95 97

Señor

SUPERINTENDENTE DE INDUSTRIA Y COM

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: P1.-**ASTRA ZENECA AB**.-Solicitud de Patente de Invención para **"NUEVOS ANTAGONISTAS DEL NPY"**.-Clase A.61.-Expediente número **00-049.694**.-

1. Me refiero a mi solicitud de patente arriba nombrada de fecha de 4 de Julio de 2000.

2. Anexos me permito presentar a usted:

(1) Copia autentica de la primera solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud sueca número 9902596-7 de 6 de Julio de 1999, junto con la traducción oficial No. 5.733, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de las solicitud sueca número 9902596-7, respecto de la cual se reivindica prioridad en el presente caso;

(3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 088534 de 30 de Junio de 2000; y

(4) Traducción Oficial No. 238/07-00, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 300582 de 14 de Julio de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

97 ~~99~~

REPUBLICA DE COLOMBIA
MINSTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DEL MINISTERIO DE RELACIONES EXTERIORES

C E R T I F I C A

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO,** como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES,** según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá.

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999

CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones

CONSTITUYO SEXTO ENCARGADO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

13 ABR 1999

PABLO MENDEZ BARAJAS
NOTARIO (E)

AstraZeneca 98
00.049644

TRADUCCION OFICIAL No. 5.733

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

----

PRV

DIRECCION NACIONAL DE PATENTES Y REGISTRO

TRADUCCION OFICIAL No. 5.733
Maria Luisa Briceño de Restrepo
Intérprete Oficial
No. 0793 del Min. de Justicia

Certificado

Por el presente se certifica que la anexa es una copia fiel de los documentos registrados originalmente ante la Oficina de Patentes y Registro en relación con la siguiente solicitud de patente.

La solicitud fue registrada originalmente en inglés.

(71) Solicitante(s) Astra AB, Södertälje SE

(21) Solicitud de patente número 9902596-7

(86) Fecha de registro 6-7-1999

Estocolmo, 25-5-2000

Por la Oficina de Patentes y Registro

(Firma)

Emma Högberg

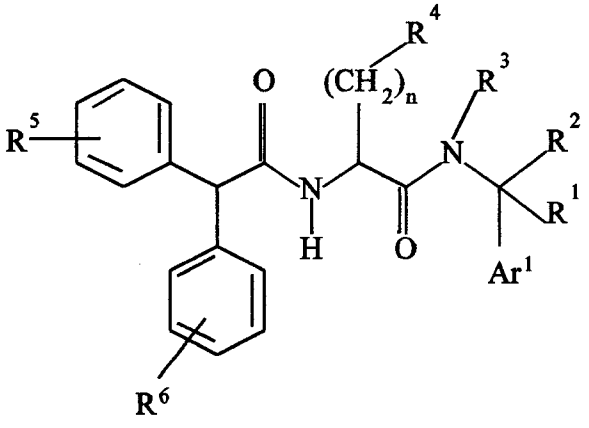
Derechos 170:-

EN ESPAÑOL, las autenticaciones de la firma anterior hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 088539 de fecha 30 de junio del 2.000

ANEXO:

Reivindicaciones

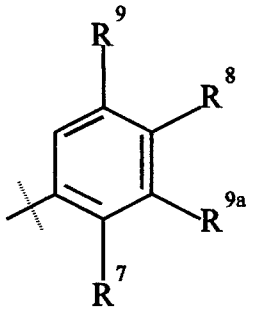
1. Un compuesto de la fórmula I



en donde

n representa 1, 2 o 3;

Ar^1 representa un fragmento estructural de la fórmula



o representa 1- o 2-naftilo, este último grupo opcionalmente sustituido por uno o más sustitutos escogidos entre OH, halo y alcoxi C_{1-7};

R^7 representa H u OH:

R^8 representa H, halo, $-(CH_2)_mOR^{16}$, $-(CH_2)_mN(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{17})CH_2C(O)OR^{16}$, $-(CH_2)_pN(R^{18})C(O)N(R^{16})R^{17}$, $-(CH_2)_pN(R^{17})C(O)N(R^{18})CH_2C(O)OR^{16}$, $(CH_2)_pN(R^{17})C(O)OR^{16a}$, $-O(CH_2)_pC(O)OR^{16}$, $N(R^{17})(CH_2)_pC(O)OR^{16}$,
o, junto con R^9 o R^{9a}, forma un grupo metilenodioxi;

R^9 y R^{9a} representan, independientemente, H, halo, OH, alquilo C_{1-7} o alcoxi C_{1-7}, y/o uno de los radicales R^9 y R^{9a} puede, junto con R^8, formar un grupo metilenodioxi;

R^{16} representa H, alquilo C_{1-7} o - $(CH_2)_q$-fenilo;

R^{16a} representa alquilo C_{1-7} o - $(CH_2)_q$-fenilo;

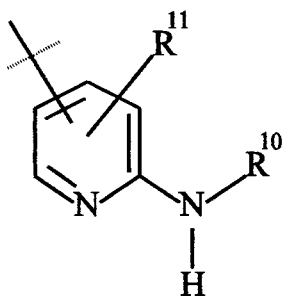
m representa 0, 1, 2 o 3;

p representa 1, 2, 3 o 4;

q representa 0 o 1

R^1 representa H, $C(O)NH_2$ o alquilo C_{1-7} (opcionalmente sustituido y/o terminado por uno o varios sustitutos escogidos entre hidroxi y amino);

R^4 representa un fragmento estructural de la fórmula II



II

R^{10} y R^{11} representan, independientemente, H o alquilo C_{1-4};

R^5 y R^6 representan, independientemente, uno o varios sustitutos opcionales escogidos entre OH, alquilo C_{1-4}, alcoxi C_{1-4}, halo, $N(R^{12})R^{13}$, $-N(R^{17})CH_2C(O)OR^{14}$ y $OCH_2C(O)OR^{15}$;

R^2, R^3, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} y R^{18} representan, independientemente, H o alquilo C_{1-7};

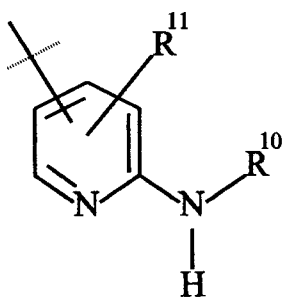
o un derivado farmaceuticamente aceptable del mismo.

2. Un compuesto como el reivindicado en la Reivindicación 1 en el que R^1 representa H o metilo.

3. Un compuesto como el reivindicado en la Reivindicación 1 o la Reivindicación 2 en el que R^2 representa H.

4. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^1 representa H o metilo.

5. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^4 representa un fragmento estructural de la fórmula



6. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^5 está ausente o bien representa un solo sustituto escogido entre OH, halo, metilo o metoxi.

7. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^6 está ausente o bien representa un solo sustituto escogido entre OH, halo, metilo o metoxi.

8. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^7 representa H.

9. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^8 representa OCH_3, halo, $-CH_2C(O)NH_2$, $-CH_2N(H)C(O)NH_2$, NH_2 u OH.

10. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^9 representa H.

11. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^{10} representa H.

12. Un compuesto como el reivindicado en cualquiera de las reivindicaciones precedentes en el que R^{11} representa H.

13. Una preparación farmacéutica que incluye un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, en mezcla con un coadyuvante, diluente o portador farmaceuticamente aceptable.

14. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para usarlo como un producto farmacéutico.

TRADUCCIÓN OFICIAL No. 5733
María Luisa Brizard de Rodrigo
Intérprete Oficial
Inscrita ante la Corte de Justicia

15. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para usarlo en el tratamiento de un desorden que se debe al neuropéptido Y.

16. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para usarlo en el tratamiento de una enfermedad cardiovascular.

17. El uso de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para la fabricación de un medicamento para usarlo en el tratamiento de un desorden que se debe al neuropéptido Y.

18. El uso de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para la fabricación de un medicamento para usarlo en el tratamiento de una enfermedad cardiovascular.

19. Un método para el tratamiento de una enfermedad cardiovascular, que consiste en la administración de una cantidad terapeuticamente efectiva de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, a una persona que sufre de tal enfermedad o es susceptible a la misma.

20. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 12 o un derivado farmaceuticamente aceptable del mismo, para usarlo en el tratamiento de un desorden que se debe al subreceptor Y_1 del neuropéptido Y.

21. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para usarlo en el tratamiento de vasoconstricción.

22. El uso de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para la fabricación de un medicamento para usarlo en el tratamiento de un desorden que se debe al subreceptor Y_1 del neuropéptido Y.

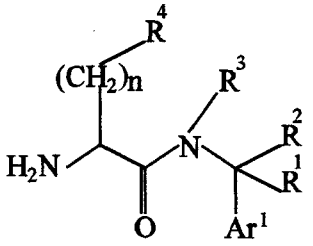
23. El uso de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, para la fabricación de un medicamento para usarlo en el tratamiento de vasoconstricción.

24. Un método para el tratamiento de vasoconstricción, que consiste en la

administración de una cantidad terapeuticamente efectiva de un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 12, o un derivado farmaceuticamente aceptable del mismo, a una persona que sufre de tal situación o es susceptible a la misma.

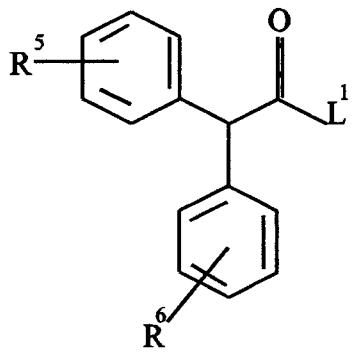
25. Un procedimiento para la preparación de un compuesto de la fórmula I definida en la Reivindicación 1, que consiste en:

(a) hacer reaccionar un compuesto de la fórmula IV,



IV

en donde Ar^1, R^1, R^2, R^3, R^4 y *n* corresponden a las definiciones dadas en la Reivindicación 1, con un compuesto de la fórmula V,

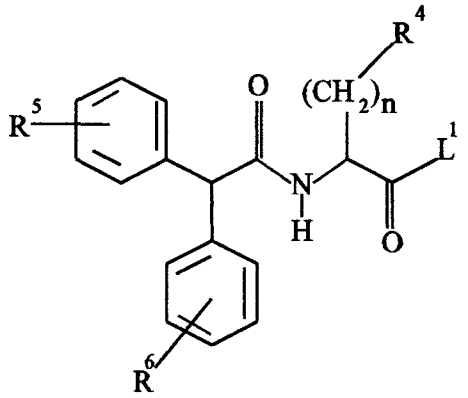


V

en donde L^1 representa un grupo que sale y R^5 y R^6 corresponden a las definiciones dadas

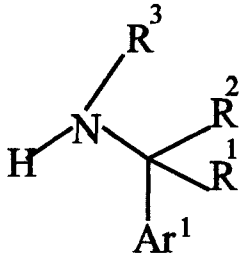
en la Reivindicación 1;

(b) hacer reaccionar un compuesto de la fórmula VI



VI

en donde L^1 corresponde a la definición dada arriba y R^4, R^5, R^6 y *n* corresponden a las definiciones dadas en la Reivindicación 1, con un compuesto de la fórmula VII



VII

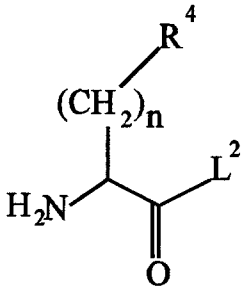
en donde Ar^1, R^1, R^2, y R^3 corresponden a las definiciones dadas en la Reivindicación 1;

(c) convertir uno de los sustitutos R^5 y/o R^6 en otro;

(d) convertir un sustituto de Ar^1 en otro; o

(e) desproteger un derivado protegido de un compuesto de la fórmula I definida en la Reivindicación 1.

26. Un compuesto de la fórmula VIII,



VIII

o un derivado protegido del mismo, en donde L^2 representa un grupo que sale y R^4 y *n* corresponden a las definiciones dadas en la Reivindicación 1

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: $99.000,oo

BOGOTA, 4 DE JULIO DEL 2000.

TRADUCTOR OFICIAL No. 5733

María Luisa Brigard de Restrepo

Intérprete Oficial

Res. No. 0765 del Min. de Justicia

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* Astra AB, Södertälje SE
Applicant (s)

(21) *Patentansökningsnummer* 9902596-7
Patent application number

(86) *Ingivningsdatum* 1999-07-06
Date of filing

Stockholm, 2000-05-25

För Patent- och registreringsverket
For the Patent- and Registration Office

Emma Högberg

Avgift
Fee 170:-

La infrascrita Anne-Marie Bondo, Notario de Estocolmo, Suecia, certifica que
Emma Högberg,
autorizado para firmar en nombre de la
PRV, Dirección Nacional de Patentes y Registros,
ha otorgado y firmado el documento que
Derechos 250.- Estocolmo, 2000-06-07
Coronas De oficio:

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

... CIA EN

FECHA ......2000 -06- 0 9 ...... 2 ...

Presta la ... FE de que ... documento es sin... A ...
Anne-Marie Boude, Notario Público Estocolmo, Suecia ......

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO	
Impuesto de Timbre	
Siete ...... dólares US$	7
Derechos Consulares	
Quince ...... dólares US$	15

CONSULADO DE COLOMBIA
ESTOCOLMO

NO SE ASUME
RESPONSABILIDAD ...

2000 JUN 30 A 11:13

JEFE DE LEGALIZACIONES
...

... 0 0 8 ...
CUYA FIRMA ... EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

TRADUCCION OFICIAL No 5.733
Maria Luisa Brickerd de Restrepo
Interprete Oficial
Res. No. 0782 del ... de ...

PHARMACEUTICALLY ACTIVE COMPOUNDS

Field of the Invention

This invention relates to novel pharmaceutically useful compounds, in particular antagonists of neuropeptide Y, the use of such compounds as medicaments, pharmaceutical compositions containing them and synthetic routes to their production.

Background

Neuropeptide Y (NPY) is a peptide consisting of 36 amino acids. In recent years it has been established that NPY is an important co-transmitter in the peripheral sympathetic nervous system.

It has been postulated (see Pharmacological Reviews (1996) **48,** 113) that the effects of sympathetic nerve activation are not only due to the neuronal release of noradrenaline but may also be the result of a simultaneous release of NPY from the sympathetic nerve terminal.

Released NPY is known to elicit marked constriction of blood vessels in both the heart (coronary arteries) and in most peripheral organs. This vasoconstrictive effect of NPY is believed to be mediated by a receptor sub-type known as Y_1.

Released NPY may also act on autonomic nerve endings to inhibit the release of neurotransmitters and, in doing so, reduce the cardiac vagal tone as a result of decreased acetylcholine release. This effect of NPY is believed to be mediated by a receptor sub-type known as Y_2.

Other NPY-receptor sub-types, including the Y_3, Y_4, Y_5 and Y_6 sub-receptors, have been identified. The precise functions of these sub-receptors have not been identified in any detail, but the Y_5 sub-receptor is thought to be involved in feeding and eating regulation (see Exp. Opin. Invest. Drugs, **6**, 437 (1997)).

Increased plasma concentrations of NPY have been found in several cardiovascular diseases including angina pectoris, myocardial infarction, congestive heart failure and hypertension. Further, emotional stress has been shown to cause a significant increase in plasma NPY levels (see Circulation (1994) **90**, I-268, Abstract No. 1445). Such observations suggest a significant pathogenic role for NPY in ischemic heart disease and hypertension. Moreover, by causing coronary vasoconstriction and reduced vagal tone, NPY may predispose a patient to ventricular fibrillation and sudden cardiac death.

Effective NPY antagonists would therefore be expected to be useful in the treatment of *inter alia* cardiovascular diseases.

Prior Art

Non-peptide antagonists of NPY have been disclosed in *inter alia* International Patent Applications WO 94/17035, WO 97/19911, WO 97/19913, WO 97/19914, WO 96/22305, and WO 99/15498.

In particular, International Patent Application WO 99/15498 discloses certain amino acid derivatives, including (*R*)-N^2-(diphenylacetyl)-*N*-(phenylmethyl)arginine amide derivatives, as antagonists of NPY. The

or represents 1- or 2-naphthyl, which latter group is optionally substituted by one or more substituents selected from OH, halo and C_{1-7} alkoxy;

R^7 represents H or OH;

R^8 represents H, halo, $-(CH_2)_mOR^{16}$, $-(CH_2)_mN(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{17})CH_2C(O)OR^{16}$, $-(CH_2)_pN(R^{18})C(O)N(R^{16})R^{17}$, $-(CH_2)_pN(R^{17})C(O)N(R^{18})CH_2C(O)OR^{16}$, $-(CH_2)_pN(R^{17})C(O)OR^{16a}$, $-O(CH_2)_pC(O)OR^{16}$, $-N(R^{17})(CH_2)_pC(O)OR^{16}$, or, together with either of R^9 or R^{9a}, forms a methylenedioxy group;

R^9 and R^{9a} independently represent H, halo, OH, C_{1-7} alkyl or C_{1-7} alkoxy, and/or one of R^9 and R^{9a} may, together with R^8, form a methylenedioxy group;

R^{16} represents H, C_{1-7} alkyl or $-(CH_2)_q$-phenyl;

R^{16a} represents C_{1-7} alkyl or $-(CH_2)_q$-phenyl;

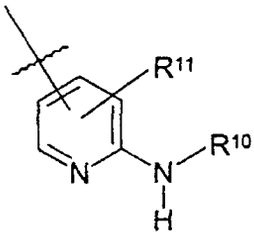
m represents 0, 1, 2, or 3;

p represents 1, 2, 3 or 4;

q represents 0 or 1;

R^1 represents H, $C(O)NH_2$ or C_{1-4} alkyl (optionally substituted and/or terminated by one or more substituents selected from hydroxy and amino);

R^4 represents a structural fragment of formula II,



II

R^{10} and R^{11} independently represent H or C_{1-4} alkyl;

R^5 and R^6 independently represent one or more optional substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halo, $N(R^{12})R^{13}$, $-N(R^{17})CH_2C(O)OR^{14}$ and $OCH_2C(O)OR^{15}$;

R^2, R^3, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} independently represent H or C_{1-7} alkyl;

or a pharmaceutically acceptable derivative thereof (herein referred to as "the compounds of the invention").

Pharmaceutically acceptable derivatives include solvates and salts. Particular salts that may be mentioned include those of hydrochloric, acetic, trifluoroacetic and camphorsulphonic acid.

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation of a diastereomeric salt or chiral HPLC techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means

(e.g. HPLC, chromatography over silica). All stereoisomers, including mixtures thereof, are included within the scope of the invention.

Alkyl groups which R^1, R^2, R^3, R^5, R^6, R^9, R^{9a}, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{16a}, R^{17} and R^{18} may represent; and alkoxy groups which R^5, R^6 and R^9 and R^{9a} may represent and with which Ar^1 (when it represents naphthyl) may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic. Further, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic. Such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen. Such alkyl and alkoxy groups may also be substituted by one or more fluoro groups.

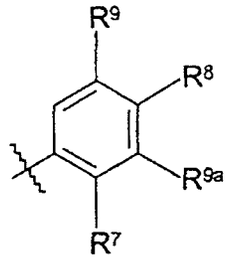
Further, alkyl groups which R^{16}, R^{17} and R^{18} may represent may also be substituted by one or two OH groups, provided that OH is not attached to the carbon atom of that alkyl group that is also attached to the rest of the group of which R^{16}, R^{17} or R^{18} (as appropriate) forms a part.

$-(CH_2)-$ containing chains which R^8, R^{16} and R^{16a} may include, may, in the $-(CH_2)-$ chain part, be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched. Such $-(CH_2)-$ containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen.

As used herein, the term "halo" includes fluoro, chloro, bromo or iodo.

For the avoidance of doubt, when a compound of formula I may comprise more than one of the substituents identified herein, the identity of each of those substituents is independent of the identity/identities of the other(s). For example, when a compound of formula I is provided in which R^8 represents $-(CH_2)_mN(R^{16})R^{17}$ and R^5 represents $-N(R^{17})CH_2C(O)OR^{14}$, then the two R^{17} substituents are not necessarily the same (though this possibility is not excluded).

Wavy lines on carbon atoms in e.g. the structural fragment



signify bond positions of the fragments.

Abbreviations are listed at the end of this specification.

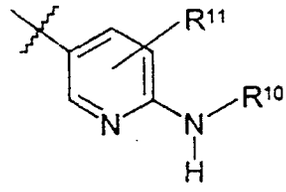
Preferred compounds of formula I include those wherein:

R^1 represents H or methyl;

R^2 represents H;

R^3 represents H or methyl;

R^4 represents a structural fragment of formula



R^5 is either absent or represents a single substituent selected from OH, halo, methyl and methoxy;

R^6 is either absent or represents a single substituent selected from OH, halo, methyl and methoxy;

R^7 represents H;

R^8 represents OCH_3, halo, $-CH_2C(O)NH_2$, $-CH_2N(H)C(O)NH_2$, NH_2 or OH;

R^9 represents H;

R^{10} represents H;

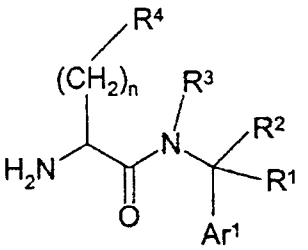
R^{11} represents H.

Preferred compounds of the invention include the compounds of the Examples disclosed hereinafter.

Preparation

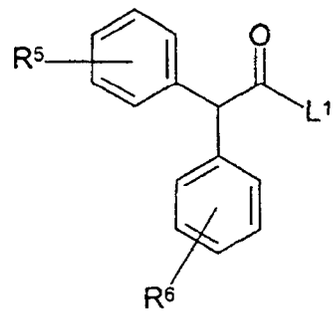
According to the invention there is also provided a process for the preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula IV,



IV

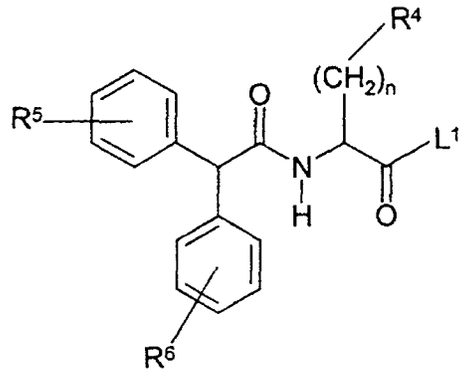
wherein Ar^1, R^1, R^2, R^3, R^4 and n are as hereinbefore defined, with a compound of formula V,



V

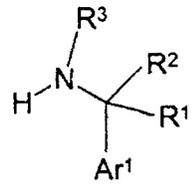
wherein L^1 represents a leaving group (e.g. OH, Hal, nitrophenoxy), Hal represents Cl, Br or I, and R^5 and R^6 are as hereinbefore defined, for example under peptide coupling conditions known to those skilled in the art (e.g. in the presence of a reaction-inert solvent (e.g. THF, dichloromethane, acetonitrile, DMF or mixtures thereof), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, pyridine or K_2CO_3) and, in the case when L^1 represents OH, in the presence of a peptide coupling agent (e.g. DCC or EDC));

(b) reaction of a compound of formula VI,



VI

wherein L^1, R^4, R^5, R^6 and n are as hereinbefore defined, with a compound of formula VII,



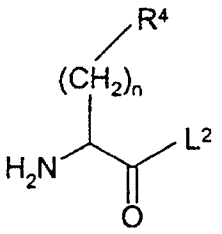
VII

wherein Ar^1, R^1, R^2 and R^3 are as hereinbefore defined, for example under peptide coupling conditions known to those skilled in the art (e.g. as described hereinbefore (process step (a));

(c) conversion of one R^5 and/or R^6 substituent to another using techniques well known to those skilled in the art; or

(d) conversion of one substituent on Ar^1 to another using techniques well known to those skilled in the art.

Compounds of formula IV may be prepared by reaction of a compound of formula VIII,



VIII

wherein L^2 represents a leaving group and R^4 and n are as hereinbefore defined, with a compound of formula VII, as hereinbefore defined, for example under peptide coupling conditions known to those skilled in the art (e.g. as described hereinbefore for the preparation of compounds of formula I (process step (a)).

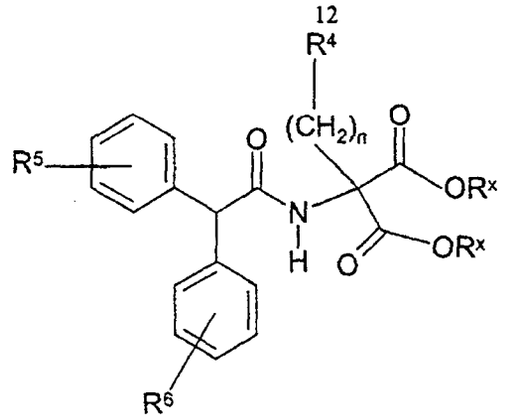
Leaving groups that L^2 may represent include "activating" groups for carboxylic acids that may be employed in the formation of amides (i.e. those that are suitable for use in the acylation of amines). Suitable groups thus include those listed in *Comprehensive Organic Chemistry*, Eds. Barton and Ollis, Vol. **2**, Pergamon Press (1979), especially those listed at pages 636 to 638 and 958-964; *Principles of Peptide Synthesis*, 2nd edition, Bodanszky, Springer-Verlag (1993); and *The Peptides, Analysis,*

Synthesis, Biology, Eds. Gross and Meienhofer, Academic Press (1979), the disclosures in which documents are hereby incorporated by reference.

Thus, suitable leaving groups that L^2 may represent include OH, OR^{20}, OPy, OSu, OBt, OAt, SH, SR^{20}, SPy, halo, N_3, CN, BF_4, 1-imidazolyl, 1-(1,2,4)-triazolyl, $O\text{-}(OEt)C{=}CH_2$, $O\text{-}CH_2C(O)OR^{20}$, OCH_2CN, $ON(H)C(O)OR^{20}$, $ON(H)C(O)R^{20}$, $ON(R^{20})_2$, $ON{=}C(Ph)_2$, $ON{=}C(CN)C(O)OEt$, $O(N(H)(R))C{=}N\text{-}R^{20}$, $O(N(H)(Et))C{=}N\text{-}(CH_2)_3\text{-}N(Me)_2$, OOC-H, $OOC\text{-}R^{20}$, $O_3S\text{-}R^{20}$, OTs, $OOC\text{-}N(R^{20})_2$, $OOC\text{-}OR^{20}$, $OP(Cl)_2$, $OP(Cl)OR^{20}$, $OP(OR^{20})_2$, $O\text{-}P^+(R^{20})_3$, $O\text{-}P^+(NMe)_3$, $OP(=O)(Cl)_2$, $OP(=O)(R^{20})_2$ and $OP(=O)(OR^{20})_2$, in which, in each case, R^{20} may represent $C_{1\text{-}7}$ alkyl, aryl (e.g. phenyl or naphthyl) or $C_{1\text{-}4}$ alkylaryl (e.g. benzyl), which aryl and alkylaryl groups are optionally substituted by one or more of halo, NO_2, CN and SO_2Me. Alkyl groups that R^{20} may represent may be linear or branched, saturated or unsaturated and/or cyclic, acyclic or part cyclic/acyclic as described hereinbefore.

Compounds of formula VI may be prepared by reaction of a compound of formula VIII in which L^2 represents OH with a compound of formula V, as hereinbefore defined, for example under peptide coupling conditions known to those skilled in the art (e.g. as described hereinbefore for the preparation of compounds of formula I (process step (a)), followed (if required) by conversion of the OH group of the resultant compound to another group that L^1 may represent under conditions well known to those skilled in the art.

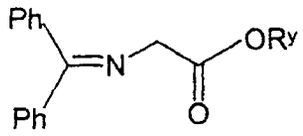
Compounds of formula VI may alternatively be prepared by hydrolytic decarboxylation of a corresponding compound of formula IX,



IX

wherein R^x represents C_{1-4} alkyl and R^4, R^5, R^6 and n are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. at between room and reflux temperature in the presence of a suitable source of the hydroxide ion (e.g. potassium hydroxide) and an appropriate solvent (e.g. water, dioxane, or a mixture thereof)), followed (if required) by conversion of the OH group of the resultant compound to another group that L^1 may represent under conditions well known to those skilled in the art.

Compounds of formula VIII may be prepared by reaction of a compound of formula X,



X

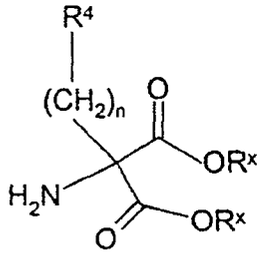
wherein R^y represents C_{1-4} alkyl or benzyl and Ph represents phenyl, with a compound of formula XI,

$$R^4\text{-}(CH_2)_n\text{-}L^3 \qquad \text{XI}$$

wherein L^3 represents a leaving group (e.g. Hal, alkanesulfonate or arenesulfonate) and R^4, n and Hal are as hereinbefore defined, for example at between -80°C and reflux in the presence of a suitable base (e.g. sodium hydride, lithium diisopropylamide or potassium carbonate) and a reaction-inert solvent (e.g. acetonitrile, THF or DMF), followed by

removal of the *N*-diphenylmethylene group under conditions known to those skilled in the art (e.g. by acidic hydrolysis or hydrogenation) as well as conversion of the OR^y group to an L^2 group (which may take place simultaneously with the removal of the *N*-diphenylmethylene group) under conditions known to those skilled in the art (e.g. by way of hydrogenation or acidic or basic hydrolysis).

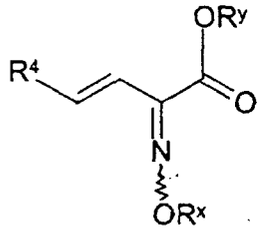
Compounds of formula VIII may alternatively be prepared by hydrolytic decarboxylation of a corresponding compound of formula XII,



XII

wherein R^4, R^x and n are as hereinbefore defined, for example under conditions as described hereinbefore for the preparation of compounds of formula VI, followed (if required) by conversion of the OH group of the resultant compound to another group that L^2 may represent under conditions well known to those skilled in the art.

Compounds of formula VIII in which n represents 2 may alternatively be prepared by reduction of a corresponding compound of formula XIII,

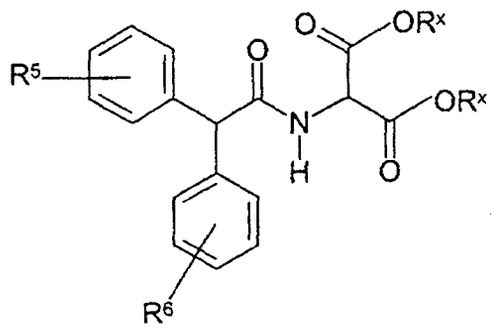


XIII

wherein the wavy bond indicates optional *cis* or *trans* stereochemistry and R^4, R^x and R^y are as hereinbefore defined, for example under conditions well known to those skilled in the art (e.g. hydrogenation in the presence

of a suitable catalyst (e.g. supported palladium) and a reaction-inert solvent (e.g. ethanol, acetic acid or a mixture thereof)), followed by conversion of the OR^y group of the resultant intermediate to an L^2 group (which conversion may take place simultaneously with the reduction step).

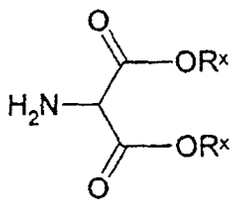
Compounds of formula IX may be prepared by reaction of a compound of formula XIV,



XIV

wherein R^5, R^6 and R^x are as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. DBU or K_2CO_3) and a reaction-inert solvent (e.g. acetonitrile or DMF).

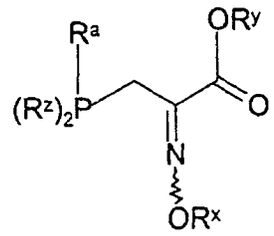
Compounds of formula XII may be prepared by reaction of a compound of formula XV,



XV

wherein R^x is as hereinbefore defined, with a compound of formula XI, as hereinbefore defined, for example under conditions described hereinbefore for the preparation of compounds of formula IX.

Compounds of formula XIII may be prepared by reaction of a compound of formula XVI,



XVI

wherein R^a and R^z independently represent phenyl or C_{1-6} alkyl (in which cases the phosphorous atom carries a positive charge which is countered by an anion (e.g. a halide ion)), or R^a represents oxo and R^z represents C_{1-6} alkoxy, and R^y is as hereinbefore defined, with a compound of formula XVII,

R^4-CHO XVII

wherein R^4 is as hereinbefore defined, for example under conditions that are known to those skilled in the art (e.g. as described in *Tetrahedron Lett.* **1988**, *29*, 3361-3364, such as in the presence of a suitable base (e.g. K_2CO_3, NaH, an alkyllithium or DBU) and a reaction-inert solvent (e.g. DMF, DMSO, benzene or dimethyl ether)).

Compounds of formula XIV may be prepared by reaction of a compound of formula V, as hereinbefore defined, with a compound of formula XV, as hereinbefore defined, for example under peptide coupling conditions known to those skilled in the art (e.g. as described hereinbefore for the preparation of compounds of formula I (process step (a))).

Compounds of formula V, VII, X, XI, XV, XVI and XVII and derivatives thereof, are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard

techniques, from readily available starting materials using appropriate reagents and reaction conditions.

Substituents on the aryl (e.g. phenyl), and (if appropriate) heterocyclic, group(s) in compounds defined herein may be converted to other substituents using techniques well known to those skilled in the art. For example, amino may be converted to amido or ureidyl, amido may be hydrolysed to amino, hydroxy may be converted to alkoxy, alkoxy may be hydrolysed to hydroxy etc.

The skilled person will also appreciate that other various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above, the functional groups of intermediate compounds may be, or may need to be, protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl and alkylcarbonyl groups (e.g. methyl- and ethylcarbonyl groups). Suitable protecting groups for amino include benzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6} alkyl, allyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by JWF McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, TW Greene & PGM Wutz, Wiley-Interscience (1991).

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned herein may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those associated hereinbefore with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis.

The above procedures may be adapted as appropriate to the particular reactants and groups involved and other variants will be evident to the skilled chemist by reference to standard textbooks and to the examples

provided hereinafter to enable all of the compounds of formula I to be prepared.

It will be appreciated by those skilled in the art that, certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Further, certain compounds of formula I may act as prodrugs of other compounds of formula I.

All prodrugs of compounds of formula I are included within the scope of the invention.

Medical and pharmaceutical use

The compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, the compounds of the invention are potent antagonists of NPY for example as demonstrated in the tests described below.

The compounds of the invention are thus expected to be useful in the treatment of diseases/disorders which are/may be mediated by NPY, such as cardiovascular diseases.

The compounds of the invention are thus indicated for use in the treatment of coronary heart diseases such as angina pectoris, myocardial infarction and syndrome X as well as high blood pressure, hypertension and chronic heart insufficiency.

According to a further aspect of the invention, there is provided a method of treatment of a cardiovascular disease, which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

By the term "treatment", we include both therapeutic (curative) or prophylactic treatment.

The compounds of the invention are also indicated for use in the treatment of other diseases in which NPY is thought to play a pathogenic role, such as chronic kidney failure, tumour diseases such as phaeochromocytoma, infections, migraine, hyperthyroidism as well as obesity and diabetes.

Compounds of the invention have been found to be selective antagonists of the NPY sub-receptor Y_1, for example as demonstrated in the tests described below.

The compounds of the invention thus find particularly utility in the inhibition of vasoconstriction and in disease states characterised thereby such as migraine, Horton's syndrome, Raynauld's disease, vasospasm

after subarachnoid haemorrhage, angina pectoris, coronary infarction, heart failure, cardiac arrhythmias, hypertension, endotoxin shock and stroke.

According to a further aspect of the invention there is provided a method of treatment of vasoconstriction, which method comprises administration of a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, by any other parenteral route or *via* inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutically acceptable non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with other therapeutic agents which are useful in the treatment of cardiovascular disease, for example β-adrenoceptor antagonists, ACE-inhibitors, diuretics, and calcium antagonists.

The skilled person will also appreciate that compounds of the invention may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable doses of the compounds of the invention in therapeutic treatment of humans are about 0.1-1 mg/kg body weight per day at peroral administration and 0.001-0.1 mg/kg body weight per minute at parenteral administration.

Compounds of the invention may have the advantage that they may be more efficacious, be less toxic, be longer acting, produce fewer side effects, have a broader range of activity, be more potent, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

Biological Tests

Test A

Binding to NPY Y_1/Y_2 Receptors *in vitro*

(a) Preparation of Receptor Containing Membranes

(i) Y_1 receptors

The main portion of the rat brain cortex was used for this preparation. The rats (male or female Sprague-Dawley rats, weighing 150-250 g) were killed using CO_2 followed by bleeding. The brains were excised, and put in ice cold buffer (0.3 M sucrose, 5 mM HEPES; pH 7.4).

The material was diluted in 10 volumes of ice cold buffer, cut in smaller pieces, and homogenised first with a polytrone followed by 10 strokes at maximum speed with a Potter-Elvehjem homogeniser.

The homogenate was centrifuged at 650 x g at 4°C for 10 minutes. The supernatant was further centrifuged at 33 000 x g at 4°C for 19 minutes. The pellets were washed once by resolving them in buffer and repeating the last centrifugation step. The final pellets were resolved in a small volume (0.3-1 mL per gram tissue) of buffer complemented with 10% (v/v) glycerol. Aliquots (~200 µL) were quickly frozen in MeOH and dry ice, and stored at -80°C until further use.

The protein concentration was determined according to Bradford (Anal. Biochem. (1976) **72**, 248). The Y_1 preparation contained approximately 70-80% Y_1 receptors.

(ii) Y_2 receptors

This preparation was performed using pig spleen from a local slaughter house (Farmek Ekonomisk, Förening, Varberg, Sweden). The preparative procedure was the same as for the Y_1 receptor above. The resulting membranes contained approximately 80-90% Y_2 receptors.

(b) Receptor Binding Assay

In a typical experiment, 150 µg of Y_1 or Y_2 receptor containing membranes was mixed with ^{3}H-NPY and test compound in different concentrations. Membranes and ligands were diluted in the assay buffer (137 mM NaCl, 2.7 mM KCl, 2.1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 0.2% (w/v) bovine serum albumin, 20 mM HEPES; pH 7.4). The samples were incubated for 60 minutes at 30°C, and the binding reaction was

stopped by rapid filtration on glass fibre filters using a cell harvester to separate unbound and bound isotope labelled ligand. The radioactivity collected on the filters was determined by liquid scintillation counting.

Non specific binding (non NPY related binding) was estimated in the presence of a high concentration (0.1 μM) of unlabelled NPY. The difference between total binding (in the absence of NPY/test compound) and non specific binding was expressed as specific binding and is used at the maximal response in each experiment.

Test B

The Effects of Test Compounds on NPY in Anaesthetised Rats

Male Sprague-Dawley rats (300-450 g) from Charles River UK were used. The animals were initially anaesthetised with sodium pentobarbitone 70 mg/kg i.p. The anaesthesia was maintained by a continuous infusion in the tail artery (12-20 mg/kg/hour). Body temperature was measured by a rectal probe and maintained by means of a heating pad and a heating lamp at 37.5-38.0°C. The rats were tracheotomised (PE 240) to facilitate spontaneous breathing. Catheters (PE 25) were inserted in the right and left jugular veins for infusions of NPY and test compound. In the tail artery a catheter (PE 25) was inserted for measurement of blood pressure (BP) and for a continuous infusion of anaesthesia. Mean arterial pressure was measured with a transducer (156PC) and heart rate was measured from the pulsating arterial pressure signal with a rate-meter. The left renal artery was dissected free and a small probe was placed around the artery (Transonic™ 0.7 VB42) in order to measure renal blood flow.

All signals were recorded on a paper chart recorder (Grass™ Polygraph) and digitised using a standard PC. The sampling rate was 10 samples per

second and the mean value was calculated and stored every 2 seconds. The computer program then calculated changes in mean arterial pressure, heart rate and renal blood flow from control values measured before drug administration.

After completion of the surgical preparation above, and a stabilisation period of 30 minutes, NPY (4 μg/kg) was intravenously administered over 20 seconds at 20 minute intervals to induce cardiovascular effects. After 2 stable readings during NPY administration, test compound was intravenously administered in three increasing doses (5, 50 and 500 nmol/kg/min.) over 20 minutes. At the end of each dosing interval, NPY was injected. A test compound was considered to be active if it attenuated the cardiovascular effect of further NPY treatment in a dose-dependent manner.

The invention is illustrated by way of the following examples.

Examples

General

Thin layer chromatography utilised Whatman No. 4420 222 silica gel plates with the following eluant systems:

$CHCl_3$: MeOH : conc. ammonium hydroxide (154:36:5) (System A);

$CHCl_3$: MeOH : conc. ammonium hydroxide (93:7:1) (System B);

ethyl acetate : hexanes (1:1) (System C); and

CH_2Cl_2 : MeOH : conc. ammonium hydroxide (177:20:3) (System D).

NMR was carried out on a Bruker AC 300 instrument

Starting materials

Example A

tert-Butyl 5-(bromomethyl)-2-pyridinylcarbamate

(a) Ethyl 6-aminonicotinate

A suspension of 6-aminonicotinic acid (25.0 g, 181 mmol) in ethanol (190 mL) was treated with $SOCl_2$ (15 mL, 206 mmol). The mixture was refluxed overnight (10 hours), and more $SOCl_2$ (16 mL) was added. Reflux was continued for a further 3 days, during which time additional $SOCl_2$ (10 mL) was added each day. The reaction mixture was cooled to room temperature before ether was added. After 24 hours at -20°C the mixture was filtered. The crude salt was dissolved in methanol (214 mL) and a solution of NaOH (40.0 g, 23.5 mmol) in methanol (90 mL) was added. The reaction mixture was stirred for 1 hour and THF (270 mL) was added. The reaction mixture was purified by flash filtration (THF/MeOH) and concentrated to give 36.2 g (97%) of the sub-title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, 3H), 4.35 (q, 2H), 4.60 (br s, 2H), 7.05 (m, 1H), 7.15 (m, 1H), 8.15 (m, 1H).

(b) Ethyl 6-[(*tert*-butoxycarbonyl)amino]nicotinate

To ethyl 6-aminonicotinate (36.0 g, 217.0 mmol; from step (a) above) in *t*-BuOH (308 mL) and acetone (103 mL) was added DMAP (0.53 g, 4.34 mmol) and di-*tert*-butyl dicarbonate (72.0 g, 330 mmol). The reaction was stirred at room temperature for 10 hours followed by addition of more di-*tert*-butyl dicarbonate (2.60 g). After 10 hours stirring at room temperature, hexane (470 mL) was added. The reaction mixture was cooled (-20°C) for 2 hours and filtered. The filtrate was washed with

hexane : dichloromethane (3:1). Drying of the filtrate *in vacuo* allowed the isolation of 40.5 g (70%) of the sub-title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, 3H), 1.50 (s, 18H), 4.40 (q, 2H), 7.75 (m, 1H), 7.80 (m, 1H), 8.60 (m, 1H).

(c) *tert*-Butyl 5-(hydroxymethyl)-2-pyridinylcarbamate

To a stirred solution of ethyl 6-[(*tert*-butoxycarbonyl)amino]nicotinate (3.50 g, 13.1 mmol; from step (b) above) in THF (20 mL) was added $LiAlH_4$ (0.91 g, 24.0 mmol) in THF (20 mL) over a period of 2 hours. The reaction mixture was stirred for 6 hours, then aqueous NH_4Cl (sat.) was added (carefully) until excess hydride had been neutralised. After filtration and evaporation of the solvent, 2.00 g (68%) of the crude sub-title compound was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 9H), 4.62 (s, 2H), 7.68 (d, 1H), 7.98 (d, 1H), 8.19 (br s, 1H), 8.29 (s, 1H).

(d) *tert*-Butyl 5-(bromomethyl)-2-pyridinylcarbamate

To a stirred suspension of *tert*-butyl 5-(hydroxymethyl)-2-pyridinylcarbamate (7.00 g, 31.2 mmol; from step (c) above) in CH_2Cl_2 (200 mL) was added triphenylphosphine (8.70 g, 33.1 mmol) and carbon tetrabromide (17.0 g, 51.2 mmol) at room temperature. Stirring was continued for 5 hours followed by evaporation of the solvent. Acetonitrile (200 mL) was added and the mixture was cooled (-20°C) for 2 hours. The mixture was then filtered and the crystalline residue washed with cold acetonitrile (2 x 10 mL). The title compound (5.96 g, 67%) was obtained as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H), 4.41 (s, 2H), 7.68 (d, 1H), 7.98 (d, 1H), 8.32 (s, 1H), 9.00 (br s, 1H).

Example B

tert-Butyl 4-formyl-2-pyridinylcarbamate

(a) *N*-(4-Methyl-2-pyridinyl)acetamide

A mixture of 2-amino-4-methylpyridine (99.0 g, 91.5 mmol) and acetic anhydride (250 mL) was warmed to 70°C for two hours. The mixture was cooled to room temperature and 100 mL ether added. The product crystallised as white needles. Filtering and drying *in vacuo* afforded 130 g (95%) of the sub-title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.30 (s, 3H), 6.85 (m, 1H), 8.05 (m, 1H), 8.10 (m, 1H), 9.30 (br s, 1H).

(b) 2-(Acetylamino)isonicotinic acid

A mixture of *N*-(4-methyl-2-pyridyl)acetamide (40.0 g, 0.26 mol; from step (a) above) and water (400 mL) was heated at 90°C until the solution was homogeneous. Potassium permanganate (100 g, 0.62 mol) was added carefully in small portions with good mechanical stirring over 2 hours. The reaction mixture was kept at 90-95°C for a further 3 hours before filtering through Celite® whilst still hot. The filtrate was concentrated to about 100 mL and concentrated HCl was added to adjust the pH to about 4. The reaction flask was cooled in an ice bath and the white solid filtered off. The crystals were washed with cold water and chloroform and dried *in vacuo* to give 12.0 g (25%) of the sub-title compound.

^{1}H NMR (300 MHz, CD_3OD): δ 2.10 (s, 3H), 7.60 (m, 2H), 8.40 (m, 1H), 8.65 (m, 1H).

(c) Ethyl 2-aminoisonicotinate

A suspension of 2-(acetylamino)isonicotinic acid (10.8 g, 60.0 mmol; from step (b) above) in ethanol (150 mL) was treated with $BF_3{\cdot}OEt_2$

(22 mL, 138 mmol). The mixture was refluxed overnight, and after cooling to room temperature 10% $NaHCO_3$ (250 mL) was added. The product was extracted with chloroform (3 x 100 mL), the combined organic extracts washed with water (250 mL) and dried ($MgSO_4$). Filtering and concentration afforded 7.46 g (79%) of the sub-title compound as pale yellow crystals.

^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, 3H), 4.35 (q, 2H), 4.60 (br s, 2H), 7.05 (m, 1H), 7.15 (m, 1H), 8.15 (m, 1H).

(d) Ethyl 2-[bis(*tert*-butoxycarbonyl)amino]isonicotinate

To ethyl 2-aminoisonicotinate (5.00 g, 30 mmol; from example (c) above) in *t*-BuOH (45 mL) and acetone (15 mL) was added DMAP (50 mg, 0.41 mmol) and di-*tert*-butyl dicarbonate (16.4 g, 75.0 mmol). The reaction mixture was stirred at room temperature overnight before hexane (60 mL) was added. The mixture was cooled in a refrigerator for 3 hours and the product removed by filtration. Drying *in vacuo* allowed the isolation of 8.71 g (79%) of the sub-title compound as a light grey solid.

^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, 3H), 1.50 (s, 18H), 4.40 (q, 2H), 7.75 (m, 1H), 7.80 (m, 1H), 8.60 (m, 1H).

(e) *tert*-Butyl 4-(hydroxymethyl)-2-pyridinylcarbamate

Ethyl 2-[bis(*tert*-butoxycarbonyl)amino]isonicotinate (35.0 g, 95.5 mmol; from example (d) above) in THF (350 mL) was treated with $LiAlH_4$ (7.25 g, 191 mmol) and refluxed for 1 hour under nitrogen. The reaction mixture was poured carefully onto crushed ice and the product extracted several times with $CHCl_3$ and $CHCl_3$: MeOH (90:10). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The sub-title compound (18.5 g, 86%) was thereby isolated as a pale yellow solid, which was shown to be pure by ^1H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 9H), 4.60 (s, 2H), 7.00 (m, 1H), 7.90 (m, 1H), 8.25 (m, 1H), 8.60 (br s, 1H).

(f) *tert*-Butyl 4-formyl-2-pyridinylcarbamate

tert-Butyl 4-(hydroxymethyl)-2-pyridinylcarbamate (1.91 g, 8.51 mmol, from step (e) above) was dissolved in dry DMSO (10 mL) and the reaction flask immersed in a water bath at 15°C. Triethylamine (1.72 g, 17.0 mmol) was added, followed by sulfur trioxide pyridine complex (2.41 g, 15.1 mmol). The reaction mixture was stirred for a further 2 hours and poured onto crushed ice. The product was extracted with $CHCl_3$ (3 x 30 mL). The combined organic extracts were washed with water (3 x 50 mL), dried ($MgSO_4$) and filtered. Removal of the solvent and subsequent flash chromatography (hexane : EtOAc (80:20)) afforded 1.57 g (83%) of the title compound as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 9H), 7.40 (d, 1H), 8.30 (br s, 1H), 8.42 (m, 1H), 8.46 (m, 1H), 10.05 (s, 1H).

Example C

tert-Butyl 5-formyl-2-pyridinylcarbamate

tert-Butyl 5-(hydroxymethyl)-2-pyridinylcarbamate (7.00 g, 31.2 mmol; from Example A step (c) above) was dissolved in dry DMSO (50 mL) and the reaction flask immersed in a water bath at 15°C. Triethylamine (13.1 mL, 94.0 mmol) was added, followed by sulfur trioxide pyridine complex (15.0 g, 94.0 mmol) in portions. The reaction mixture was stirred for a further 45 minutes and poured onto crushed ice (300 mL). The product was extracted with ether (4 x 300 mL). The combined organic extracts were washed with aqueous NaCl (sat.), dried ($MgSO_4$) and filtered. Removal of the solvent and recrystallisation from

hexane/CH_2Cl_2 afforded 5.40 g (78%) of the title compound as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (s, 9H), 8.20 (s, 2H), 8.82 (s, 1H), 9.02 (br s, 1H), 9.98 (s, 1H).

Example 1

3-(6-Amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-hydroxybenzyl)propanamide

(a) Diethyl 2-[(2,2-diphenylacetyl)amino]malonate

A mixture of diethyl aminomalonate hydrochloride (5.0 g, 23 mmol) and diisopropylethylamine (10.3 mL, 59 mmol) in dichloromethane (100 mL) was cooled to 0°C. Solid diphenylacetyl chloride (5.4 g, 23 mmol) was added and the mixture was stirred for 1 h before being warmed to rt and quenched with water. The reaction mixture was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and evaporated to provide the sub-title compound (8.72 g, 96%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.23 (m, 10H), 6.63 (d, 1H), 5.18 (d, 1H), 5.03 (s, 1H), 4.33-4.17 (m, 4H), 1.29 (t, 6H).

(b) Diethyl 2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}methyl)-2-[(2,2-diphenylacetyl)amino]malonate

A mixture of diethyl 2-[(2,2-diphenylacetyl)amino]malonate (1.6 g, 4.3 mmol; from step (a) above) and *tert*-butyl 5-(bromomethyl)-2-pyridinylcarbamate (1.6 g, 5.5 mmol; from Example A above) in acetonitrile (65 mL) was treated with DBU (1.9 mL, 12 mmol) and the resulting mixture stirred for 3 h. The acetonitrile was removed and the residue was taken up in ethyl acetate. This solution was washed with dilute $KHSO_4$ solution and then brine, dried (sodium sulfate), filtered and

then concentrated *in vacuo* to provide the sub-title compound (2.4 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.79-7.72 (m, 2H), 7.39-7.24 (m, 10H), 7.08 (dd, 1H), 6.81 (s, 1H), 4.94 (s, 1H), 4.30-4.19 (m, 4H), 3.58 (s, 2H), 1.56 (s, 9H), 1.30-1.22 (m, 6H).

(c) 3-{6-[(*tert*-Butoxycarbonyl)amino]-3-pyridinyl}-*N*-(2,2-diphenylacetyl)-alanine

A solution of diethyl 2-({6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-methyl)-2-[(2,2-diphenylacetyl)amino]malonate (2.4 g, 4.1 mmol; from step (b) above) in dioxane : water (132 mL of 5:1) was treated with potassium hydroxide (4.6 g, 82 mmol) and then heated to reflux for 1 h. The dioxane was removed and the residue was taken up in ethyl acetate. This solution was washed with $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo* to provide the sub-title compound (1.7 g, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (br s, 1H), 7.86-7.77 (m, 2H), 7.40-7.25 (m, 10H) 7.18 (dd, 1H), 6.55 (d, 1H), 4.98 (s, 1H), 4.81 (m, 1H), 3.21-3.10 (m, 2H), 1.53 (s, 9H).

(d) *tert*-Butyl 5-{2-[(2,2-diphenylacetyl)amino]-3-[(4-hydroxybenzyl)-amino]-3-oxopropyl}-2-pyridinylcarbamate

A mixture of 3-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-*N*-(2,2-diphenylacetyl)alanine (435 mg, 0.9 mmol; from step (c) above) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192 mg, 1.0 mmol) in tetrahydrofuran : dichloromethane : acetonitrile (45 mL of 4:2:3) was stirred for 10 min before 4-hydroxybenzylamine (123 mg, 1.0 mmol) and diisopropylethylamine (159 μL, 0.9 mmol) were added. The mixture was stirred overnight at rt, the solvents were removed and the

residue taken up in ethyl acetate/tetrahydrofuran. This solution was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1), provided the sub-title compound (234 mg, 44%).

R_f 0.5 (System B)

(e) 3-(6-Amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-hydroxybenzyl)propanamide

tert-Butyl 5-{2-[(2,2-diphenylacetyl)amino]-3-[(4-hydroxybenzyl)amino]-3-oxopropyl}-2-pyridinylcarbamate (234 mg, 0.4 mmol; from step (d) above) was dissolved in trifluoroacetic acid/dichloromethane (15 mL of 2:1) and stirred for 2 h. Evaporation of the solvent followed by column chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1), provided the title compound (140 mg, 72%) as a white solid.

m.p. 229-230°C

R_f 0.6 (System A)

^1H NMR (300 MHz, CD_3OD): δ 7.69 (s, 1H), 7.31-7.17 (m, 9H), 7.12-7.06 (m, 2H), 6.98 (d, 2H), 6.71 (d, 2H), 6.44 (d, 1H), 5.00 (s, 1H), 4.62 (m, 1H), 4.28-4.15 (m, 2H), 2.93 (m, 1H), 2.74 (m, 1H).

Preparative chiral chromatography was performed on a Chiralpak™ AD column to separate the enantiomers of the title compound. The racemate (from step (e) above), dissolved in methanol containing 2% acetic acid (7 mg/mL), was injected onto the column (250 x 20 mm ID) and the pure enantiomers were collected and evaporated to dryness. The total amount of racemate that was resolved was 14 mg. The yield for the two enantiomers was 6.5 mg each, with an enantiomeric excess of

>99%, as determined on an analytical scale Chiralpak™ AD column (250 x 4.6 mm ID).

Preparative chromatography was performed on a Gilson gradient HPLC system (mod. 306, Villiers-le-Bel, France) with a dynamic mixer (mod. 811C) and a Gilson (mod. 231 XL) automatic injector equipped with a 10 mL injection loop. The pure enantiomers were collected using a Gilson fraction collector (mod. 206). The flow rate of the mobile phase was 10 mL/min. The analytical HPLC-system comprised a Gynkotek Pump, Model 380 (Germering, Germany), a Kontron 465 Auto Sampler (Milano, Italy) and a JASCO variable wavelength UV-975 Detector (Tokyo, Japan). The chromatographic data was collected using Chromeleon (version 4.3, Dionex, Germering, Germany). The flow rate of the mobile phase was 1.0 mL/min. The mobile phase used for both analytical and preparative scale chromatography consisted of 70% *iso*-hexane and 30% *iso*-propanol (HPLC grade).

Example 2

3-(6-Amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-methoxybenzyl)propanamide

(a) *tert*-Butyl 5-{2-[(2,2-diphenylacetyl)amino]-3-[(4-methoxybenzyl)amino]-3-oxopropyl}-2-pyridinylcarbamate

A mixture of 3-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-*N*-(2,2-diphenylacetyl)alanine (1.2 g, 2.5 mmol; from Example 1 step (c) above) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.55 g, 2.8 mmol) in tetrahydrofuran : dichloromethane : acetonitrile (65 mL of 7:2:4) was stirred for 10 min before 4-methoxybenzylamine (0.34 mL, 2.6 mmol) was added. The mixture was stirred overnight

before the solvents were removed and the residue taken up in ethyl acetate/methanol. This solution was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and evaporated. Chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1), provided the sub-title compound (700 mg, 45%).

m.p. 180-188°C

R_f 0.6 (System B)

^1H NMR (300 MHz, CD_3OD): δ 7.95 (d, 1H), 7.67 (d, 1H), 7.48 (dd, 1H), 7.30-7.18 (m, 8H), 7.12-7.08 (m, 2H), 7.03 (d, 2H), 6.69 (d, 2H), 4.99 (s, 1H), 4.69 (m, 1H), 4.23 (dd, 2H), 3.77 (s, 3H), 3.02 (m, 1H), 2.85(m, 1H), 1.58 (s, 9H).

(b) 3-(6-Amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-methoxybenzyl)propanamide

tert-Butyl 5-{2-[(2,2-diphenylacetyl)amino]-3-[(4-methoxybenzyl)amino]-3-oxopropyl}-2-pyridinylcarbamate (700 mg, 1.1 mmol; from step (a) above) was dissolved in trifluoroacetic acid : dichloromethane (60 mL of 2:1) and stirred for 1¼ h. Evaporation of the solvent, followed by column chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1), provided the title compound (502 mg, 71%) as a white solid.

m.p. 211-212°C

R_f 0.3 (System B)

^1H NMR (300 MHz, CD_3OD): δ 7.69 (d, 1H), 7.30-7.18 (m, 9H), 7.13-7.09 (m, 2H), 7.05 (d, 2H), 6.82 (d, 2H), 6.44 (d, 1H), 5.00 (s, 1H), 4.62 (m, 1H), 4.25 (dd, 2H), 3.78 (s, 3H), 2.93 (m, 1H), 2.75 (m, 1H).

Example 3

4-(2-Amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-hydroxybenzyl)butanamide

(a) Ethyl 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-(methoxyimino)-3-butenoate

To a stirred solution of [(2-methoxyimino-2-ethoxycarbonyl)ethyl]-triphenylphosphonium bromide (*Tetrahedron Lett.* **1988**, *29*, 3361-3364; 4.3 g, 8.9 mmol) in dimethylformamide (40 mL) was added potassium carbonate (2.6 g, 18 mmol) and *tert*-butyl 4-formyl-2-pyridinylcarbamate (2.0 g, 8.9 mmol; from Example B above). After 6 h the dimethylformamide was removed and the residue was taken up in dichloromethane. This solution was washed with water, dried (sodium sulfate), filtered and evaporated. Chromatography on silica gel eluting with ethyl acetate : hexane (1:3) provided the sub-title compound (2.8 g, 91%).

R_f 0.5 (System C)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 1H), 8.03 (s, 1H), 7.56 (d, 1H), 7.59 (s, 1H), 7.34 (d, 1H), 7.10 (d, 1H), 4.40 (q, 2H), 4.16 (s, 3H), 1.56 (s, 9H), 1.40 (t, 3H).

(b) Ethyl 2-amino-4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-butanoate

Ethyl 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-(methoxyimino)-3-butenoate (2.8 g, 8.0 mmol; from step (a) above) was dissolved in ethyl acetate : ethanol (250 mL of 1:1) by warming gently under an inert atmosphere (N_2). Palladium on carbon (200 mg of 10%) was added, and the flask evacuated then filled with hydrogen from a balloon. After stirring for 3 h, the catalyst was removed *via* filtration and the solvent was

evaporated. The residue was purified by column chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1), to provide the sub-title compound (2.2 g, 83%).

R_f 0.5 (System B)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 1H), 7.82 (s, 1H), 7.71 (br s, 1H), 6.83 (d, 2H), 4.20 (q, 2H), 3.43 (m, 1H), 2.65-2.85 (m, 2H), 2.08 (m, 1H), 1.87 (m, 1H), 1.51 (s, 11H), 1.28 (t, 3H).

(c) Ethyl 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-[(2,2-diphenyl-acetyl)amino]butanoate

A mixture of ethyl 2-amino-4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}butanoate (2.2 g, 6.8 mmol; from step (b) above) and diisopropylethylamine (1.4 mL, 8.2 mmol) in dichloromethane (40 mL) was cooled to 0°C. Solid diphenylacetyl chloride (1.5 g, 6.8 mmol) was added, and the mixture was stirred for 1 h before being warmed to rt and quenched with water. The reaction mixture was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo* to provide the sub-title compound (3.1 g, 88%).

R_f 0.7 (ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H), 7.90 (s, 1H), 7.77 (s, 1H), 7.40-7.21 (m, 10H), 6.69 (d, 1H), 6.18 (d, 1H), 4.99 (s, 1H), 4.69 (m, 1H), 4.18 (q, 2H), 2.62-2.45 (m, 2H), 2.20 (m, 1H), 1.96 (m, 1H), 1.54 (s, 9H), 1.28 (t, 3H).

(d) 4-{2-[(*tert*-Butoxycarbonyl)amino]-4-pyridinyl}-2-[(2,2-diphenyl-acetyl)amino]butanoic acid

A solution of ethyl 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoate (3.1 g, 6.0 mmol; from step (c) above) in dioxane : water (120 mL of 5:1) was treated with potassium

hydroxide (3.3 g, 59 mmol). The mixture was heated to reflux for 1 h before the dioxane was removed and the residue taken up in ethyl acetate. This solution was washed with $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo* to provide the sub-title compound (2.9 g, 98%).

^1H NMR (300 MHz, $CDCl_3$): δ 9.91 (br s, 1H), 7.92 (s, 1H), 7.58 (d, 1H), 7.40-7.22 (m, 10H), 6.71-6.63 (m, 2H), 5.05 (s, 1H), 4.60 (m, 1H), 2.70 (m, 1H), 2.58-2.42 (m, 2H), 2.29 (m, 1H), 2.54 (s, 9H).

(e) *tert*-Butyl 4-{3-[(2,2-diphenylacetyl)amino]-4-[(4-hydroxybenzyl)-amino]-4-oxobutyl}-2-pyridinylcarbamate

A solution of 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoic acid (500 mg, 1.0 mmol; from step (d) above) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (215 mg, 1.1 mmol) in tetrahydrofuran : dichloromethane : acetonitrile (26 mL of 6:2:5) was stirred for 10 min before 4-hydroxybenzylamine (126 mg, 1.0 mmol) was added. The mixture was stirred overnight, the solvents were removed and the residue was taken up in ethyl acetate. This solution was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo*. Chromatography on silica gel eluting, with chloroform : ethanol : conc. ammonium hydroxide (186:14:1) provided the sub-title compound (394 mg, 65%).

R_f 0.5 (System B)

(f) 4-(2-Amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-hydroxy-benzyl)butanamide

tert-Butyl 4-{3-[(2,2-diphenylacetyl)amino]-4-[(4-hydroxybenzyl)amino]-4-oxobutyl}-2-pyridinylcarbamate (394 mg, 0.6 mmol; from step (e)

above) was dissolved in trifluoroacetic acid : dichloromethane (15 mL of 2:1) and stirred for 1 h. Evaporation of the solvent followed by column chromatography on silica gel, eluting with chloroform : methanol : conc. ammonium hydroxide (177:20:3), provided the title compound (295 mg, 90%) as a white solid.

m.p. 95-100°C

R_f 0.4 (System D)

^{1}H NMR (300 MHz, CD_3OD): δ 7.71 (d, 1H), 7.37-7.21 (m, 10H), 7.08 (d, 2H), 6.72 (d, 2H), 6.32-6.28 (m, 2H), 5.09 (s, 1H), 4.36 (m, 1H), 4.30-4.19 (m, 2H), 2.51-2.32 (m, 2H), 2.03 (m, 1H), 1.94 (m, 1H).

Example 4

4-(2-Amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-methoxybenzyl)butanamide

(a) *tert*-Butyl 4-{3-[(2,2-diphenylacetyl)amino]-4-[(4-methoxybenzyl)-amino]-4-oxobutyl}-2-pyridinylcarbamate

A solution of 4-{2-[(*tert*-butoxycarbonyl)amino]-4-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoic acid (1.5 g, 3.0 mmol; from Example 3 step (d) above) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.64 g, 3.3 mmol) in tetrahydrofuran : dichloromethane (45 mL of 7:2) was stirred for 5 minutes before 4-methoxybenzylamine (0.4 mL, 3.0 mmol) was added. The mixture was stirred for 3 h before the solvents were removed and the residue taken up in ethyl acetate. This solution was washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (465:20:2), provided the sub-title compound (1.17 g, 63%).

m.p. 192-197°C

R_f 0.6 (System B)

^{1}H NMR (300 MHz, CD_3OD): δ 8.02 (d, 1H), 7.69 (s, 1H), 7.34-7.20 (m, 10H), 7.16 (d, 2H), 6.83 (d, 2H), 6.70 (d, 1H), 5.09 (s, 1H), 4.39 (m, 1H), 4.32-4.22 (m, 2H), 3.78 (s, 3H), 2.63-2.47 (m, 2H), 2.19 (m, 1H), 1.98 (m, 1H), 1.53 (s, 9H).

(b) 4-(2-Amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-methoxybenzyl)butanamide

tert-Butyl 4-{3-[(2,2-diphenylacetyl)amino]-4-[(4-methoxybenzyl)amino]-4-oxobutyl}-2-pyridinylcarbamate (1.0 g, 1.6 mmol; from step (a) above) was dissolved in trifluoroacetic acid : dichloromethane (45 mL of 2:1) and stirred for 2 h. Evaporation of the solvent followed by column chromatography on silica gel, eluting with chloroform : methanol : conc. ammonium hydroxide (186:14:1), provided the title compound (425 mg, 47%) as a white solid.

m.p. 184-187°C

R_f 0.4 (System B)

^{1}H NMR (300 MHz, CD_3OD): δ 7.71 (d, 1H), 7.37-7.21 (m, 10H), 7.16 (d, 2H), 6.82 (d, 2H), 6.32-6.28 (m, 2H), 5.09 (s, 1H), 4.37 (m, 1H), 4.33-4.22 (m, 2H), 3.77 (s, 3H), 2.51-2.33 (m, 2H), 2.02 (m, 1H), 1.93 (m, 1H).

Example 5

4-(6-Amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-(4-methoxybenzyl)butanamide

(a) Ethyl 4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-2-(methoxyimino)-3-butenoate

To a stirred solution of [(2-methoxyimino-2-ethoxycarbonyl)ethyl]-triphenylphosphonium bromide (*Tetrahedron Lett.* **1988**, *29*, 3361-3364; 4.3 g, 8.9 mmol) in dimethylformamide (40 mL) was added potassium carbonate (2.6 g, 18 mmol) and *tert*-butyl 5-formyl-2-pyridinylcarbamate (2.0 g, 8.9 mmol; from Example C above). After 6 h the dimethylformamide was removed and the residue taken up in dichloromethane. This solution was washed with water, dried (sodium sulfate), filtered and concentrated *in vacuo*. Chromatography on silica gel, eluting with ethyl acetate : hexane (1:3), provided the sub-title compound (2.8 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, 1H), 8.08 (s, 1H), 8.00 (dd, 1H), 7.88 (dd, 1H), 7.56 (d, 1H), 7.15 (d, 1H), 4.40 (q, 2H), 4.15 (s, 3H), 1.55 (s, 9H), 1.41 (t, 3H).

(b) Ethyl 2-amino-4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-butanoate

Ethyl 4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-2-(methoxyimino)-3-butenoate (2.8 g, 8.0 mmol; from step (a) above) was dissolved in ethyl acetate : ethanol (200 mL of 5:3) by warming gently under an inert atmosphere (N_2). Palladium on carbon (200 mg of 10%) was added and the flask was evacuated then filled with hydrogen from a balloon. After stirring for 7 h, the catalyst was removed *via* filtration and the solvent was evaporated. The residue was purified by column chromatography on silica

gel, eluting with chloroform : ethanol : conc. ammonium hydroxide (186:14:1) to provide the sub-title compound (1.7 g, 66%).

^{1}H NMR (300 MHz, CD_3OD): δ 8.09 (d, 1H), 7.78 (d, 1H), 7.62 (dd, 1H), 4.17 (q, 2H), 3.42 (m, 1H), 2.68 (t, 2H), 2.00 (m, 1H), 1.89 (m, 1H), 1.53 (s, 9H), 1.29 (t, 3H).

(c) Ethyl 4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoate

A mixture of ethyl 2-amino-4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}butanoate (1.7 g, 5.2 mmol; from step (b) above) and diisopropylethylamine (1.1 mL, 6.3 mmol) in dichloromethane (30 mL) was cooled to 0°C. Solid diphenylacetyl chloride (1.2 g, 5.2 mmol) was added and the mixture was stirred for 1 h before being warmed to rt. Stirring was continued overnight before the reaction mixture was quenched with water, washed with dilute $KHSO_4$ solution, dried (sodium sulfate), filtered and concentrated *in vacuo* to provide the sub-title compound (2.6 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H), 7.83 (d, 1H), 7.54 (br s, 1H), 7.40-7.22 (m, 11H), 6.20 (d, 1H), 4.98 (s, 1H), 4.68 (m, 1H), 4.17 (q, 2H), 2.57-2.38 (m, 2H), 2.14 (m, 1H), 1.90 (m, 1H), 1.53 (s, 9H), 1.28 (t, 3H).

(d) 4-{6-[(*tert*-Butoxycarbonyl)amino]-3-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoic acid

A solution of ethyl 4-{6-[(*tert*-butoxycarbonyl)amino]-3-pyridinyl}-2-[(2,2-diphenylacetyl)amino]butanoate (2.5 g, 4.8 mmol; from step (c) above) in dioxane : water (120 mL of 5:1) was treated with potassium hydroxide (2.7 g, 48 mmol). The mixture was then heated to reflux for 45 minutes before the dioxane was removed and the residue taken up in

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}propanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-3-(6-amino-3-pyridinyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)-benzyl]-2-[(2,2-diphenylacetyl)amino]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)-benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-3-(6-amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]propanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}propanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}propanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}propanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-3-(6-amino-3-pyridinyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-[4-(2-hydroxyethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-*N*-[4-(2-hydroxyethyl)benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-[4-(hydroxymethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]propanamide;

3-(6-amino-3-pyridinyl)-*N*-[4-(hydroxymethyl)benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)propanamide;

3-(6-amino-3-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)propanamide;

3-(6-amino-3-pyridinyl)-*N*-(4-hydroxybenzyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-[(2,2-diphenylacetyl)amino]propanamide;

3-(6-amino-3-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}propanamide;

3-(6-amino-3-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}propanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-4-(2-amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]butanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}butanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}butanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}butanamide;

N-(4-{[(aminocarbonyl)amino]methyl}benzyl)-4-(2-amino-4-pyridinyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)-benzyl]-2-[(2,2-diphenylacetyl)amino]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-*N*-[4-({[(dimethylamino)carbonyl]amino}methyl)-benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-4-(2-amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]butanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}butanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}butanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}butanamide;

N-[4-(2-amino-2-oxoethyl)benzyl]-4-(2-amino-4-pyridinyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-[4-(2-hydroxyethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-(2-hydroxyethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-*N*-[4-(2-hydroxyethyl)benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-2-[(2,2-diphenylacetyl)amino]-*N*-[4-(hydroxymethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-[4-(hydroxymethyl)benzyl]butanamide;

4-(2-amino-4-pyridinyl)-*N*-[4-(hydroxymethyl)benzyl]-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)butanamide;

4-(2-amino-4-pyridinyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}-*N*-(4-hydroxybenzyl)butanamide;

4-(2-amino-4-pyridinyl)-*N*-(4-hydroxybenzyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-[(2,2-diphenylacetyl)amino]butanamide;

4-(2-amino-4-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-chlorophenyl)acetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-methoxyphenyl)acetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2,2-bis(4-hydroxyphenyl)acetyl]amino}butanamide;

4-(2-amino-4-pyridinyl)-*N*-(1,3-benzodioxol-5-ylmethyl)-2-{[2-(4-hydroxyphenyl)-2-phenylacetyl]amino}butanamide.

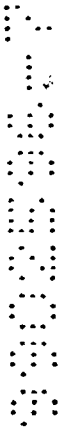
Compounds listed in Example 7, when tested in Test A above, exhibit an IC_{50} value of less than 5 μM (Y_1 receptors).

Abbreviations

ACE	=	angiotensin-converting enzyme
At	=	7-azabenzotriazole
Bt	=	benzotriazole
t-BuOH	=	*tert.*-butanol
br	=	broad (in relation to NMR)

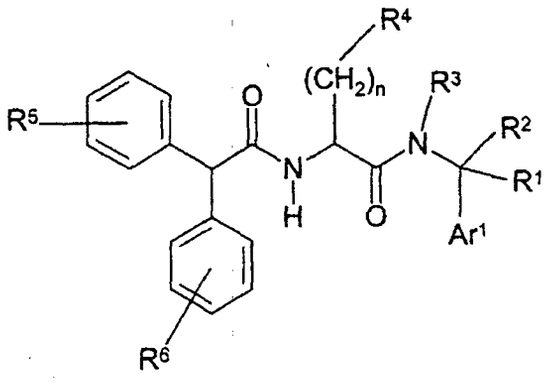
	d	=	doublet (in relation to NMR)
	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCC	=	dicyclohexylcarbodiimide
	dd	=	doublet of doublets (in relation to NMR)
	DMAP	=	4-dimethylaminopyridine
	DMF	=	*N*,*N*-dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDC	=	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
	Et	=	ethyl
	EtOAc	=	ethyl acetate
	h	=	hour(s)
	HCl	=	hydrochloric acid
	HEPES	=	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	HPLC	=	high performance liquid chromatography
	m	=	multiplet (in relation to NMR)
	Me	=	methyl
	MeOH	=	methanol
	m.p.	=	melting point
	NPY	=	neuropeptide Y
	PE	=	polyethylene
	Ph	=	phenyl
	Py	=	pyridyl
	q	=	quartet (in relation to NMR)
	rt	=	room temperature
	s	=	singlet (in relation to NMR)
	Su	=	succinimide
	t	=	triplet (in relation to NMR)
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography

Ts = *p*-toluenesulfonyl



Claims

1. A compound of formula I,

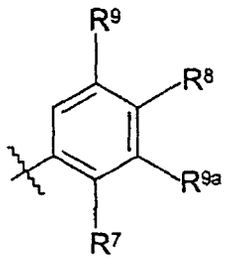


I

wherein

n represents 1, 2 or 3;

Ar^1 represents a structural fragment of the formula



or represents 1- or 2-naphthyl, which latter group is optionally substituted by one or more substituents selected from OH, halo and C_{1-7} alkoxy;

R^7 represents H or OH;

R^8 represents H, halo, $-(CH_2)_mOR^{16}$, $-(CH_2)_mN(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{16})R^{17}$, $-(CH_2)_pC(O)N(R^{17})CH_2C(O)OR^{16}$, $-(CH_2)_pN(R^{18})C(O)N(R^{16})R^{17}$, $-(CH_2)_pN(R^{17})C(O)N(R^{18})CH_2C(O)OR^{16}$, $-(CH_2)_pN(R^{17})C(O)OR^{16a}$, $-O(CH_2)_pC(O)OR^{16}$, $-N(R^{17})(CH_2)_pC(O)OR^{16}$, or, together with either of R^9 or R^{9a}, forms a methylenedioxy group;

R^9 and R^{9a} independently represent H, halo, OH, C_{1-7} alkyl or C_{1-7} alkoxy, and/or one of R^9 and R^{9a} may, together with R^8, form a methylenedioxy group;

R^{16} represents H, C_{1-7} alkyl or $-(CH_2)_q$-phenyl;

R^{16a} represents C_{1-7} alkyl or $-(CH_2)_q$-phenyl;

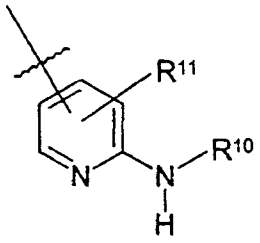
m represents 0, 1, 2, or 3;

p represents 1, 2, 3 or 4;

q represents 0 or 1;

R^1 represents H, $C(O)NH_2$ or C_{1-4} alkyl (optionally substituted and/or terminated by one or more substituents selected from hydroxy and amino);

R^4 represents a structural fragment of formula II,



II

R^{10} and R^{11} independently represent H or C_{1-4} alkyl;

R^5 and R^6 independently represent one or more optional substituents selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halo, $N(R^{12})R^{13}$, $-N(R^{17})CH_2C(O)OR^{14}$ and $OCH_2C(O)OR^{15}$;

R^2, R^3, R^{12}, R^{13}, R^{14}, R^{15}, R^{17} and R^{18} independently represent H or C_{1-7} alkyl;

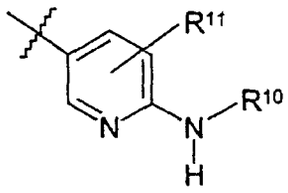
or a pharmaceutically acceptable derivative thereof.

2. A compound as claimed in Claim 1, wherein R^1 represents H or methyl.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^2 represents H.

4. A compound as claimed in any one of the preceding claims, wherein R^3 represents H or methyl.

5. A compound as claimed in any one of the preceding claims, wherein R^4 represents a structural fragment of formula



6. A compound as claimed in any one of the preceding claims, wherein R^5 is either absent or represents a single substituent selected from OH, halo, methyl and methoxy.

7. A compound as claimed in any one of the preceding claims, wherein R^6 is either absent or represents a single substituent selected from OH, halo, methyl and methoxy.

8. A compound as claimed in any one of the preceding claims, wherein R^7 represents H.

9. A compound as claimed in any one of the preceding claims, wherein R^8 represents OCH_3, halo, $-CH_2C(O)NH_2$, $-CH_2N(H)C(O)NH_2$, NH_2 or OH.

10. A compound as claimed in any one of the preceding claims, wherein R^9 represents H.

11. A compound as claimed in any one of the preceding claims, wherein R^{10} represents H.

12. A compound as claimed in any one of the preceding claims, wherein R^{11} represents H.

13. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.

15. A compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a disorder which is mediated by neuropeptide Y.

16. A compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a cardiovascular disease.

17. The use of a compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in the treatment of a disorder which is mediated by neuropeptide Y.

18. The use of a compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in the treatment of a cardiovascular disease.

19. A method of treatment of a cardiovascular disease, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

20. A compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for use in the treatment of a disorder which is mediated by neuropeptide Y sub-receptor Y_1.

21. A compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for use in the treatment of vasoconstriction.

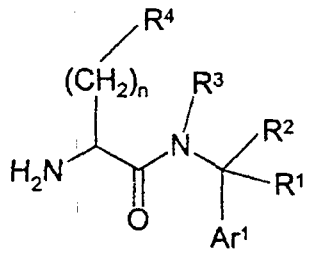
22. The use of a compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in the treatment of a disorder which is mediated by neuropeptide Y sub-receptor Y_1.

23. The use of a compound as defined in any one Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for use in the treatment of vasoconstriction.

24. A method of treatment of vasoconstriction, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

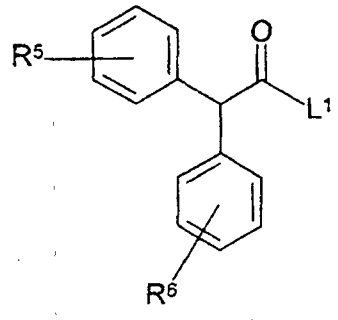
25. A process for the preparation of a compound of formula I, as defined in Claim 1, which comprises:

(a) reaction of a compound of formula IV,



IV

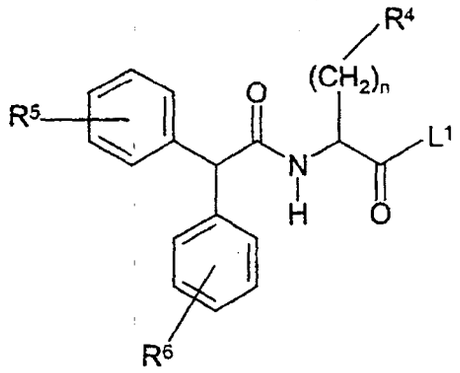
wherein Ar^1, R^1, R^2, R^3, R^4 and n are as defined in Claim 1, with a compound of formula V,



V

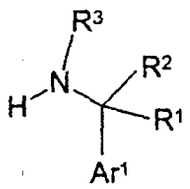
wherein L^1 represents a leaving group and R^5 and R^6 are as defined in Claim 1;

(b) reaction of a compound of formula VI,



VI

wherein L^1 is as defined above and R^4, R^5, R^6 and n are as defined in Claim 1, with a compound of formula VII,



VII

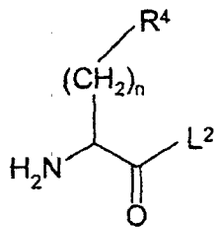
wherein Ar^1, R^1, R^2 and R^3 are as defined in Claim 1;

(c) conversion of one R^5 and/or R^6 substituent to another;

(d) conversion of one substituent on Ar^1 to another; or

(e) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

26. A compound of formula VIII,

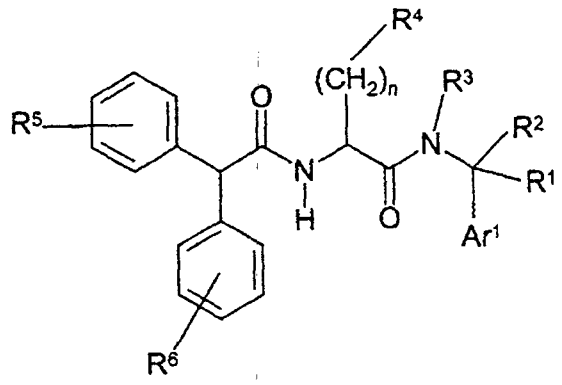


VIII

or a protected derivative thereof, wherein L^2 represents a leaving group and R^4 and n are as defined in Claim 1.

ABSTRACT

There is provided compounds of formula I,



I

wherein n, Ar^1, R^1, R^2, R^3, R^4, R^5 and R^6 have meanings given in the description, which are useful as antagonists of neuropeptide Y and in particular in the treatment of cardiovascular diseases, for example vasoconstriction.

168 770

Traducción No. 238/07-00

El presente documento lleva dos sellos redondos en tintilla azul y otro sobrepuesto en papel dorado que dicen en idioma sueco:

ANNE-MARIE BONDE * NOTARIO PUBLICO EN ESTOCOLMO

Lleva el sello No. 002160 del Consulado de Colombia en Estocolmo, de fecha 2000-06-21, firmado por Maria Smith Rueda, Encargada de las Funciones Consulares.

Lleva el sello No. 088534 del Ministerio de Relaciones Exteriores, de fecha 2000-06-30, firmado por el Jefe de Legalizaciones.

Certifico que esta traducción es correcta y fiel a su original.

Suzanne
Dorlhac

169

CERTIFICADO NOTARIAL (INDIVIDUO) **NOTARIAL CERTIFICATE (INDIVIDUAL)**

A los 19 días del mes de Junio 2000, compareci personalmente ante mi, THOMAS ANTONSSON, NILS-ÅKE BERGMAN, MARCEL LINSCHOTEN y CHRISTER WESTERLUND

On this 19 day of June 2000 personally appeared before me, a Notary Public, THOMAS ANTONSSON, NILS-AKE BERGMAN, MARCEL LINSCHOTEN y CHRISTER WESTERLUND

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

De oficio:

Anne-Marie Bonde
Notario Público en Estocolmo, Suecia

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA
Fecha 2000-06-21 No: 260
Previa la confrontación correspondiente D
FE de que la firma que aparece en este doc
mento es similar a la REGISTRADA aquí p
Anne-Marie Bonde, Notario Público,
Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Siete dólares US$ 7
Derechos Consulares
Quince dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

ASSIGNMENT

The undersigned,

Thomas Antonsson a Swedish citizen, Nils-Åke Bergman a Swedish citizen, Marcel Linschoten a Dutch citizen and Christer Westerlund a Swedish citizen
all

domiciled in
AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden

hereby state under oath to be the sole and true inventor of

NEW NPY ANTAGONISTS

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

.....
Thomas Antonsson

.....
Nils-Åke Bergman

.....
Marcel Linschoten

.....
Christer Westerlund

TRASPASO

abajo firmado

Thomas Antonsson un ciudadano Sueco, Nils-Ake Bergman un ciudadano Sueco, Marcel Linschoten un ciudadano Alemán y Christer Westerlund un ciudadano Sueco

todos

domiciliado en

AstraZeneca R&D Mölndal, S-431 83 Mölndal, Suecia

declamos bajo juramento ser único y verdadero inventores de.

NUEVOS ANTAGONISTAS DEL NPY

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

organizada y existente de conformidad con la leves de

Suecia

domiciliada en

S-151 85 Södertälje, Suecia

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

.....

.....

.....

.....

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE GONDE