERMEDIATE III



Reagents and Conditions:

- 20 i) DEAD, PPh_3 , $(\text{PhO})_2\text{PON}_3$, THF
 ii) Lindlar, EtOH

Synthesis of Intermediate IIIStep 1

A solution of diphenylposphonylazide (473 mg, 1.72 mmol) in THF (10 mL) was added dropwise over 20 minutes to a stirred solution of 1R,2S,trans-2-phenyl-1-cyclohexanol (303 mg, 1.72 mmol), triphenylphosphene (451 mg, 1.72 mmol), and diethyl ozodicarboxylate (300 mg, 1.72 mmol) in dry THF (10 mL) at room temperature. The resulting mixture was stirred for 3 days, then the solvent removed *in vacuo*. The product was purified by chromatography (silica, 10-20% ethyl acetate in heptane) to leave a clear oil A (217 mg, 63%).

^1H , NMR (CDCl_3): 1.34-2.4 (8H, m, $4 \times \text{CH}_2$), 2.76-2.80 (1H, m, CH), 3.94 (1H, d, CH-N_3 , $J = 2.8$ Hz), 7.22-7.34 (5H, m, Ph);

IR (film): 3028, 2984, 2860, 2103, 1602, 1486, 1447, and 1267; $[\alpha]_{\text{D}}^{18} + 81.4^\circ$ ($c = 1.05$, acetone).

Step 2

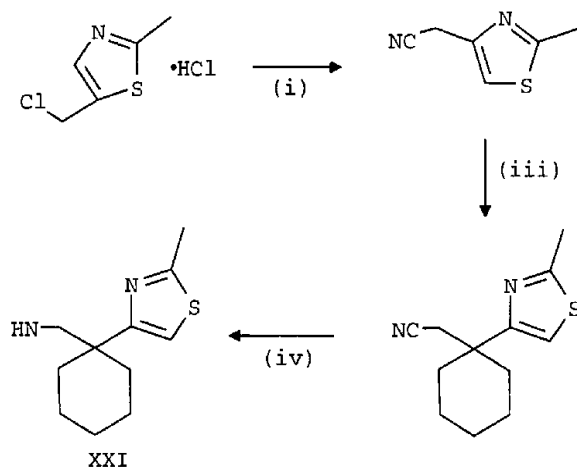
A (1.89 mg, 0.84 mmol) was hydrogenated in absolute ethanol (50 mL) at 30°C and 45 psi over Lindlar catalyst (25 mg). The catalyst was filtered off and the solvent removed to yield an oil (130 mg, 79%).

^1H NMR (CDCl_3): 1.01 (2H, bs, NH_2), 1.35-2.06 (8H, m, $4 \times \text{CH}_2$), 2.77-2.83 (1H, m, CH), 3.24-3.26 (1H, m, CHCH_2), 7.20-7.34 (5H, m, Ph);

IR (film): 3360, 3060, 3025, 2927, 2855, 1601, 1582, 1495, and 1447;

$[\alpha]_{\text{D}}^{21} + 72.9^\circ$ ($c = 1.04$, methanol).

PREPARATION OF INTERMEDIATE XXI



Reagents and Conditions:

- 5 (i) (a) EtOAc, NaHCO₃ (aq); (b) 95% Ethanol, water, potassium cyanide
 reflux
- (ii) Sodium hydride, 1,5-dibromopentane, DMSO, Et₂O, room temperature, Ar
- (iii) Raney Nickel, EtOH-NH₃, H₂, 50 psi, 35°C

Synthesis of Intermediate XXIStep 1

- 10 4-Chloromethyl-2-methyl thiazole hydrochloride (1 g, 5.4 mmol) was taken
up in sodium bicarbonate saturated aqueous solution and extracted with EtOAc,
dried (MgSO₄), and concentrated in vacuo. The residue was dissolved in 95%
ethanol (50 mL) and potassium cyanide (353 mg, 5.4 mmol) followed by water
15 (5 mL) were added to the reaction mixture. The mixture was refluxed for 18 hours
and cooled to room temperature. The reaction mixture was taken up in EtOAc and
washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was

-87-

purified on silica with a gradient of heptane to 1:1 heptane/EtOAc to give 4-cyanomethyl-2-methyl thiazole (180 mg, 24%).

^1H NMR (CDCl_3): δ 2.71 (3H, s, CH_3), 3.85 (2H, s, CH_2CN), 7.13 (1H, s, ArH);

IR (film): 2923.0, 2863.7, 2255.6, 1525.0, 1412.0, 1261.0, 1101.0, 1020.0, and

5 799.0 cm^{-1} ;

MS m/e (ES^+) 139.06 ($\text{M}+\text{H}^+$).

Step 2 As for Intermediate II, Step 1

1-Cyano-1-(2-methyl thiazol-4-yl)cyclohexane isolated in 100% yield.

^1H NMR (CDCl_3): δ 1.70-2.00 (8H, mm, cyclohexyl), 2.12-2.20 (2H, m,

10 cyclohexyl), 2.70 (3H, s, CH_3), 7.12 (1H, s, ArH);

IR (film): 2929.0, 2858.7, 1453.1, and 1227.0 cm^{-1} ;

MS m/e (APCI) 207.12 ($\text{M}+\text{H}^+$) (100%).

Step 3 As for Intermediate II, Step 2

Intermediate XXI, 1-aminomethyl-1-(2-methyl thiazol-4-yl)cyclohexane was

15 isolated in 98% yield.

^1H NMR (CDCl_3): δ 1.68-2.00 (8H, mm, cyclohexyl), 2.03-2.20 (4H, mm,

2 \times cyclohexyl H, NH_2), 2.69 (2H, s, CH_2NH_2), 2.70 (3H, s, CH_3), 7.12 (1H, s,

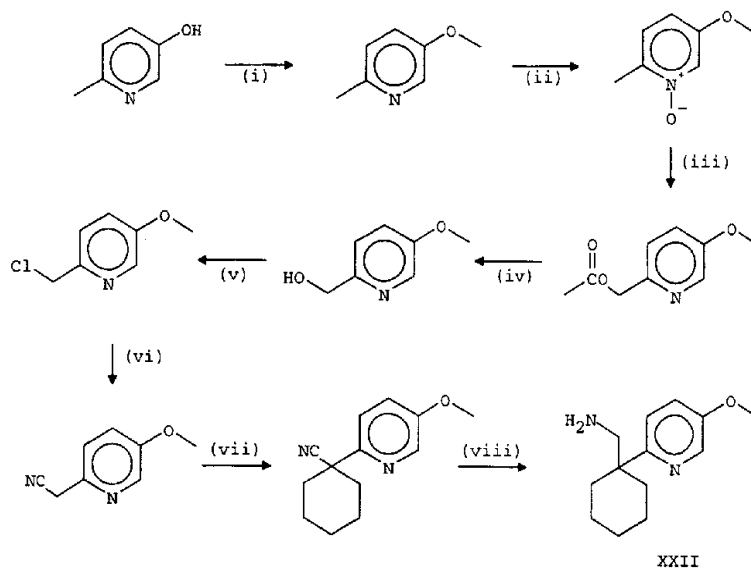
ArH);

IR (film): 2927.0, 2857.0, 2237.0, 1667.0, 1515.0, 1453.0, 1376.0, 1185.0, 1169.0,

20 1141.0, 957.0, and 745.0 cm^{-1} ;

MS m/e (APCI) 211.15 ($\text{M}+\text{H}^+$), 207.13 (100%).

PREPARATION OF INTERMEDIATE XXII



Reagents and Conditions:

- (i) Sodium hydride, methyl iodide, DMF, 0°C-room temperature under argon
- 5 (ii) M-chloro-peroxy-benzoic acid, sodium sulphate, DCM, room temperature
- (iii) Acetic anhydride, reflux
- (iv) Potassium hydroxide, methanol, reflux
- (v) Thionyl chloride, DCM, reflux
- (vi) Potassium cyanide, 95% ethanol, water, reflux
- 10 (vii) Sodium hydride, 1,5-dibromopentane, DMSO, Et₂O, room temperature, Ar
- (viii) Raney Nickel, EtOH-NH₃, H₂, 57 psi, 35°C

Synthesis of Intermediate XXIIStep 1

- To a stirred suspension of sodium hydride (60% dispersed in oil) (1.8 g,
 15 45 mmol) in DMF (60 mL) at 0°C under argon was added a solution of 2-hydroxy-

5-methyl-pyridine (4.91 g, 45 mmol) in DMF (60 mL). Effervescence was observed, and the reaction mixture was allowed to warm to 18°C. Methyl iodide (2.8 mL, 45 mmol) was added to the reaction mixture which was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was quenched by the addition of isopropanol (20 mL), followed by water (20 mL) 30 minutes later, under argon. The reaction mixture was taken up in EtOAc and washed with NaHCO₃ (aq), dried (MgSO₄), and concentrated in vacuo to give 2-methyl-5-methoxy-pyridine as a pure volatile liquid (2.93 g, 53%).

¹H NMR (CDCl₃): δ 2.49 (3H, s, CH₃-C), 3.83 (3H, s, OCH₃), 7.05-7.13 (2H, mm, pyridyl H4 and 5), 8.19 (1H, d, J = 2.8 Hz, pyridyl H2);

IR (film): 2924.0, 2854.0, 1575.0, 1497.0, 1464.0, 1378.0, 1270.0, 1243.0, 1211.0, and 1034.0 cm⁻¹.

Step 2

To a solution of 2-methyl-5-methoxy-pyridine (2.93 g, 24 mmol) in DCM (100 mL) was added sodium sulphate (5 g, 35 mmol), followed by m-chloroperoxy-benzoic acid (10 g, 58 mmol), and mixture was stirred at room temperature for ~48 hours. The reaction mixture was filtered, and the white solid was washed with DCM. The filtrate was concentrated and purified by normal phase chromatography eluting with a gradient of 1:1 EtOAc/heptane to EtOAc to give 2-methyl-5-methoxy-pyridine-N-oxide (2.41 g, 72%).

¹H NMR (DMSO): δ 2.27 (3H, s, C-CH₃), 3.79 (3H, s, OCH₃), 6.96 (1H, dd, J = 2.4 and 8.8 Hz, pyridyl H5), 7.36 (1H, d, J = 8.8 Hz, pyridyl H4), 8.08 (1H, d, J = 2.4 Hz, pyridyl H2);

IR (film): 3386.0, 1616.0, 1566.0, 1516.0, 1452.0, 1375.0, 1304.0, 1197.0, 1172.0, 1131.0, 1030.0, 996.0, and 960.0 cm⁻¹;

MS m/e (ES) 140 (M+H⁺).

Step 3

A mixture of 2-methyl-5-methoxy-pyridyl-N-oxide (1.082 g, 7.8 mmol) and acetic anhydride (excess, 5 mL) was gently warmed to reflux for 10 minutes. The

-90-

reaction mixture was allowed to cool to room temperature before being taken up in EtOAc, washed (NaHCO₃ (aq)), dried (MgSO₄), and concentrated in vacuo to give crude 2-acetoxy-methyl-5-methoxy-pyridine which was taken through to the next step without further purification.

5
10
15
20
25

O
 \parallel
 OCCH_3

¹H NMR (CDCl₃): δ 2.13 (3H, s, OCCH₃), 3.87 (3H, s, CH₃O), 5.16 (2H, s, CH₂OC), 7.20 (1H, dd, J = 3.2 and 8.8 Hz, pyridyl H), 7.30 (1H, d, J = 8.4 Hz, pyridyl H), 8.30 (1H, d, J = 3.2 Hz, pyridyl H);
IR (film): 2943.0, 1740.0, 1576.0, 1499.0, 1377.0, 1293.0, 1227.0, and 1029.0 cm⁻¹;
MS m/e (ES) 182.16 (100%) (M+H⁺).

15 Step 4

To a stirred solution of 2-acetoxy-methyl-5-methoxy-pyridine (1.41 g, 7.8 mmol) in methanol (30 mL) was added excess potassium hydroxide (1.6 g), and the mixture was refluxed for 2 hours. The solvent was removed in vacuo, and the residue was purified by column chromatography eluting with a heptane to ethyl acetate gradient. The extremely volatile 2-hydroxy-methyl-5-methoxy-pyridine was obtained as a solution in ethyl acetate (0.68 g, 63% yield).

20
25

¹H NMR (CDCl₃): δ 3.87 (3H, s, OCH₃), 4.70 (2H, s, CH₂OH), 7.18-7.24 (2H, m, pyridyl H4 and 5), 8.25 (1H, d, J = 2.8 Hz, pyridyl H2);
IR (film): 3346.0, 1575.0, 1499.0, 1271.0, 1210.0, and 1028.0 cm⁻¹;
MS m/e (ES) 140.18 (M+H⁺).

Step 5

30
To a solution of 2-hydroxy-methyl-5-methoxy-pyridine (0.68 g, 4.9 mmol) in dry DCM was added dropwise excess thionyl chloride (2.0 mL), and the mixture was refluxed for 2 hours. The solvent was removed in vacuo, and the residue was taken up in EtOAc and washed with NaHCO₃ (aq), dried (MgSO₄, and

-91-

concentrated in vacuo. The extremely volatile 2-chloromethyl-5-methoxy-pyridine was obtained as a solution in ethyl acetate to give (984.0 mg, 83.5%) yield.

¹H NMR (CDCl₃): δ 3.87 (3H, s, OCH₃), 4.65 (2H, s, CH₂Cl), 7.21 (1H, dd, J = 2.8 and 8.4 Hz, pyridyl H4), 7.39 (1H, d, J = 8.4 Hz, pyridyl H5), 8.27 (1H, d, J = 2.8 Hz, pyridyl H2);

IR (film): 3337.1, 2930.0, 2854.7, 1731.3, 1639.5, 1537.9, 1423.2, 1301.9, and 1158.0 cm⁻¹;

MS m/e (ES) 158.15 (M+H⁺) (100%).

Step 6 As for Intermediate XXI, Step 1

2-Cyanomethyl-5-methoxy-pyridine was isolated in 73% pure yield.

¹H NMR (CDCl₃): δ 3.87 (3H, s, OCH₃), 3.88 (2H, s, CH₂CN), 7.22 (1H, dd, J = 3.2 and 8.8 Hz, pyridyl H4), 7.34 (1H, dd, J = 0.4 and 8.4 Hz, pyridyl H5), 8.27 (1H, d, J = 2.8 Hz, pyridyl H2);

IR (film): 2922.8, 1575.5, 1496.0, and 1271.5 cm⁻¹;

MS m/e (APCI) 149.18 (M+H⁺) (100%).

Step 7 As for Intermediate II, Step 1

-1-Cyano-1-(4-methoxypyrid-2-yl)cyclohexane was isolated in 60% yield.

NMR (CDCl₃): δ 1.76-2.12 (10H, mm, cyclohexyl), 3.87 (3H, s, OCH₃), 7.21 (1H, dd, J = 2.8 and 8.8 Hz, pyridyl H4), 7.51 (1H, dd, J = 0.8 and 9.6 Hz, pyridyl H5), 8.29 (1H, d, 3.2 Hz, pyridyl H2);

IR (film): 2935.0, 2863.7, 1575.0, 1478.0, 1299.0, 1269.0, 1244.0, and 1017.0 cm⁻¹;

MS m/e (ES) 217.16 (M+H⁺).

Step 8 As for Intermediate II, Step 2

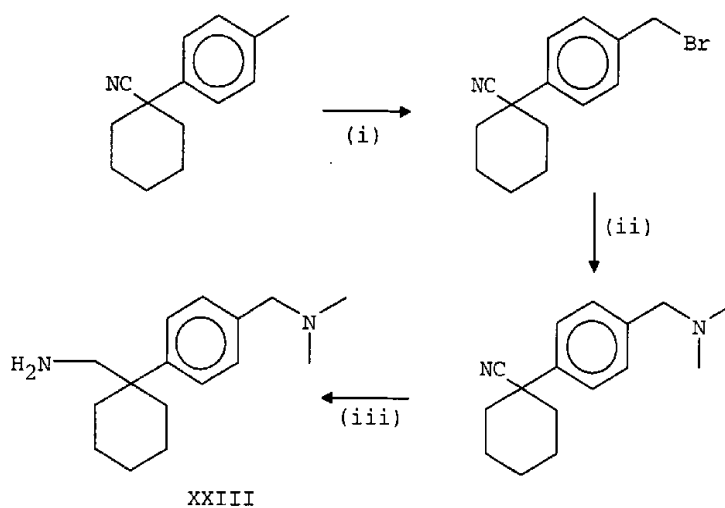
Intermediate XXII, 1-amino-methyl-1-(4-methoxy-pyrid-2-yl)cyclohexane was isolated in 82% yield.

^1H NMR (DMSO): δ 1.13-1.58 (8H, mm, cyclohexyl), 2.14-2.22 (2H, m, cyclohexyl), 2.56 (2H, s, NH_2CH_2), 3.80 (3H, s, OCH_3), 7.30 (2H, m, pyridyl H4 and H5), 8.26 (1H, m, pyridyl H2);

IR (film): 2925.0, 2858.6, 1569.4, and 1477.8 cm^{-1} ;

5 MS m/e (APCI) 221.14 ($\text{M}+\text{H}^+$).

PREPARATION OF INTERMEDIATE XXIII



Reagents and Conditions:

- (i) N-Bromo-succinimide, benzoyl peroxide, carbon tetrachloride, room temperature under argon
- (ii) Dimethyl amine, DCM, room temperature
- (iii) Raney Nickel, EtOH·NH₃, 50 psi, 30°C

Synthesis of Intermediate XXIIIStep 1

- To a solution of 1-(4-methyl-phenyl)-1-cyclohexyl-carbonitrile (2 g, 0.01 m) in CCl₄ (20 mL) under argon at room temperature was added N-bromo-succinimide (1.96 g, 0.011 m) followed by benzoyl peroxide (30% water) (2.3 mg, 1.6 mmol) in CCl₄ (10 mL), and the reaction mixture was refluxed for 5 hours. The mixture was cooled to room temperature, filtered, washed with DCM, and concentrated in vacuo. The residue was purified by normal phase chromatography

-94-

eluting with a gradient of heptane to 10% EtOAc:heptane to give the bromide (2.57 g, 92%).

^1H NMR (CDCl_3): δ 1.71-1.86 (8H, mm, cyclohexyl), 2.14 (2H, d, J = 11.96 Hz, cyclohexyl), 4.49 (2H, s, $\text{CH}_2\text{-Br}$), 7.41 (2H, d, J = 8.54 Hz, 2ArH), 7.47 (2H, d, J = 8.06 Hz, 2ArH);

IR (film): 2936.0, 2860.0, 2232.0, 1914.0, 1789.0, 1765.0, 1610.0, 1515.0, 1451.0, 1415.0, 1355.0, and 1231.0 cm^{-1} .

Step 2

To a stirred solution of 1-(4-bromomethyl-phenyl)-1-cyclohexyl-carbonitrile (0.89 g, 3.2 mmol) in DCM (30 mL) under argon at room temperature was added dimethylamine (2 M in THF) (6.42 mL, 12.8 mmol), and the reaction mixture was stirred for 20 hours at room temperature. 1N NaOH (aq) (15 mL) was added to the reaction mixture, and the solution was stirred for 10 minutes. The reaction mixture was taken up in water and extracted with DCM, dried and concentrated in vacuo. The residue was purified on silica (normal phase) eluting with a gradient of heptane to ethyl acetate to give the dimethylamine in 76% yield (593 mg).

^1H NMR (CDCl_3): δ 1.72-1.88 (8H, m, cyclohexyl), 2.15 (2H, d, J = 11.71, cyclohexyl), 2.24 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.4 (2H, s, CH_2NMe_2), 7.32 (2H, d, J = 8.3 Hz, 2ArH);

IR (film): 3375.0, 2932.9, 2859.7, 1645.8, 1455.6, and 1042.0 cm^{-1} ;

MS m/e (APCI) 243.2 ($\text{M}+\text{H}^+$).

Step 3 As for Intermediate II, Step 2

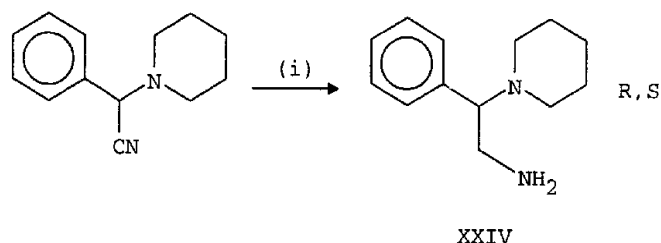
Intermediate XXIII, 1-aminomethyl-1-[4-(N,N -dimethylaminomethyl)-phenyl]cyclohexane was isolated in quantitative yield.

^1H NMR (CDCl_3): δ 1.22-1.63 (8H, mm, cyclohexyl), 2.07-2.17 (2H, m, cyclohexyl), 2.25 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.68 (2H, s, CH_2NH_2), 3.41 (2H, s, $\text{ArCH}_2\text{NMe}_2$), 7.27 (4H, 2 \times d, J = 6.8 Hz, 4 \times ArH);

IR (film): 2931.0, 2856.0, 2814.0, 2766.0, 1513.0, and 1455.0 cm^{-1} ;

MS m/e (ES) 247 ($\text{M}+\text{H}^+$).

PREPARATION OF INTERMEDIATE XXIV



Reagents and Conditions:

- (i) Lithium aluminum hydride/aluminum chloride, Et₂O THF 0°C

5

Synthesis of Intermediate XXIVStep 1

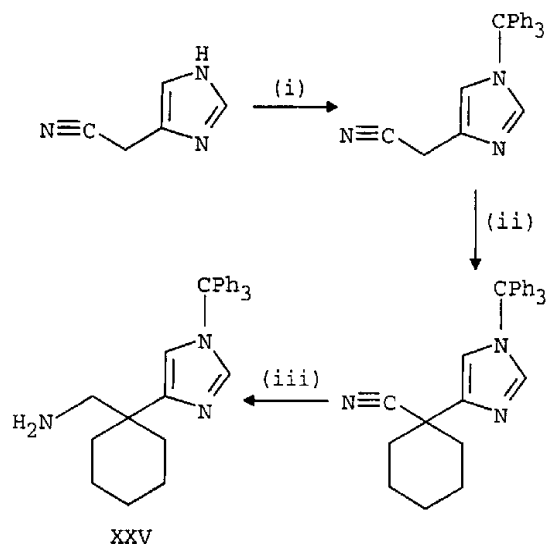
To an ice-cold solution of Et₂O (30 mL) under nitrogen was added aluminum chloride (0.5 g, 3.74 mmol), with stirring, over 2 minutes. This solution was added to an ice-cold solution of lithium aluminum hydride, 1 M in Et₂O (3.74 mL, 3.74 mmol) in anhydrous THF (50 mL) stirring under nitrogen. The reducing solution was allowed to warm to room temperature before gradually adding alpha-(1-piperidino)phenylacetonitrile (0.75 g, 3.74 mmol) dissolved in THF (20 mL). The reaction mixture was stirred for 3 hours before cooling and adding a 1:1 mixture of H₂O/THF. Fifty percent aqueous potassium hydroxide (20 mL) was added producing two layers. The organic layer was separated, dried (K₂CO₃), and concentrated in vacuo. The residue was purified on silica eluting with a gradient of DCM to 25% MeOH/DCM to give pure XXIV as a white oil (0.47 g, 62%).

¹H NMR (CDCl₃): δ 1.28-1.40 (2H, m, piperidino CH's), 1.48-1.63 (4H, m, piperidino CH's), 2.17-2.51 (6H, m, NH₂ and 4 piperidino CH's), 2.99-3.04 (1H, m, CHCHNH₂), 3.19-3.24 (1H, m, CHCHNH₂), 3.45-3.48 (1H, m, CHCH₂NH), 7.20-7.37 (5H, m, ArH);

IR (film): 2932.0, 2853.0, 2804.0, 1492.0, 1452.0, 1158.0, 1104.0, and 765.0 cm^{-1} ;

MS m/z (ES+) 205.2 ($M+H^+$, 100%).

PREPARATION OF INTERMEDIATE XXV



Reagents and Conditions:

- (i) Triphenylmethylchloride, triethylamine, DMF, room temperature
- 5 (ii) Sodium hydride, 1,5-dibromopentane, DMSO, room temperature
- (iii) Lithium aluminum hydride/aluminum chloride, Et₂O, THF, 0°C

Synthesis of Intermediate XXVStep 1

- To a stirred solution of 4-cyanomethylimidazole (2.24 g, 20.9 mmol) in
- 10 DMF (50 mL) was added triphenylmethylchloride (6.42 g, 23.0 mmol) and triethylamine (2.12 g, 20.9 mmol). The reaction mixture was stirred at room temperature overnight. The DMF was evaporated in vacuo and the residue taken up in ethyl acetate (100 mL). The resulting white solid was filtered off and discarded. The filtrate was evaporated in vacuo and purified on silica with a gradient of
- 15 heptane to 2:5 heptane/EtOAc to give the desired product (6.52 g, 89%).

¹H NMR (CDCl₃): δ 3.69 (2H, s, CH₂N), 6.84 (1H, d, 1.0 Hz, imidazole CH),
7.10-7.15 (6H, m, 6 ArH), 7.32-7.37 (9H, m, 9 ArH), 7.41 (1H, d, 1.5 Hz,
imidazole CH);
IR (film): 3059, 1597, 1493, 1445, 1412, 1240, 1187, 1156, 1120, 1087, 1037, 991,
5 907, 871, and 751 cm⁻¹;
Analysis C₂₄H₁₉N₃: C, H, N;
mp 139-142°C.

Step 2 As for Intermediate II, Step 1

The desired compound was isolated in 63% yield.

10 ¹H NMR (CDCl₃): δ 1.20-1.35 (1H, m, cyclohexyl CH), 1.65-1.90 (7H, m,
cyclohexyl CH), 2.13-2.18 (2H, m, cyclohexyl CH), 6.82 (1H, d, 1.5 Hz, imidazole
CH), 7.09-7.50 (6H, m, ArH), 7.30-7.36 (9H, m, ArH), 7.39 (1H, d, 1.0 Hz,
imidazole CH);
IR (film): 3060, 2934, 2859, 2233, 1492, 1446, 1161, 1134, 1036, 974, 907, 832,
15 and 747 cm⁻¹;
MS (ES⁺) 418.5 (M⁺+H);
Analysis C₂₉H₂₇N₃: C, H, N;
mp 184-186°C.

Step 3 As for Intermediate XXIV, Step 1

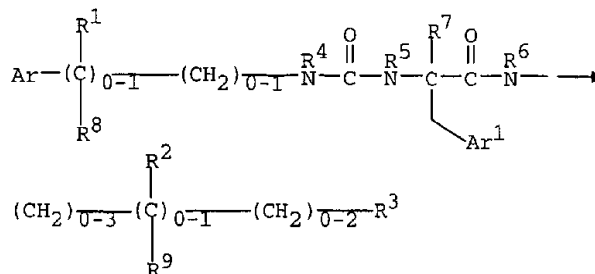
20 The Intermediate XXV was isolated in 73% yield.

¹H NMR (CDCl₃): 1.10-1.70 (2H, br s, NH₂), 1.26-1.52 (8H, m, cyclohexyl CH),
1.95-1.99 (2H, m, cyclohexyl CH), 2.67 (2H, s, CH₂NH₂), 6.54 (1H, d, 1.6 Hz,
imidazole CH), 7.12-7.17 (6H, m, ArH), 7.31-7.35 (9H, m, ArH), 7.41 (1H, d,
1.6 Hz, imidazole CH);
25 IR (film): 3374, 3059, 2927, 2852, 1598, 1493, 1445, 1324, 1231, 1184, 1118,
1087, 1036, 906, 870, 825, and 747 cm⁻¹.

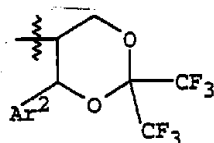
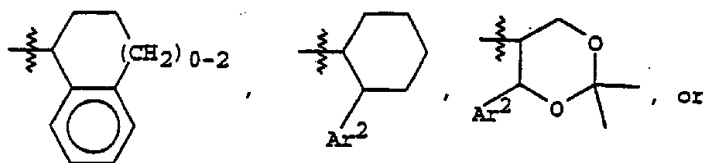
-100-
CLAIMS

What is claimed is:

1. A compound of Formula I



- 5 or a pharmaceutically acceptable salt thereof wherein
 Ar is phenyl or pyridyl unsubstituted or substituted by from 1 to
 3 substituents selected from alkyl, halogen, alkoxy, nitro, amino,
 NH₂CH₂-, cyano, CF₃-, -NHCONH₂, and CO₂R¹;
 R¹ is hydrogen or straight, branched, or cyclic alkyl of from 1 to 7 carbon
 10 atoms;
 R⁸ is hydrogen or forms a ring with R¹ of from 3 to 7 carbon atoms;
 R² is hydrogen or straight, branched, or cyclic alkyl of from 1 to 8 carbon
 atoms;
 R⁹ is hydrogen or forms a ring of from 3 to 7 carbon atoms with R²;
 15 Ar¹ can be independently selected from Ar and can also include pyridyl-N-
 oxide, indolyl, pyridyl, and imidazole;
 R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen and
 methyl;
 R³ can be independently selected from Ar or is hydrogen, hydroxy, NMe₂,
 20 N-methyl-pyrrole,



wherein Ar^2 is phenyl or pyridyl

with the proviso that when Ar^1 is phenyl, said phenyl is substituted; $-[CR^1(R^6)]_{0-1}-$
 $(CH_2)_{0-1}-$ is not $-(CH_2)_{1-2}-$; and $-(CH_2)_{0-3}-[CR^2(R^9)]_{0-1}-(CH_2)_{0-2}-$ is not $-(CH_2)_{1-6}-$.

2. A compound according to Claim 1 wherein

Ar is phenyl unsubstituted or substituted with 1 or 2 substituents selected
 from isopropyl, chloro, nitro, and cyano;

R^2 forms a ring of from 5-7 carbon atoms with R^9 ;

R^4 , R^5 , and R^6 are hydrogen;

R^7 is methyl or hydrogen; R^3 is 2-pyridyl or hydroxy; and

Ar^1 is indolyl, pyridyl, pyridyl-N-oxide, and imidazolyl.

3. A compound according to Claim 1 wherein

Ar is unsubstituted phenyl;

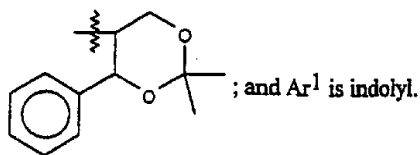
R^1 is cyclopentyl or tert-butyl;

R^4 and R^5 are hydrogen;

R^7 is methyl;

R^6 is hydrogen;

R^3 is phenyl with two isopropyl substituents, unsubstituted phenyl, or



4. A compound according to Claim 1 wherein

Ar is 2,6-diisopropyl-phenyl, 4-nitrophenyl, and 4-cyanophenyl;



-102-

R^4 , R^5 , and R^6 are hydrogen;

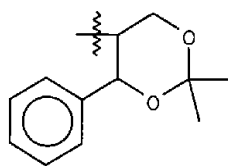
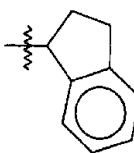
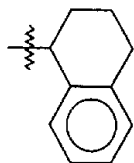
R^7 is methyl;

R^2 is hydrogen or forms a ring of 6 carbon atoms with R^9 ;

R^3 is hydroxyl,

5

2-pyridyl,



and Ar^1 is indolyl, pyridyl-N-oxide, pyridyl.

5. A compound according to Claim 1 and selected from:

N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;

10

N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-N-methyl-propionamide;

N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-1-methyl-ureido]-3-(1H-indol-3-yl)-propionamide.

6. A compound according to Claim 4 and selected from:

15

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-(1-oxy-pyridin-2-yl)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide; and

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-pyridin-2-yl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

7. A compound according to Claim 1 and selected from:

- 5 N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)ureido]-3-(1H-indol-3-yl)-N-methyl-propionamide;
- 10 N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-3-methyl-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- N-Cyclohexylmethyl-2-[3-(2,6-diisopropyl-phenyl)-1-methyl-ureido]-3-(1H-indol-3-yl)-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-(1-oxy-pyridin-2-yl)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 15 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-3-pyridin-2-yl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-3-(2-trifluoromethyl-phenyl)-propionamide;
- 2-Methyl-3-(2-nitro-phenyl)-2-[3-(4-nitro-phenyl)-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 20 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-imidazol-4-yl)-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- N-Cyclohexylmethyl-2-[3-(2,6-dimethoxy-phenyl)ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;
- 25 3-(1H-Indol-3-yl)-2-methyl-2-[3-[1-(4-nitro-phenyl)-ethyl]-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 3-(1H-Indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide;
- 4-(3-{2-(1H-Indol-3-yl)-1-methyl-1-[(1-pyridin-2-yl-cyclohexylmethyl)-carbamoyl]-ethyl}-ureido)-benzoic acid ethyl ester;
- 30 3-(1H-Indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-2-[3-(4-trifluoromethylphenyl)-ureido]-propionamide;

-104-

2-[3-(4-Cyano-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide

N-Cyclohexylmethyl-3-(1H-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide; and

5 N-(1-Hydroxy-cyclohexylmethyl)-3-(1H-indol-3-yl)-2-methyl-2-[3-(4-nitro-phenyl)-ureido]-propionamide.

8. A compound according to Claim 1 and named:

(S)-N-(2,6-Diisopropyl-phenyl)-2-[3-(2,2-dimethyl-1-phenyl-propyl)-ureido]-3-(1H-indol-3-yl)-propionamide.

10 9. A compound according to Claim 1 and selected from:

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-3-(1H-indol-3-yl)-2-methyl-propionamide;

N-(2-Cyclohexyl-ethyl)-2-[3-(2,6-diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide;

15 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-propionamide:

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-propionamide;

20 2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(2-phenyl-cyclohexyl)-propionamide;

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-N-indan-1-yl-3-(1H-indol-3-yl)-2-methyl-propionamide; and

2-[3-(2,6-Diisopropyl-phenyl)-ureido]-3-(1H-indol-3-yl)-2-methyl-N-(1-pyridin-2-yl-cyclohexylmethyl)-propionamide.

25 10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

11. A method of antagonizing the effects of neuromedin B and/or gastrin-releasing peptide at bombesin receptors which comprises administering a compound according to Claim 1 to a patient.
 - 5 12. A method of treating depression in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 13. A method of treating seasonal affective disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 - 10 14. A method of treating feeding disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 - 15 15. A method of treating gastrointestinal disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 16. A method of treating sleeping disorders in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 - 20 17. A method of treating memory impairment in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
 18. A method of treating cancer in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
-

19. A method of treating small cell lung carcinoma in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
20. A method of treating psychoses in a patient in need of said treatment comprising administering a therapeutically effective amount of a compound according to Claim 1.
21. Use of a compound according to Claim 1 for the manufacture of a medicament for antagonizing the effects of neuromedin B and/or gastrin releasing peptide at bombesin receptors.
22. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of depression.
23. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of seasonal affective disorders.
24. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of feeding disorders.
25. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of gastrointestinal disorders.
26. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of sleeping disorders.
27. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of memory impairment.
28. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of cancer.



29. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of small cell lung carcinoma.
30. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment of psychoses.
- 5 31. A compound of Formula I, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
32. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
- 10 33. A method of antagonizing the effects of neuromedin B and/or gastrin releasing peptide at bombesin receptors, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
34. A method of treating depression, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
- 15 35. A method of treating seasonal affective disorders, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
36. A method of treating feeding disorders, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
- 20 37. A method of treating gastrointestinal disorders, substantially as herein described with reference to one or more of the examples but excluding comparative examples.



38. A method of treating sleeping disorders, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
39. A method of treating memory impairment, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
- 5 40. A method of treating cancer, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
41. A method of treating small cell lung carcinoma, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
- 10 42. A method of treating psychoses, substantially as herein described with reference to one or more of the examples but excluding comparative examples.
43. Use of a compound according to claim 1 for the manufacture of a medicament, substantially as herein described with reference to one or more of the examples but excluding comparative examples.

15 DATED this 14th Day of December 1999

WARNER-LAMBERT COMPANY

Attorney: IVAN A. RAJKOVIC
Fellow Institute of Patent Attorneys of Australia
of BALDWIN SHELSTON WATERS

