SPRUSON & FERGUSON

Australia

Patents Act 1990

669160

Notice Of Entitlement

I, John David O'Connor, of 31 Market Street, Sydney, New South Wales, 2000, Australia, Patent Attorney for the Applicant/Nominated Person in respect of Application No. 36428/93 state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:-

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is the applicant of the applications listed in the Declaration under Article 8 of the PCT.

The basic applications listed on the Declaration under Article 8 of the PCT are the first applications made in a Convention country in respect of the invention.

Dated 9 September 1994

John David O'Connor

IRN: 277662

INSTR CODE: 58167

[N:\LIBF]07689:GSA

AU9336428

(12) PATENT ABRIDGMENT (11) Document No. AU-B-36428/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 669160

(54) Title
IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

International Patent Classification(s)
(51)[5] C07D 403/14 A61K 031/41 C07D 405/14 C07D 409/14
C07D 413/14 C07D 417/14 A61K 031/415

(21) Application No. : 36428/93 (22) Application Date : 05.03.93

(87) PCT Publication Number : WO93/18029

(30) Priority Data

(31) Number	(32) Date	(33) Country
9205482	13.03.92	GB UNITED KINGDOM
9215731	24.07.92	GB UNITED KINGDOM

(43) Publication Date : 05.10.93

(44) Publication Date of Accepted Application : 30.05.96

(71) Applicant(s)
MERCK SHARP & DOHME LIMITED

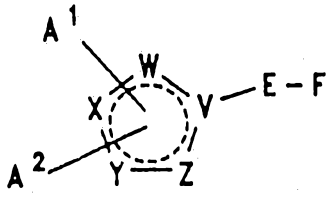
(72) Inventor(s)
VICTOR GIULIO MATASSA; AUSTIN JOHN REEVE; HELEN ROUTLEDGE; FRANCINE STERNFELD; LESLIE JOSEPH STREET

(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(56) Prior Art Documents
WO 91/18897
EP 313397
EP 497512

(57) Claim

1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

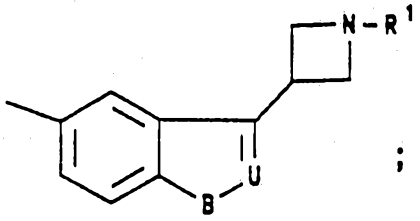
.../2

A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



;

U represents nitrogen or $C-R^2$;

B represents oxygen, sulphur or $N-R^3$;

R^1, R^2 and R^3 independently represent hydrogen or C_{1-6} alkyl;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

.../3

13. A method for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in any one of claims 1 to 6, 11 or 12 or a pharmaceutically acceptable salt thereof or a prodrug thereof or of a composition of claim 7.

OPI DATE 05/10/93 APPLN. ID 36428/93
AOJP DATE 09/12/93 PCT NUMBER PCT/GB93/00474

AU9336428

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 403/14, A61K 31/41

A1

(11) International Publication Number: WO 93/18029

(43) International Publication Date: 16 September 1993 (16.09.93)

(21) International Application Number: PCT/GB93/00474

(22) International Filing Date: 5 March 1993 (05.03.93)

(30) Priority data:
9205482.4 13 March 1992 (13.03.92) GB
9215731.2 24 July 1992 (24.07.92) GB

(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MATASSA, Victor, Giulio [GB/GB]; The Duck Street Barns, Furneux Pelham, Hertfordshire SG9 0LA (GB). REEVE, Austin, John [GB/GB]; 160 Godfrey Way, Great Dunmow, Essex CM6 2SQ (GB). ROUTLEDGE, Helen [GB/GB]; 176 South Street, Bishop's Stortford, Hertfordshire CM23 3HZ (GB). STERNFELD, Francine [GB/GB]; 10 Richmond Gardens, London NW4 4RT (GB). STREET, Leslie, Joseph [GB/GB]; 99 Spruce Hill, Harlow, Essex CM18 7ST (GB).

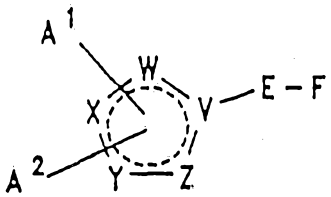
(74) Agent: THOMPSON, John; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

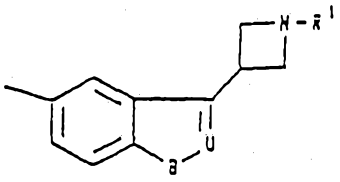
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

669160

(54) Title: IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES



(I)



(II)

(57) Abstract

A class of substituted imidazole, triazole and tetrazole derivatives of formula (I), wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring; two, three or four of V,W,X,Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V,W,X,Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring; E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; F represents a group of formula (II); U represents nitrogen or C-R^2; B represents oxygen, sulphur or N-R^3; are selective agonists of 5-HT_1-like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated.

IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

The present invention relates to a class of substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

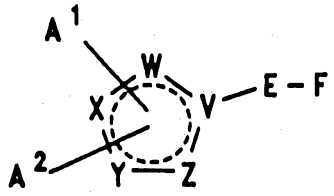
5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke et al., The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

EP-A-0313397 and WO-A-91/18897 describe separate classes of tryptamine derivatives substituted by various five-membered heteroaliphatic rings, which are stated to be specific to a particular type of "5-HT_1-like" receptor and thus to be effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. However, neither EP-A-0313397 nor WO-A-91/18897 discloses or suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

EP-A-0497512, published on 5th August 1992, describes a class of substituted imidazole, triazole and tetrazole derivatives which are stated to be selective agonists of 5-HT_1-like receptors and hence to be of

particular use in the treatment of migraine and associated conditions.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

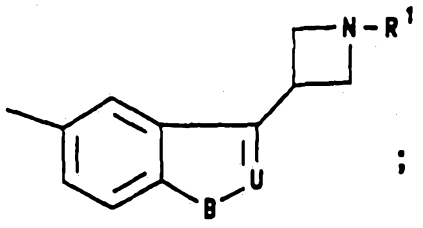
two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



;

U represents nitrogen or C-R^2;

B represents oxygen, sulphur or N-R^3;

R^1, R^2 and R^3 independently represent hydrogen or C_{1-6} alkyl;

R^X and R^Y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^X and R^Y together represent a C_{2-6} alkylene group;

R^Z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid,

acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to

6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable hete. .cycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, NR^vR^w, $-NR^vCOR^w$, $-NR^vCO_2R^w$, $-NR^vSO_2R^w$, $-CH_2NR^vSO_2R^w$, $-NHCONR^vR^w$, $-CONR^vR^w$, $-SO_2NR^vR^w$ and $-CH_2SO_2NR^vR^w$, in which R^v and R^w independently represent

hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl, or R^v and R^w together represent a C_{2-6} alkylene group.

When R^x and R^y, or R^v and R^w, together represent a C_{2-6} alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

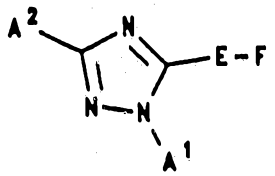
When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, $-COR^x$, $-CO_2R^x$ or $-SO_2R^x$, in which R^x is as defined above.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

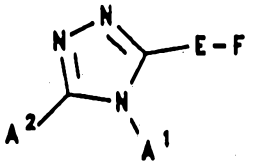
The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

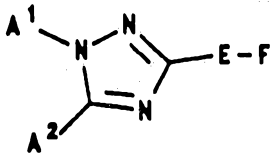
It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of isomeric forms having differing substitution patterns. These may suitably be represented by formulae IA to IT as follows:



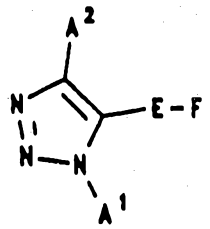
(IA)



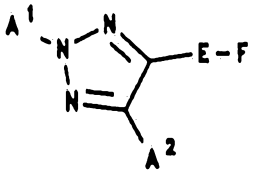
(IB)



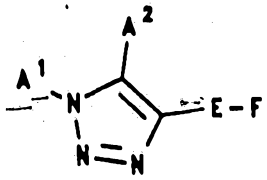
(IC)



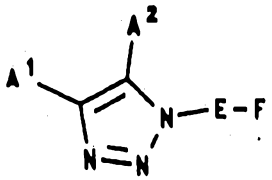
(ID)



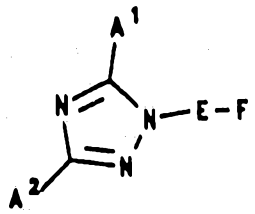
(IE)



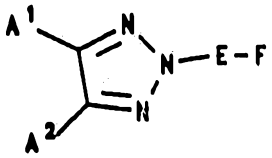
(IF)



(IG)

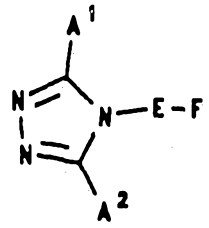


(IH)

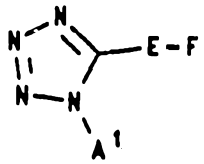


(IJ)

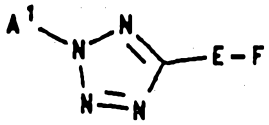
30



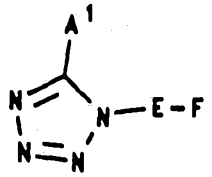
(IK)



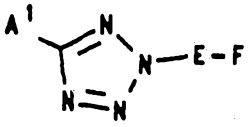
(IL)



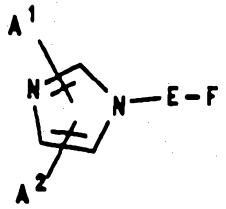
(IM)



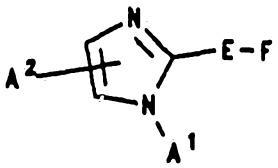
(IN)



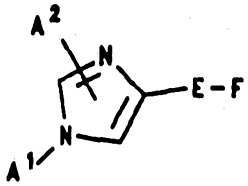
(IP)



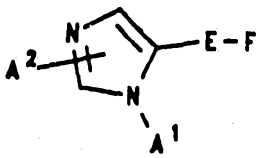
(IQ)



(IR)



(IS)



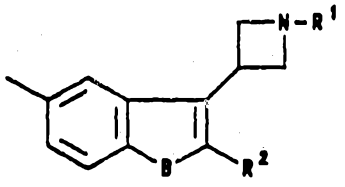
(IT)

wherein A^1, A^2, E and F are as defined above. Preferred imidazole, triazole and tetrazole rings of formula I include the rings represented by formulae IA, IC, IG, IH, IK, IL, IN and IQ above, especially IH and IK.

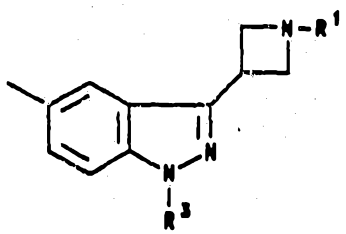
The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or

2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:

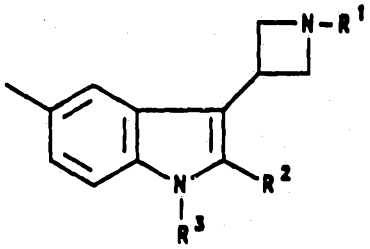


(FA)



(FB)

wherein B, R^1, R^2 and R^3 are as defined above. Preferably, the group F represents an indole moiety of structure FC:



(FC)

wherein R^1, R^2 and R^3 are as defined above, in particular wherein R^2 and R^3 are both hydrogen.

It will be appreciated that when four of V, W, X, Y and Z represent nitrogen and the other represents carbon, i.e. when the ring of formula I is a tetrazole ring, then the group A^2 will be a non-bonded electron pair. Otherwise, A^1 and A^2 will independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen,

cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$.

Suitable values for the groups A^1 and/or A^2 include C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl or $-NR^xR^y$, in which R^x and R^y are as defined above. Examples of optional substituents on the groups A^1 and/or A^2 suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylaminocarbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})alkylaminosulphonylmethyl.

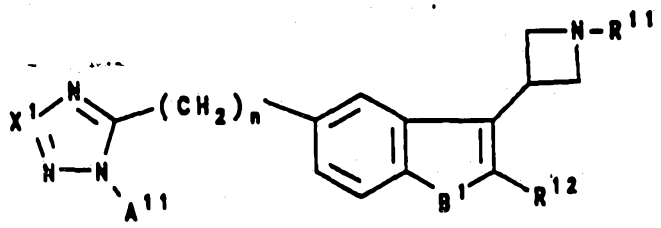
Particular values of A^1 and/or A^2 include hydrogen, methyl, methoxymethyl, aminomethyl, dimethylaminomethyl, acetylaminomethyl, benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylaminoethyl, benzoylaminoethyl, methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl, t-butoxycarbonylaminoethyl, methylsulphonylaminoethyl, aminocarbonylaminoethyl, methylaminocarbonylaminoethyl, t-butylaminocarbonylaminoethyl, phenylaminocarbonylaminoethyl, pyrrolidylcarbonylaminoethyl, cyclopropyl, phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl,

methylaminocarbonylphenyl, methylsulphonylaminomethylphenyl, aminosulphonylmethylphenyl, methylaminosulphonylmethylphenyl, dimethylaminosulphonylmethylphenyl, benzyl, trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl, methylsulphonylaminobenzyl, aminocarbonylaminobenzyl, aminocarbonylbenzyl, methylaminocarbonylbenzyl, methylsulphonylbenzyl, methylaminosulphonylbenzyl, pyridylmethyl, methoxypyridylmethyl, amino, methylamino, benzylamino, dimethylamino, t-butoxycarbonylaminoethylamino and methylsulphonylaminoethylamino.

Preferred values of A^1 and/or A^2 include hydrogen, methyl, ethyl and amino.

Preferred values for the groups R^1, R^2 and R^3 include hydrogen and methyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

X^1 represents nitrogen or A^{12}-C;

n is zero, 1, 2 or 3;

B^1 represents oxygen, sulphur or N-R^{13};

A^{11} and A^{12} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may

be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

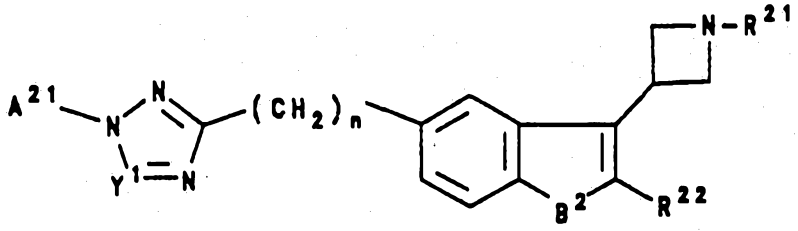
R^{11}, R^{12} and R^{13} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups A^{11} and A^{12} suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, C_{1-6} alkylsulphonyl, arylsulphonyl, amino, mono- or di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, arylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulphonylamino, arylsulphonylamino, C_{1-6} alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C_{1-6})alkylamino-carbonylamino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C_{1-6})alkylaminocarbonyl, C_{1-6} alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C_{1-6})alkyl-aminosulphonylmethyl.

Particular values of A^{11} and A^{12} with respect to formula IIA include hydrogen, methyl, ethyl and amino. When X^1 represents A^{12}-C, the group A^{11} is preferably hydrogen or methyl.

Preferably, R^{12} and R^{13} each represents hydrogen. Preferred values of R^{11} with respect to formula IIA include hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

Y^1 represents nitrogen or A^{22}-C;

n is zero, 1, 2 or 3;

B^2 represents oxygen, sulphur or N-R^{23};

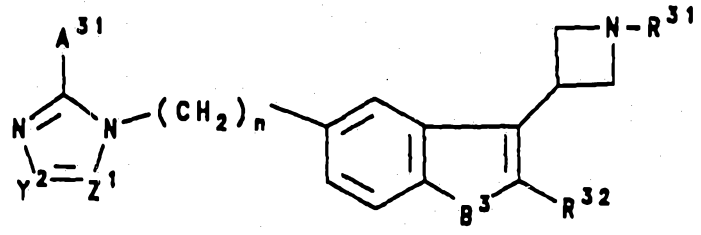
A^{21} and A^{22} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{21}, R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups A^{21} and A^{22} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{21} and A^{22} with respect to formula IIB include hydrogen, methyl and ethyl.

Preferably, R^{22} and R^{23} each represents hydrogen. Preferred values of R^{21} with respect to formula IIB include hydrogen and methyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

Y^2 represents nitrogen or A^{32}-C;

Z^1 represents nitrogen or CH;

n is zero, 1, 2 or 3;

B^3 represents oxygen, sulphur or N-R^{33};

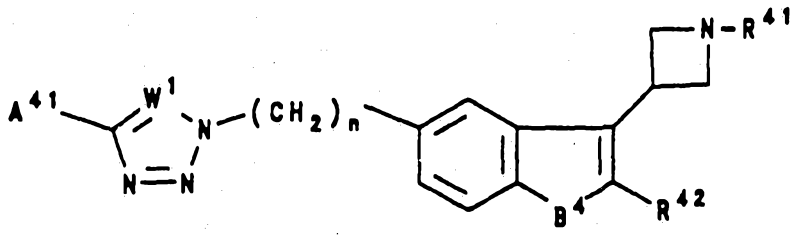
A^{31} and A^{32} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{31}, R^{32} and R^{33} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups A^{31} and A^{32} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{31} and A^{32} with respect to formula IIC include hydrogen, methyl and amino.

Preferably, R^{32} and R^{33} each represents hydrogen. Preferred values of R^{31} include hydrogen and methyl.

A still further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:



(IID)

wherein

W^1 represents nitrogen or C-A^{42};

n is zero, 1, 2 or 3;

B^4 represents oxygen, sulphur or N-R^{43};

A^{41} and A^{42} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{41}, R^{42} and R^{43} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the groups A^{41} and A^{42} correspond to those indicated for the groups A^{11} and A^{12} with respect to formula IIA above. Particular values of A^{41} and A^{42} with respect to formula IID include hydrogen and methyl.

Preferably, R^{42}, and R^{43} each represents hydrogen. Preferred values of R^{41} include hydrogen and methyl.

Specific compounds within the scope of the present invention include:

N-methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine;

N-methyl-3-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(imidazol-1-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(2-(1-methyltetrazol-5-yl)ethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]azetidine;
and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring

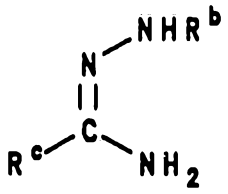
to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium

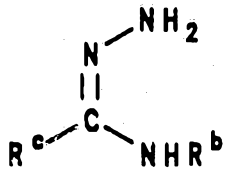
carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The 1,2,4-triazole compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with a compound either of formula III or of formula IV, or a salt thereof:



(III)

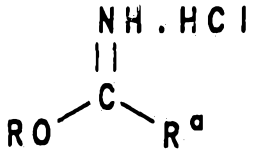


(IV)

wherein one of R^a, R^b and R^c is a group of formula A^1, another is a group of formula A^2, and the third is a group of formula -E-F, as defined with reference to formula I above.

Suitable reactive derivatives of the acid R^a-CO_2H include esters, for example C_{1-4} alkyl esters; thioesters, for example pyridylthioesters; acid anhydrides, for example $(R^a\text{-}CO)_2O$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

A preferred reactive derivative of the acid R^a-CO_2H is the iminoether derivative of formula V:



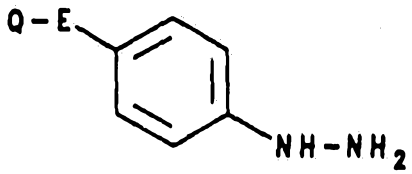
(V)

where R is C_{1-4} alkyl.

The reagent of formula III may be generated in situ in the reaction mixture. For example, the reaction may be effected by treating a compound of formula V above with an alkyl hydrazine, e.g. methyl hydrazine, followed by a suitable carboxylic acid such as formic acid.

The reaction is conveniently carried out by heating the reagents together, optionally in a solvent, for example tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol, at about 20°C to 100°C for about 1 to 6 hours.

Where R^a is a group of formula -E-F and the group F is an indole moiety of structure FC as defined above, the reactive derivative of a carboxylic acid of formula HO_2C-E-F may be prepared by reacting a compound of formula VI:



(VI)

wherein Q represents a reactive carboxylate moiety, and E is as defined above; with a compound of formula VII or a carbonyl-protected form thereof:



(VII)

wherein R^2 is as defined above and R^P represents an amino-protecting group; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3.

Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

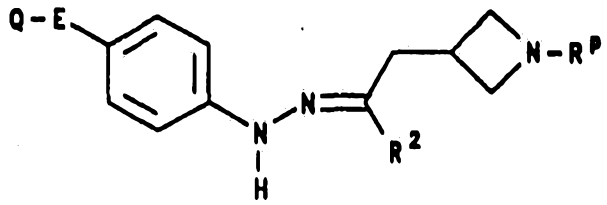
Suitable examples of amino-protecting groups for the substituent R^P include carboxylic acid groups such as chloroacetyl, trifluoroacetyl, formyl, benzoyl, phthaloyl, phenylacetyl or pyridinecarbonyl; acid groups derived from carbonic acid such as ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, biphenylisopropoxy-carbonyl, p-methylbenzyloxycarbonyl, p-nitrobenzyloxy-carbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxy-carbonyl, p-(p'-methoxyphenylazo)benzyloxycarbonyl or t-amyloxycarbonyl; acid groups derived from sulphonic acid, e.g. p-toluenesulphonic acid; and other groups such as benzyl, p-methoxybenzyl, trityl, o-nitrophenylsulphenyl or benzylidene.

Preferred amino-protecting groups include t-butoxycarbonyl, benzyloxycarbonyl and p-methoxybenzyl.

The removal of the protecting group present in the resultant compound may be effected by an appropriate procedure depending upon the nature of the protecting group. Typical procedures include hydrogenation in the presence of a palladium catalyst (e.g. palladium carbon

or palladium black) for benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl, p-(p'-methoxyphenylazo)benzyloxycarbonyl and trityl groups; treatment with hydrogen bromide in glacial acetic acid or trifluoroacetic acid for benzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl and t-butoxycarbonyl groups; treatment with acetic acid and/or a mineral acid such as hydrochloric acid or sulphuric acid for trityl, t-butoxycarbonyl, formyl and benzylidene groups; and treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone for p-methoxybenzyl groups.

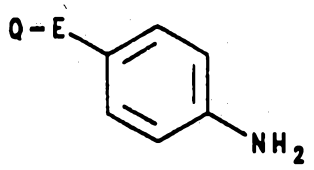
The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:



(VIII)

wherein Q, E, R^2 and R^P are as defined above; followed by cyclisation using a suitable reagent, such as a polyphosphate ester, to give a compound of formula Q-E-F.

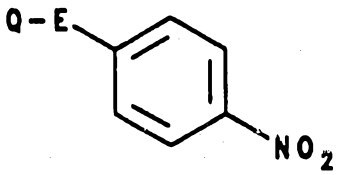
The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:



(IX)

wherein Q and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced <u>in situ</u> using, for example, tin(II) chloride/conc. HCl, sodium sulphite/conc. HCl, or sodium sulphite/conc. H_2SO_4.

The anilines of formula IX may be prepared by reduction of the corresponding nitro compounds of formula X:



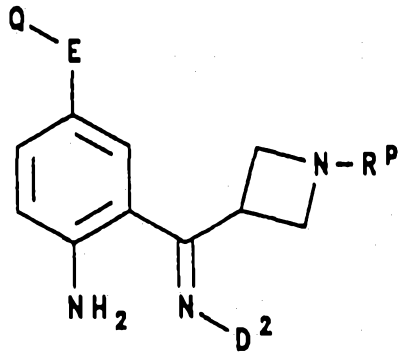
(X)

wherein Q and E are as defined above; typically by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

Where they are not commercially available, the nitro compounds of formula X may be synthesized by standard methods well known to those skilled in the art.

Where R^a is a group of formula -E-F and the group F is an indazole moiety of structure FB as defined

above, the reactive derivative of a carboxylic acid of formula HO_2C-E-F may be prepared by the cyclisation of a compound of formula XI:

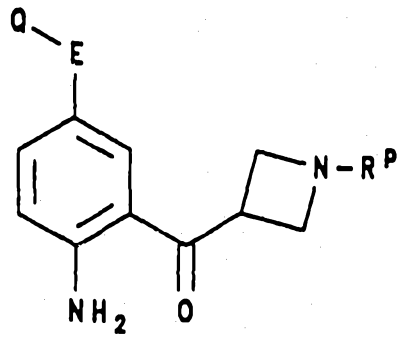


(XI)

wherein Q, E and R^P are as defined above; and D^2 represents a readily displaceable group; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3.

The cyclisation of compound XI is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

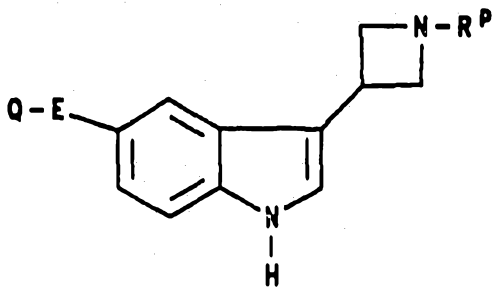
The readily displaceable group D^2 in the compounds of formula XI suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^2 in the desired compound of formula XI represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XII:



(XII)

wherein Q, E and R^P are as defined above; or a protected derivative thereof; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:



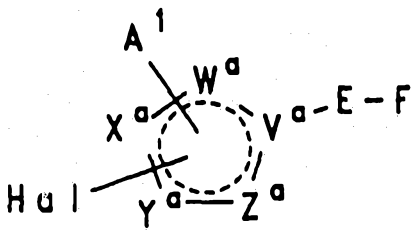
(XIII)

wherein Q, E and R^P are as defined abcve; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivative of formula XIII may be prepared by methods analogous to those described in the

accompanying Examples, or by procedures well known from the art.

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:



(XIV)

wherein A^1, E and F are as defined above, Hal represents halogen, and two of V^a, W^a, X^a, Y^a and Z^a, to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which provides an anion $^-A^2$, where A^2 is as previously defined.

Reagents which may provide the anion $^-A^2$ include Grignard reagents A^2MgHal (where Hal = halogen); organocuprate reagents such as $LiA^2{}_2Cu$; organolithium reagents A^2Li; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

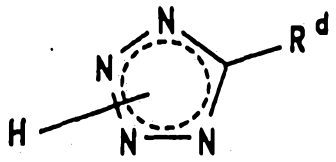
The 1,2,3-triazole compounds according to the present invention may be prepared by a process which comprises the cycloaddition of an alkyne of formula $R^a-C\equiv C-R^b$ with an azide of formula R^c-N_3, where R^a, R^b and R^c are as defined above.

The cycloaddition reaction may be conveniently effected in a suitable solvent such as tetrahydrofuran, ideally by heating in an autoclave for 8 hours.

The tetrazole compounds in accordance with the invention may be prepared by a process which comprises the cycloaddition of a nitrile of formula $N{\equiv}C\text{-}R^d$ with an azide of formula $R^e\text{-}N_3$, where one of R^d and R^e represents a group of formula A^1 and the other is a group of formula -E-F, as defined previously.

The cycloaddition reaction is conveniently effected by heating the reactants together at an elevated temperature, e.g. a temperature in the region of 150°C, in a suitable solvent such as N-methylpyrrolid-2-one, advantageously in the presence of triethylamine hydrochloride. The product obtained from the cycloaddition reaction will generally be a mixture of isomers substituted by the A^1 group at positions 1 and 2 of the tetrazole ring, corresponding to structures IL and IM respectively as defined above. These isomers may conveniently be separated using conventional techniques such as chromatography.

In an alternative process, the tetrazole compounds of the invention may be prepared by a method which comprises reacting a compound of formula $R^e\text{-}L$ with a tetrazole derivative of formula XV:



(XV)

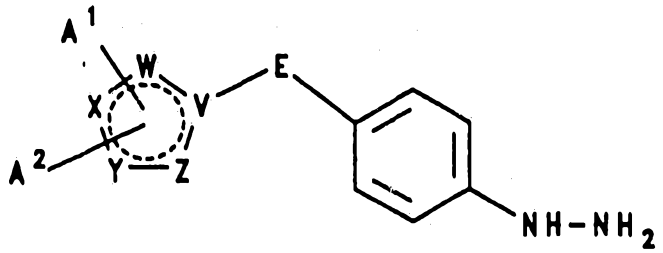
wherein one of R^d and R^e represents a group of formula A^1 and the other is a group of formula -E-F, as defined above, and L represents a suitable leaving group; in the presence of a base such as triethylamine.

The leaving group L suitably represents halogen, e.g. bromine or iodine, or a sulphonate derivative such as tosylate or mesylate.

The reaction is conveniently carried out in a suitable organic solvent, e.g. acetonitrile, at room temperature.

The tetrazole derivatives of formula XV may be prepared by cycloaddition of a nitrile of formula $N\equiv C-R^d$ with sodium azide, advantageously under the conditions described above for the reaction between the nitrile $N\equiv C-R^d$ and the azide R^e-N_3; followed by acidification with a mineral acid such as hydrochloric acid.

In a further process, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a method which comprises reacting a compound of formula XVI:

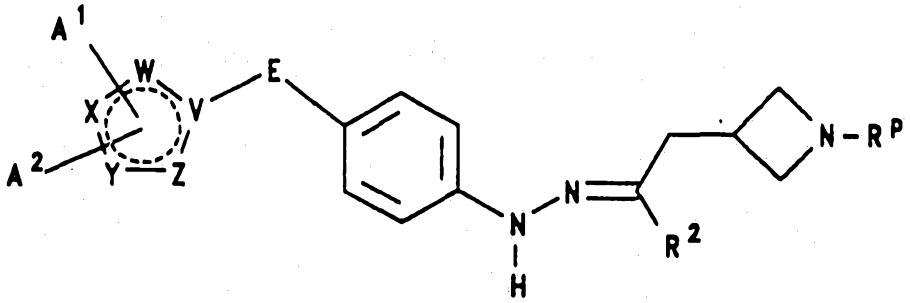


(XVI)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; with a compound of formula VII as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed by removal of the protecting group R^p;

and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3.

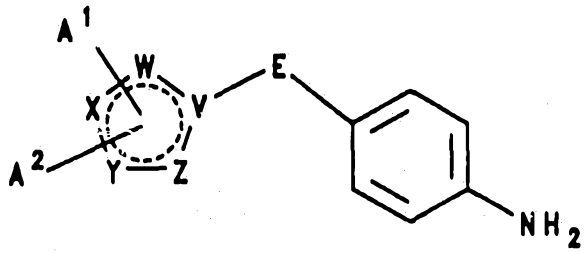
As with that between compounds VI and VII, the reaction between compounds XVI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVII:



(XVII)

wherein V, W, X, Y, Z, A^1, A^2, E, R^2 and R^P are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

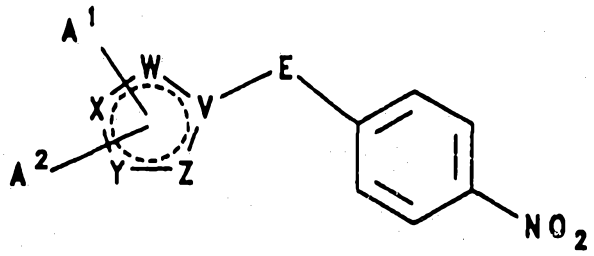
The hydrazines of formula XVI may be prepared from the corresponding anilines of formula XVIII:



(XVIII)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; by methods analogous to those described above with reference to the compounds of formula IX.

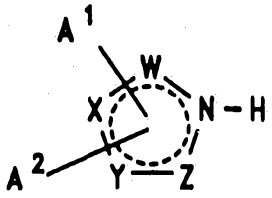
The anilines of formula XVIII may be prepared from the corresponding nitro compounds of formula XIX:



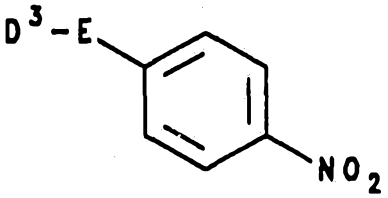
(XIX)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined above; by methods analogous to those described above with reference to the compounds of formula X.

The nitro compounds of formula XIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. For example, where V represents a nitrogen atom, the relevant compounds of formula XIX may be prepared by reacting the anion of a compound of formula XX with a compound of formula XXI:



(XX)



(XXI)

wherein W, X, Y, Z, A^1, A^2 and E are as defined above, and D^3 represents a readily displaceable group.

Where compound XX is a triazole or tetrazole derivative, the anion thereof may be generated by carrying out the reaction in a base such as triethylamine. Where compound XX is an imidazole derivative, the anion thereof may conveniently be

generated if the reaction is carried out in the presence of sodium hydride using N,N-dimethylformamide as solvent. Where salts of the compounds of formula XX are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-dimethylformamide solution in place of the compounds of formula XX themselves, with no requirement in this instance for additional base to be present in the reaction mixture.

The readily displaceable group D^3 in the compounds of formula XXI is suitably a halogen atom, preferably bromine; except when the moiety D^3 is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D^3 is preferably fluorine.

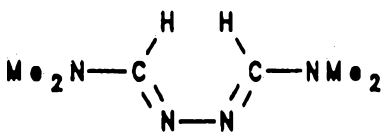
In an alternative approach, the compounds of formula XIX wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-1-yl moiety and A^1 and A^2 are both hydrogen may be prepared by reacting 4-amino-1,2,4-triazole with a compound of formula XXI as defined above, followed by deamination of the resulting 1-substituted 4-amino-4H-1,2,4-triazolium salt by treatment with nitrous acid and subsequent neutralisation. This transformation, which may be accomplished in two separate steps or advantageously as a "one-pot" procedure with both steps combined, is conveniently effected using reaction conditions analogous to those described in J. Org. Chem., 1989, 54, 731.

Where they are not commercially available, the nitro compounds of formula XXI above may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art.

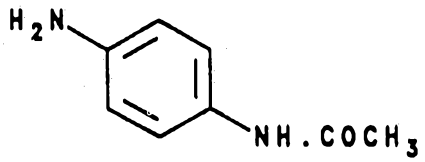
In an alternative approach to the 1,2,4-triazole derivatives, the nitro compounds of formula XIX

may be prepared from those of formula X above by appropriate modification of the moiety Q using, for example, methods analogous to those described above with reference to the compounds of formulae III and IV. Thus, for example, since Q in the compounds of formula X represents a reactive carboxylate moiety, the compounds of formula XIX may be prepared therefrom by reaction with a compound of formula A^2-C(=NNHA^1)NH_2 or A^2-C(=NNH_2)NHA^1.

Following a further representative pathway, the aniline derivatives of formula XVIII wherein the five-membered heteroaromatic ring is a 1,2,4-triazol-4-yl moiety, E is a bond and A^1 and A^2 are both hydrogen may be prepared by reacting the hydrazine derivative of formula XXII with the acetanilide of formula XXIII:



(XXII)



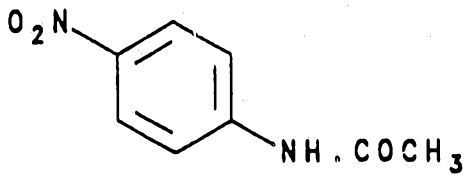
(XXIII)

followed by removal of the N-acetyl protecting group.

The reaction between compounds XXII and XXIII is conveniently effected in refluxing toluene, advantageously in the presence of a catalytic quantity of p-toluenesulphonic acid. Subsequent removal of the N-acetyl protecting group is typically effected in hot aqueous 5N hydrochloric acid.

The hydrazine derivative of formula XXII can be prepared from N,N'-diformylhydrazine by reaction with thionyl chloride/N,N-dimethylformamide, as reported in J. Chem. Soc. (C), 1967, 1664, and subsequent treatment with sodium methoxide in methanol.

The acetanilide of formula XXIII may be prepared by reduction of the corresponding nitro compound of formula XXIV:

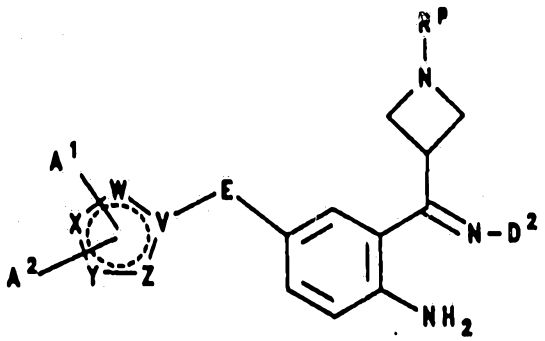


(XXIV)

typically by transfer hydrogenation using a hydrogenation catalyst in the presence of a hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

The nitro compound of formula XXIV is commercially available from the Aldrich Chemical Company Ltd., Gillingham, United Kingdom.

In a still further process, the compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be prepared by a method which comprises cyclising a compound of formula XXV:



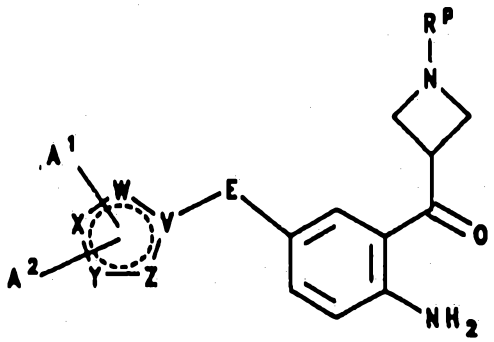
(XXV)

wherein V, W, X, Y, Z, A^1, A^2, E, R^P and D^2 are as defined above; followed by removal of the protecting group R^P;

and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3.

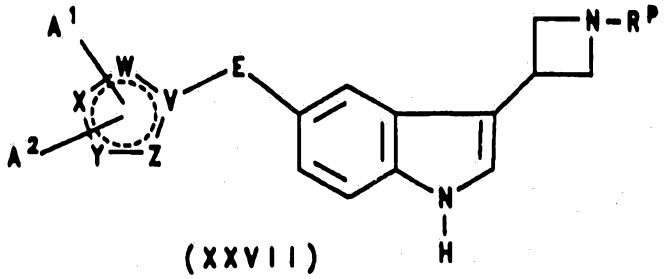
As with the cyclisation of compound XI, that of compound XXV is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The compounds of formula XXV may, for example, be prepared from the corresponding compound of formula XXVI:



(XXVI)

wherein V, W, X, Y, Z, A^1, A^2, E and R^P are as defined above; or a protected derivative thereof; which in turn may be prepared from the corresponding compound of formula XXVII:

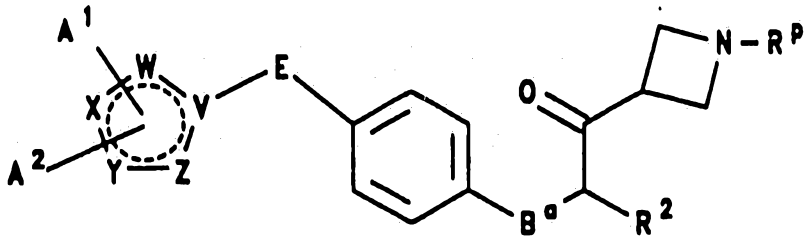


(XXVII)

wherein V, W, X, Y, Z, A^1, A^2, E and R^P are as defined above; using methods analogous to those described above

with reference to the compounds of formulae XII and XIII. Thus, for example, since Q in the compounds of formula XIII represents a reactive carboxylate moiety, the 1,2,4-triazole derivatives of formula XXVII may be prepared therefrom by reaction with a compound of formula A^2-C(=NNHA^1)NH_2 or A^2-C(=NNH_2)NHA^1.

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XXVIII:

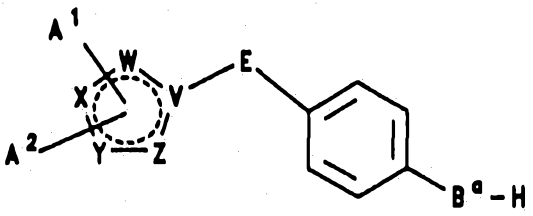


(XXVIII)

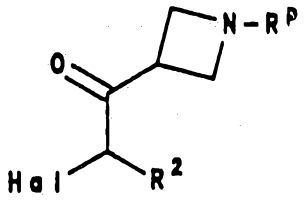
wherein V, W, X, Y, Z, A^1, A^2, E, R^2 and R^P are as defined above, and B^a represents oxygen or sulphur; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moiety R^1.

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XXVIII may be prepared by reacting a compound of formula XXIX with a compound of formula XXX:



(XXIX)

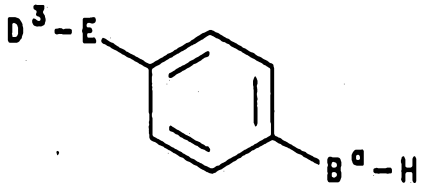


(XXX)

wherein V, W, X, Y, Z, A^1, A^2, E, B^a, R^2 and R^p are as defined above, and Hal represents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XXIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XX as defined above is reacted with a compound of formula XXXI:

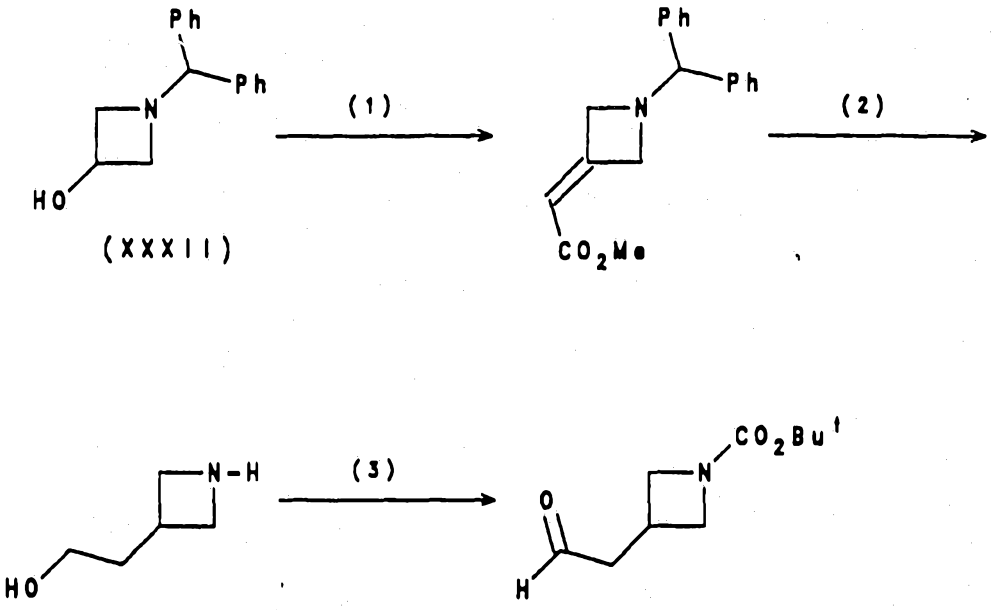


(XXXI)

wherein D^3, E and B^a are as defined above; to afford an intermediate of formula XXIX wherein V is nitrogen.

The compounds of formula XXX and XXXI, where they are not commercially available, may be prepared by standard procedures well known in the art.

The preparation of a typical intermediate of formula VII is illustrated by the following reaction scheme:



The starting compound XXXII is known from J. Chem. Soc., Chem Commun., 1968, 93. Step 1 of the reaction scheme comprises oxidation of the hydroxy group of compound XXXII to a carbonyl group using pyridine.SO_3 in dimethyl sulphoxide (DMSO) and triethylamine; followed by reaction of the resulting azetidinone derivative with the Horner-Emmons reagent $MeO_2C.CH_2.PO(OEt)_2$ in the presence of sodium hydride, using tetrahydrofuran (THF) as the solvent. In Step 2, the double bond of the azetidine olefin ester is hydrogenated over palladium-charcoal in methanol; the methyl ester group is then reduced to hydroxymethyl by treatment with lithium aluminium hydride in THF; and the diphenylmethyl protecting group is in turn removed by treatment with palladium hydroxide on charcoal, with methanol serving as the solvent. Step 3 involves protection of the azetidine nitrogen as the N-t-butoxycarbonyl (N-BOC) carbamate derivative; and, finally, Swern oxidation of the side

chain terminal hydroxy group to an aldehyde moiety by treatment with oxalyl chloride in DMSO/triethylamine.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compound of formula XV above in which R^d is a group of formula -E-F is itself a compound of formula I in which A^1 is hydrogen and A^2 represents a non-bonded electron pair. In particular, a compound of formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. Similarly, a compound of formula I wherein R^1 represents hydrogen initially obtained may be converted into a compound of formula I wherein R^1 is other than hydrogen, for example by conventional N-alkylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the

formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to 5-HT_1-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-^{3}H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC_{50}) is below 1 μM in each case.

The activity of test compounds as agonists of the 5-HT_1-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of

New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as $-\log_{10}EC_{50}$ (pEC_{50}) values, from plots of percentage 5-HT (1 μm) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC_{50} values in this assay of not less than 5.0 in each case.

EXAMPLE 1

N-Methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Bisoxalate

INTERMEDIATE 1

N-tert-Butyloxycarbonyl-3-formylmethylazetidine

1. N-Diphenylmethylazetidin-3-ol

Aminodiphenylmethane (100g, 0.54mols) was added to a solution of epichlorohydrin (50g, 0.54mols) in DMSO (135ml) and stirred at 25°C for 3 days. The solution was then heated at 70°C for 3 days before cooling to room temperature, adding 10% NaOH solution, and extracting with Et_2O (2 x 800ml). The combined extracts were washed with water (2 x 1l), dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica-gel eluting with CH_2Cl_2/MeOH (98:2) to give the title-azetidinol (33.5g); δ (360MHz, $CDCl_3$) 2.30 (1H, br s, OH), 2.87-2.91 (2H, m, 2 of CH of CH_2), 3.51-3.55 (2H, m, 2 of CH of CH_2), 4.34 (1H, s, CH), 4.41-4.48 (1H, m, CH-OH), 7.13-7.39 (10H, m, Ar-H).

2. N-Diphenylmethylazetidin-3-one

Triethylamine (112.1g, 1.11mols) was added to a solution of N-diphenylmethylazetidin-3-ol (26.6g, 0.11mol) in DMSO

(300ml). The solution was cooled to 10°C and a solution of sulphur trioxide-pyridine complex (112g, 0.7mol) in DMSO (500ml) added, rapidly. Stirring was continued at 10°C for 0.75h and the mixture then warmed to 25°C and stirred for 1h. The solution was poured into ice-water (2l) and extracted with EtOAc (3 x 1l). The combined extracts were washed with water (500ml) and brine (500ml) and dried (Na_2SO_4). The crude product was purified by chromatography through silica-gel eluting with petroleum ether/EtOAc (2:1) to give the desired ketone (25.8g), mp 74-75°C; δ (360MHz, $CDCl_3$) 4.00 (4H, s, 2 of CH_2), 4.59 (1H, s, CH), 7.19-7.49 (10H, m, Ar-H).

3. Methyl (1-diphenylmethylazetidin-3-ylidene)acetate

Methyl diethylphosphonoacetate (11.0g, 52.0mmol) in THF (10ml) was added dropwise to a stirred suspension of sodium hydride (2.1g, 60% dispersion in oil, 52.5mmol) in THF (40ml), at 10°C. The mixture was stirred for 0.6h and a solution of the preceding azetidinone (11.3g, 48.0mmol) in THF (50ml) then added dropwise at 10°C. The mixture was heated at 50°C for 3h before removing the solvent under vacuum and redissolving the residue in CH_2Cl_2 (200ml). The solution was washed with water (50ml) and sodium bisulphite solution (2 x 50ml) and dried (Na_2SO_4). Chromatography of the residue obtained, after removing the solvent, through silica-gel eluting with CH_2Cl_2/MeOH (98:2) gave the desired ester (13.1g), mp 83-84°C; δ (360MHz, $CDCl_3$) 3.65 (3H, s, CO_2Me), 3.88 (2H, m, 2 of

CH of CH_2), 4.14-4.17 (2H, m, 2 of CH of CH_2), 4.52 (1H, s, CH), 5.65-5.68 (1H, m, vinyl-H), 7.17-7.44 (10H, m, Ar-H).

4. N-Diphenylmethyl-3-carbomethoxymethylazetidine

A mixture of the compound from step 3 (21.0g, 71.7mmol), $Pd(OH)_2$ (3.0g, 20% on C), methanol (500ml) and 2N HCl (37ml) was hydrogenated on a Parr shake apparatus for 2h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. Saturated K_2CO_3 solution was added (50ml) and extracted with CH_2Cl_2 (2 x 250ml). The combined extracts were washed with H_2O (250ml) and brine (100ml), dried (Na_2SO_4) and evaporated to give the title-product as a pale yellow oil (19.3g); δ (360MHz, $CDCl_3$) 2.58 (2H, d, J = 7.3Hz, CH_2), 2.75-2.81 (3H, m, 2 of CH of CH_2 and CH), 3.35-3.38 (2H, m, 2 of CH of CH_2), 3.62 (3H, s, CO_2Me), 4.31 (1H, s, CH), 7.14-7.18, 7.23-7.27 and 7.38-7.40 (total 10H, each m, Ar-H).

5. Ethyl-2-(1-diphenylmethylazetidin-3-yl)alcohol

Diisobutylaluminium hydride (119ml of a 1M solution in toluene, 0.119mol) was added dropwise to a stirred solution of the preceding ester (10.0g, 33.9mmol) in toluene (500ml), at -35°C, over a 0.5h period. The solution was warmed to 25°C, stirred for 2h, and then cooled to 0°C and quenched by addition of methanol (10ml), 2N NaOH (5ml) and H_2O (5ml). The

mixture was warmed to 25°C, filtered through celite and the solvent removed under vacuum. The residue was chromatographed on silica-gel eluting with ethyl acetate/hexane (1:1) to give the title-alcohol as a white crystalline solid, (4.1g), mp 98-99°C; (Found: C, 80.73; H, 8.06; N, 5.38. $C_{18}H_{21}NO$ requires C, 80.86; H, 7.92; N, 5.24%); δ (360MHz, $CDCl_3$) 1.64 (1H, br s, OH), 1.82 (2H, m, CH_2), 2.51-2.58 (1H, m, CH), 2.87-2.91 and 3.29-3.33 (both 2H, each m, 2 of CH_2), 3.70 (2H, t, J = 6.4Hz, CH_2), 4.33 (1H, s, CH), 7.15-7.40 (10H, m, Ar-H).

6. Ethyl-2-(1-H-azetidin-3-yl)alcohol. Hydrochloride

$Pd(OH)_2$ (0.8g, 20% on C) was added to a solution of the preceding alcohol (4.0g, 15.0mmol) in methanol (200ml) and 1N HCl (10ml), and the mixture hydrogenated on a Parr shake apparatus for 24h, at 55 psi. The mixture was filtered through celite and the solvent removed under vacuum. Diphenyl methane was removed by triturating the residue with ether and decanting. The remaining product was dried under vacuum to give the desired product (2.0g); δ (250MHz, D_2O) 1.86-1.94 (2H, m, CH_2), 2.98-3.16 (1H, m, CH), 3.60 (2H, t, J = 6.4Hz, CH_2), 3.86-3.96 and 4.14-4.22 (both 2H, both m, 2 of CH_2).

7. Ethyl-2-(1-tert-butyloxycarbonylazetidin-3-yl)alcohol

A mixture of the product from step 6 (1.44g, 10.5mmol),

triethylamine (3.21ml, 22.9mmol) and $(BOC)_2O$ (3.43g, 15.7mmol), in THF (90ml) was stirred at 25°C for 2 days. The solvent was removed under vacuum, water (70ml) added and extracted with EtOAc (3 x). The combined extracts were dried ($MgSO_4$), evaporated and the residue chromatographed on silica-gel eluting with CH_2Cl_2/MeOH (95:5) to give the title-product (2.12g); δ (250MHz, $CDCl_3$) 1.42 (9H, s, 3 of CH_3), 1.56 (1H, s, OH), 1.82-1.90 (2H, m, CH_2), 2.56-2.76 (1H, m, CH), 3.58-3.67 (4H, m, CH_2 and 2 of CH of CH_2), 4.00-4.06 (2H, m, 2 of CH of CH_2).

8. N-tert-Butyloxycarbonyl-3-formylmethylazetidine

Dimethylsulphoxide (1.98g, 25.3mmol) was added dropwise to a solution of oxalyl chloride (1.61g, 12.6mmol) in CH_2Cl_2 (80ml), at -75°C. The mixture was stirred for 0.25h before adding a solution of the preceding alcohol (2.12g, 10.6mmol) in CH_2Cl_2 (50ml), at -75°C, and stirring for 1h. Triethylamine (5.38g, 52.7mmol) was added and the reaction mixture warmed to 25°C and stirred for 1h. Water (50ml) and saturated K_2CO_3 solution (25ml) were added and the mixture stirred vigorously before separation of the aqueous phase and further extraction with CH_2Cl_2 (2 x). The combined extracts were dried ($MgSO_4$), the solvent removed under vacuum, and the crude product chromatographed on silica-gel eluting with diethyl ether. The desired product (1.9g) was obtained as a pale yellow solid, mp 52-54°C; (Found: C, 60.05; H, 8.57; N, 7.09. $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.6; N, 7.03%); δ (360MHz, $CDCl_3$) 1.34

(9H, s, 3 of CH_3), 2.76 (2H, d, J = 7.4Hz, $C\underline{H}_2CHO$), 2.77-2.96 (1H, s, CH), 3.46-3.52 (2H, m, 2 of CH of CH_2), 4.02-4.08 (2H, m, 2 of CH of CH_2), 9.70 (1H, s, aldehyde-H).

INTERMEDIATE 2

4-(2-Methylimidazol-1-ylmethyl)phenylhydrazine Hydrochloride

1. 4-(2-Methylimidazol-1-ylmethyl)nitrobenzene

Sodium hydride (2.45g, 61.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (5.0g, 60.9mmol) in DMF (100ml). The mixture was stirred at room temperature for 0.25h before adding 4-nitrobenzyl bromide (13.2g, 61.0mmol) and heating at 110°C for 2h followed by stirring at room temperture for 16h. Water (200ml) and ethyl acetate (500ml) were added, the aqueous separated and extracted with ethyl acetate (2 x 500ml). The combined extracts were washed with water (3 x 250ml), dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica-gel eluting with CH_2Cl_2/MeOH (96:4) to give the title-product (1.58g); δ (360MHz, $CDCl_3$) 2.34 (3H, s, CH_3), 5.16 (2H, s, CH_2), 6.87 (1H, d, J = 1.3Hz, Ar-H), 7.03 (1H, d, J = 1.3Hz, Ar-H), 7.19 (2H, d, J = 9.5Hz, Ar-H), 8.22 (2H, d, J = 9.5Hz, Ar-H).

2. 4-(2-Methylimidazol-1-ylmethyl)phenylaniline Hydrochloride

Pd-C (1.5g, 10%) was added to a mixture of the preceding nitrobenzene (14.4g, 66.4mmol), water (12ml), 5N HCl (14.6ml), and ethanol (85ml) and the slurry hydrogenated at 40 psi in a Parr flask for 0.5h. The catalyst was removed by filtration through celite, the solvents removed under vacuum, and the resulting solid recrystallised from EtOH/Et_2O to give the title-aniline (12.0g); δ (360MHz, D_2O) 2.62 (3H, s, CH_3), 5.21 (2H, s, CH_2), 6.90 (2H, d, J = 8.4Hz, Ar-H), 7.19 (2H, d, J = 8.4Hz, Ar-H), 7.31 (2H, s, Ar-H).

3. 4-(2-Methylimidazol-1-ylmethyl)phenylhydrazine Hydrochloride

A solution of $NaNO_2$ (5.21g, 76.5mmol) in H_2O (70ml) was added to a stirred solution of the preceding aniline hydrochloride (15.34g, 68.6mmol) in conc^n. HCl (140ml), cooled to -15°C. After addition (0.25h) the mixture was stirred for 0.5h at -15°C and then filtered through a sinter directly into an addition funnel. The resulting solution was added to a rapidly stirred solution of $SnCl_2.2H_2O$ (61.9g, 0.275mol) in conc^n. HCl (100ml) at such a rate as to maintain the temperature below -5°C. The mixture was warmed to room temperature, the precipitate filtered off, and the solid washed several times with Et_2O. In order to remove tin salts the free base was generated by dissolving in

H_2O (120ml), basifying with NH_4OH solution and extracting with CH_2Cl_2 (2 x). The hydrochloride salt was regenerated by addition of ethereal HCl to the CH_2Cl_2 solution of the free base. The product was filtered and dried under vacuum (11.4g); δ (360MHz, D_2O) 2.62 (3H, s, CH_3), 5.26 (2H, s, CH_2), 7.02 (2H, d, J = 8.4Hz, Ar-H), 7.28 (2H, d, J = 8.4Hz, Ar-H), 7.29 (1H, d, J = 1.5Hz, Ar-H), 7.30 (1H, d, J = 1.5Hz, Ar-H).

N-Methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Bisoxalate

1. 1H-3-[5-(2-Methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine

N-tert-Butyloxycarbonyl-3-formylmethylazetidine (0.3g, 1.51mmol) was added to a solution of 4-(2-methylimidazol-1-ylmethyl)phenylhydrazine (0.36g, 1.51mmol) in 4% H_2SO_4 (25ml) and the resulting solution refluxed for 3h. The mixture was then cooled to room temperature, basified with K_2CO_3 and extracted with n-butanol (2 x 100ml). The combined extracts were dried ($MgSO_4$), evaporated, and the residue chromatographed through silica-gel eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1) to give the title-indole (0.186g, 46%), mp 88-90°C; δ (250MHz, CD_3OD) 2.02 (3H, s, CH_3), 3.76-3.86 (4H, m, 2 of CH_2), 4.04-4.20 (1H, m, CH of azetidine), 5.06 (2H, s, CH_2), 6.70 (1H, d, J = 1.4Hz, Ar-H), 6.82 (1H, dd, J = 1.5

and 8.4Hz, Ar-H), 6.90 (1H, d, J = 1.4Hz, Ar-H), 7.12 (1H, s, Ar-H), 7.23 (1H, d, J = 8.4Hz, Ar-H), 7.26 (1H, d, J = 1.5Hz, Ar-H).

2. N-Methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Bisoxalate

To a cooled and stirred solution of the preceding 1H-azetidine (0.174g, 0.65mmol), $NaCNBH_3$ (51mg, 0.82mmol), and acetic acid (98mg, 1.64mmol), in methanol (20ml), was added a solution of formaldehyde (65mg, 0.82mmol; 38% w/v) in methanol (10ml), at such a rate as to keep the temperature of the solution at 0°C. The mixture was stirred at 0°C for 0.25h and then warmed to room temperature and stirred for 1h. Saturated K_2CO_3 solution (15ml) was added and the methanol removed under vacuum. The aqueous was extracted with EtOAc (3 x 100ml), the combined extracts dried ($MgSO_4$) and the solvent removed under vacuum. The residue was chromatographed on silica-gel eluting with CH_2Cl_2/MeOH/NH_3 (70:8:1) and the bisoxalate salt of the resulting product was prepared (91mg), mp 125-126°C; (Found: C, 53.03; H, 5.27; N, 11.17. $C_{17}H_{20}N_4.2.2\ (C_2H_2O_4).0.30H_2O.0.1(CH_3OH)$ requires C, 53.02; H, 5.26; N, 11.50%); m/e 281 (M^++1); δ (360MHz, D_2O) 2.64 (3H, s, CH_3), 3.00 and 3.09 (total 3H, both s, N-CH_3), 4.17-4.24, 4.38-4.58 and 4.74-4.86 (total 5H, both m, CH and 2 of CH_2 of azetidine), 5.41 (2H, s, CH_2), 7.18-7.20 (1H, m, Ar-H), 7.31 (2H, s, Ar-H), 7.53 (1H, d, J = 1.0Hz, Ar-H), 7.56-7.59 (2H, m, Ar-H).

EXAMPLE 2

N-Methyl-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine. Oxalate

1. 4-(1,2,4-Triazol-1-yl)nitrobenzene

1,2,4-Triazole sodium derivative (90%) (17.74g, 0.18mol) and 1-fluoro-4-nitrobenzene (25g, 0.18mol), in DMF, (150ml) was stirred at room temperature for 4 days. Water (300ml) and ethyl acetate (500ml) were added and the mixture extracted. The organic layer was separated, washed with water (3 x 300ml), dried ($MgSO_4$) and evaporated to give the desired product (24.8g); δ (360MHz, $CDCl_3$) 7.92 (2H, d, J = 9.1Hz, Ar-H), 8.17 (1H, s, Ar-H), 8.40 (2H, d, J = 9.1Hz, Ar-H), 8.48 (1H, s, Ar-H).

2. 4-(1,2,4-Triazol-1-yl)phenylhydrazine

Prepared from 4-(1,2,4-triazol-1-yl)nitrobenzene using the procedure described for the preparation of Intermediate 2; δ (360MHz, $CDCl_3$) 3.66 (2H, br s, NH_2), 5.36 (1H, br s, NH), 6.88-6.96 and 7.44-7.50 (both 2H, both m, Ar-H), 8.06 (1H, s, Ar-H), 8.42 (1H, s, Ar-H).

3. 1H-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine

N-tert-Butyloxycarbonyl-3-formylmethylazetidine (0.4g,

2.01mmol) was added to a solution of 4-(1,2,4-triazol-1-yl)phenylhydrazine (0.35g, 2.01mmol) in 4% H_2SO_4 (50ml) and the mixture refluxed for 16h. The mixture was then cooled to room temperature, basified (K_2CO_3) and extracted with n-butanol (5 x). The crude product obtained was chromatographed on silica-gel eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1) to give the title-azetidinylindole (0.186g, 39%); δ (360MHz, CD_3OD) 3.80-3.88 (4H, m, 2 of CH_2 of azetidine), 4.12-4.23 (1H, m, CH), 7.23 (1H, s, Ar-H), 7.39 (2H, s, Ar-H), 7.65 (1H, d, J = 2.5Hz, Ar-H), 8.04 (1H, s, Ar-H), 8.89 (1H, s, Ar-H).

4. N-Methyl-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine. Oxalate

Prepared from the product of step 3 using the procedure described for Example 1. The oxalate salt was prepared, mp 175-177°C; (Found: C, 54.17; H, 5.15; N, 19.04. $C_{14}H_{15}N_5.1.2(C_2H_2O_4).0.125H_2O$ requires C, 54.17; H, 4.89, N, 19.26%); δ (360MHz, D_2O) 2.99 and 3.07 (total 3H, s, CH_3), 4.17-4.22, 4.35-4.57 and 4.72-4.79 (total 5H, m, azetidine-H), 7.42-7.47 (1H, m, Ar-H), 7.53 (1H, s, Ar-H), 7.58-7.62 (1H, m, Ar-H), 7.74-7.76 (1H, m, Ar-H), 8.22 (1H, s, Ar-H), 9.82 (1H, s, Ar-H).

EXAMPLE 3

N-Methyl-3-[5-imidazol-1-yl-1H-indol-3-yl]azetidine. Hemioxalate. Monohydrate

1. 4-Imidazol-1-ylphenylhydrazine. Dihydrochloride

Prepared from imidazole and 1-fluoro-4-nitrobenzene as described for Example 2, step 1 and Intermediate 2; δ (360MHz, D_2O) 7.36-7.46 (2H, m, Ar-H), 7.80-7.88 (3H, m, Ar-H), 8.04-8.06 (1H, m, Ar-H), 9.30 (1H, s, Ar-H).

2. 1H-3-[5-Imidazol-1-yl-1H-indol-3-yl]azetidine

The title-compound was prepared from 4-imidazol-1ylphenylhydrazine dihydrochloride using the procedure described for Example 2, step 3; δ (360MHz, CD_3OD) 4.05-4.16 and 4.26-4.34 (total 5H, each m, azetidine-H), 7.04 (1H, s, Ar-H), 7.20 (1H, dd, J = 2.0 and 8.6Hz, Ar-H), 7.33 (1H, s, Ar-H), 7.42 (1H, d, J = 8.6Hz, Ar-H), 7.43 (1H, s, Ar-H), 7.64 (1H, d, J = 2.0Hz, Ar-H), 7.95 (1H, s, Ar-H).

3. N-Methyl-3-[5-imidazol-1-yl-1H-indol-3-yl]azetidine. Hemioxalate. Monohydrate

Prepared from the preceding 1H-azetidine using the procedure described for Example 1. The hemioxalate monhydrate salt was prepared, mp 215-218°C; (Found: C, 61.24;

H, 6.14; N, 17.01. $C_{15}H_{16}N_4.0.5(C_2H_2O_4).0.9H_2O$ requires C, 61.29; H, 6.04; N, 17.87%); m/e 253 (M^++1); δ (360MHz, D_2O) 3.04 and 3.12 (total 3H, each s, CH_3), 4.22-4.27, 4.43-4.62 and 4.78-4.86 (total 5H, each m, azetidine-H), 7.39 (1H, s, Ar-H), 7.40 (1H, d, J = 8.6Hz, Ar-H), 7.61 (1H, s, Ar-H), 7.65-7.71 (3H, m, Ar-H), 8.45 (1H, s, Ar-H).

EXAMPLE 4

N-Methyl-3-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine. Succinate. Monohydrate

1. 4-(1H-Tetrazol-5-ylmethyl)nitrobenzene

Triethylamine hydrochloride (41.25g, 0.3mol) and sodium azide (39g, 0.6mol) were added to a solution of 4-nitrophenylacetonitrile (32.4g, 0.2mol) in anhydrous N-methylpyrrolidin-2-one (500ml) and the mixture heated at 150°C for 4h. The solution was cooled to room temperature and poured into 2N HCl (2l) whereupon a solid crystallised out. The product was filtered, washed with water (500ml) and hexane and dried in vacuo (37.4g); δ (250MHz, $CDCl_3$) 4.34 (2H, s, CH_2), 7.42 (2H, d, J = 8.7Hz, Ar-H), 8.12 (2H, d, J = 8.7Hz, Ar-H).

2. 4-(1-Methyltetrazol-5-ylmethyl)nitrobenzene

A solution of methyl iodide (34.1ml, 0.5mol) in acetonitrile

(100ml) was added dropwise, over 1h, to a solution of 4-(1H-tetrazol-5-ylmethyl)nitrobenzene (20.5g, 0.1mol), and triethylamine (18.7ml, 0.25mol), in acetonitrile (500ml), at room temperature. The mixture was stirred for 3h, the solvent removed under vacuum and residue dissolved in EtOAc (500ml). The solution was washed with water (2 x) and brine (1 x) and the solvent evaporated. The crude product was chromatographed through silica-gel eluting with EtOAc/hexane (1:1) → EtOAc (100%) to give 2 components. The more polar product (7.9g) was identified as the desired 1-methyl substituted tetrazole. The less polar product (7.0g) was identified as being the 2-substitution product; δ (360MHz, $CDCl_3$, more polar isomer) 3.94 (3H, s, CH_3), 4.40 (2H, s, CH_2), 7.42 (2H, d, J = 8.7Hz, Ar-H), 8.21 (2H, d, J = 8.7Hz, Ar-H).

3. 4-(1-Methyltetrazol-5-ylmethyl)phenylhydrazine. Hydrochloride

The title-hydrazine was prepared from the preceding nitrobenzene using the procedures described for Intermediate 2; δ (360MHz, D_2O) 4.02 (3H, s, CH_3), 4.32 (2H, s, CH_2), 7.05 (2H, d, J = 8.5Hz, Ar-H), 7.31 (2H, d, J = 8.5Hz, Ar-H).

4. 1H-3-[5-(1-Methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine

The title-compound was prepared from the preceding hydrazine and N-tert-butyloxycarbonyl-3-formylmethyl azetidine according to the procedure described for Example 1, mp 85-87°C; (Found: C, 62.89; H, 6.25; N, 30.14. $C_{14}H_{16}N_6.0.15(C_2H_2OH)$ requires C, 62.40; H, 6.19; N, 30.53%); δ (360MHz, CD_3OD) 3.68-3.90 (4H, m, 2 of CH_2), 3.80 (3H, s, CH_3), 4.03-4.20 (1H, m, CH of azetidine), 4.32 (2H, s, CH_2), 6.85 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.12 (1H, s, Ar-H), 7.22 (1H, d, J = 8.4Hz, Ar-H), 7.38 (1H, d, J = 1.5Hz, Ar-H).

5. N-Methyl-3-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine. Succinate. Monohydrate

Prepared from the preceding 1H-azetidine using the general N-methylation procedure. The succinate monohydrate salt was prepared, mp 65-67°C; (Found: C, 57.25; H, 6.59; N, 22.17. $C_{15}H_{18}N_6.0.7(C_4H_6O_4).0.5H_2O$ requires C, 57.16; H, 6.25; N, 22.45%); δ (360MHz, D_2O) 2.41 (2H, s, succinic acid), 2.97 and 3.06 (total 3H, both s, CH_3), 3.97 (3H, s, CH_3), 4.13-4.19, 4.27-4.51 and 4.69-4.74 (total 5H, each m, azetidine H), 4.40 (2H, s, CH_2), 7.11 (1H, d, J = 8.4Hz, Ar-H), 7.44 (2H, s, Ar-H), 7.49 (1H, d, J = 8.4Hz, Ar-H).

EXAMPLE 5

N-Methyl-3-[5-(2-(1-methyltetrazol-5-yl)ethyl)-1H-indol-3-yl]azetidine. Benzoate

The title-compound was prepared from 4-nitrophenethyl nitrile as described for Example 4. The benzoate salt was prepared, mp 165-167°C; (Found: C, 66.30; H, 6.33; N, 20.15. $C_{16}H_{20}N_6.C_7H_6O_2$ requires C, 66.01; H, 6.26; N, 20.08%); δ (250MHz, D_2O) 3.04 and 3.14 (total 3H, both s, CH_3), 3.20-3.38 (4H, m, 2 of CH_2), 3.56 and 3.60 (total 3H, both s, CH_3), 4.12-4.20, 4.28-4.54 and 4.68-4.84 (total 5H, each m, azetidine-H), 7.08-7.18, 7.43-7.64 and 7.90-7.96 (total 9H, m, Ar-H and benzoic acid).

EXAMPLE 6

N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Hemioxalate

Prepared from N-tert-butyloxycarbonyl-3-formylazetidine and 4-(1,2,4-triazol-1-ylmethyl)nitrobenzene using the procedures described for Example 1. The hemioxalate salt was prepared, mp 100-102°C; (Found: C, 60.26; H, 6.09; N, 20.03. $C_{15}H_{17}N_5.0.65(C_2H_2O_4).0.2\ (Et_2O).0.1H_2O$ requires C, 59.97; H, 6.03; N, 20.45%); δ (360MHz, D_2O) 3.00 and 3.09 (total 3H, both s, N-CH_3), 4.16-4.22, 4.33-4.56 and 4.71-4.77 (total 5H, each m, CH and 2 of CH_2 of azetidine), 5.50 (2H, s, CH_2), 7.22-7.24, 7.47-7.56 and 7.90-7.92 (total 4H, each m, Ar-H), 8.05 and 8.54 (total 2H, each s, Ar-H).

EXAMPLE 7

N-Methyl-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]azetidine. 1.75 Benzoate. 0.8 Hydrate

1. 4-(1,2,4-Triazol-4-yl)phenylhydrazine

a) 4'-Aminoacetanilide

A solution of 4'-nitroacetanilide (5.0g, 27.8mmol) in EtOH/EtOAc (160ml, 1:1), H_2O (15ml) and 5N HCl (5.6ml, 28.0mmol) was hydrogenated over 10% Pd-C (0.50g) at 50 psi for 0.25h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. The free base was generated by dissolving the product in H_2O, basifying with 2N NaOH and extracting into EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated to give the title-aniline (3.75g, 90%); δ (250MHz, $CDCl_3/D_4$-MeOH) 2.10 (3H, s, CH_3), 6.68 (2H, d, J = 8.8Hz, Ar-H), 7.27 (2H, d, J = 8.8Hz, Ar-H).

b) 4'-(1,2,4-Triazol-4-yl)acetanilide

A mixture of the preceding aniline (3.52g, 23.4mmol), N,N-dimethylformamide azine (3.33g, 23.4mmol; J. Chem. Soc. C. 1967, 1664) and p-toluenesulphonic acid monohydrate (0.223g, 1.17mmol), in anhydrous toluene (100ml), was heated at reflux for 17h. The beige coloured precipitate was filtered off and

washed with toluene and CH_2Cl_2 and dried under vacuum to give the desired triazole (4.29g, 91%); δ (250MHz, D_4-MeOH, D_6-DMSO) 2.14 (3H, s, CH_3), 7.60 (2H, d, J = 8.8Hz, Ar-H), 7.78 (2H, d, J = 8.8Hz, Ar-H), 8.96 (2H, s, Ar-H).

c) 4'-(1,2,4-Triazol-4-yl)phenylaniline

A solution of the preceding acetanilide (4.91g, 24.3mmol) in 5N HCl (100ml) was heated at 125°C for 1.5h. The mixture was cooled to 0°C, basified with conc. aqueous NaOH solution and extracted with CH_2Cl_2 (x 5). The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on silica-gel eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give the title-aniline (2.94g, 76%); δ (250MHz, $CDCl_3$) 3.80 (2H, s, NH_2), 6.71 (2H, d, J = 8.8Hz, Ar-H), 7.08 (2H, d, J = 8.8Hz, Ar-H), 8.36 (2H, s, Ar-H).

d) 4'-(1,2,4-Triazol-4-yl)phenylhydrazine

Prepared from the preceding aniline using the procedure described for Example 1, Intermediate 2; δ (250MHz, $CDCl_3$) 3.51 (3H, br s, $NHNH_2$), 6.96 (2H, d, J = 8.8Hz, Ar-H), 7.23 (2H, d, J = 8.8Hz, Ar-H), 8.44 (2H, s, Ar-H).

N-Methyl-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]azetidine. 1.75 Benzoate. 0.8 Hydrate

Prepared from the preceding hydrazine and N-tert-butyloxycarbonyl-3-formylazetidine using the procedures described for Examples 1 and 2. The 1.75 benzoate 0.8 hydrate salt was prepared, mp ≈ 30°C (hygroscopic); (Found: C, 65.66; H, 5.97; N, 14.53. $C_{14}H_{15}N_5.1.75\ C_6H_5CO_2H.\ 0.8H_2O$ requires C, 65.49; H, 5.67; N, 14.55%); m/e 254 $(M+1)^+$; δ (360MHz, D_2O) 2.98 and 3.07 (total 3H, each s, N-CH_3), 4.16-4.22, 4.35-4.56 and 4.72-4.77 (total 5H, each m, CH and 2 of CH_2 of azetidine), 7.28-7.34, 7.43-7.64 and 7.88-7.90 (total 12H, each m, Ar-H and benzoic acid), 8.78 (2H, s, Ar-H).

EXAMPLE 8

N-Methyl-3-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. 1.5 Benzoate. 0.7 Hydrate

Prepared from N-tert-butyloxycarbonyl-3-formyl azetidine and 4-(imidazol-1-ylmethyl)nitrobenzene using the procedures described for Example 1. The 1.5 benzoate 0.7 hydrate salt was prepared, mp ≈ 45°C (hygroscopic); (Found: C, 69.07; H, 6.64; N, 11.97. $C_{16}H_{18}N_4.1.5C_6H_5CO_2H.0.7H_2O$ requires C, 68.87; H, 6.19; N, 12.12%); m/e 267 $(M+1)^+$; δ (360MHz, D_6-DMSO) 2.39 (3H, s, N-CH_3), 3.28-3.82 (5H, m, CH and 2 of CH_2 of azetidine), 5.20 (2H, s, CH_2), 6.86 (1H, s, Ar-H), 7.01 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.16 (1H, s, Ar-H), 7.29 (1H, s, Ar-H), 7.31 (1H, d, J = 8.4Hz, Ar-H), 7.45-7.60 (6H, m, Ar-H), 7.73 (1H, s, Ar-H), 7.92-7.95 (3H, m, Ar-H), 10.96 (1H, s, NH).

EXAMPLE 9

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

N-Methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Bisoxalate

N-Methyl-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine. Oxalate

N-Methyl-3-[5-imidazol-1-yl-1H-indol-3-yl]azetidine. Hemioxalate. Monohydrate

N-Methyl-3-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine. Succinate. Monohydrate

N-Methyl-3-[5-(2-(1-methyltetrazol-5-yl)ethyl)-1H-indol-3-yl]azetidine. Benzoate

N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]azetidine. Hemioxalate

N-Methyl-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]azetidine. 1.75 Benzoate. 0.8 Hydrate

N-Methyl-3-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]azetidine. 1.5 Benzoate. 0.7 Hydrate

TABLE FOR DOSES CONTAINING FROM 1-25MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

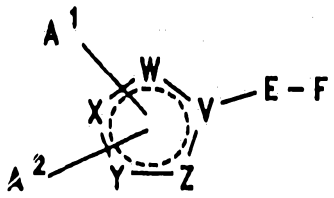
TABLE FOR DOSES CONTAINING FROM 26-100MG OF THE ACTIVE COMPOUND

	Amount-mg		
Active Compound	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein the broken circle represents two non-adjacent double bonds in any position in the five-membered ring;

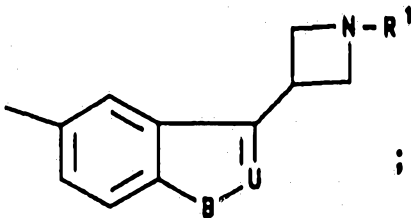
two, three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon provided that, when two of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, then the said nitrogen atoms are in non-adjacent positions within the five-membered ring;

A^1 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

A^2 represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when two or three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A^2 represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, $-OR^x$, $-SR^x$, $-NR^xR^y$, $-NR^xCOR^y$, $-NR^xCO_2R^y$, $-NR^xSO_2R^y$, or $-NR^zCTNR^xR^y$;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



;

U represents nitrogen or C-R^2;

B represents oxygen, sulphur or N-R^3;

R^1, R^2 and R^3 independently represent hydrogen or C_{1-6} alkyl;

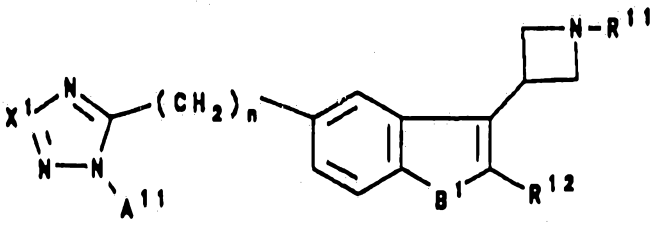
R^X and R^Y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^X and R^Y together represent a C_{2-6} alkylene group;

R^Z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula =N.G; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

X^1 represents nitrogen or A^{12}-C;

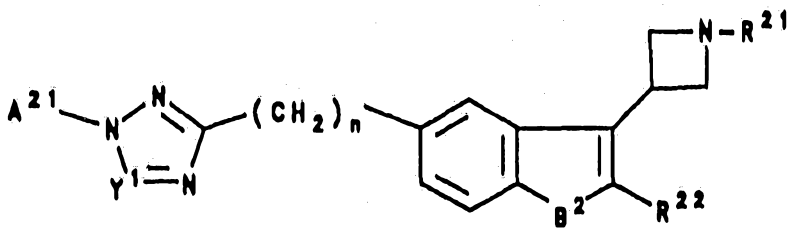
n is zero, 1, 2 or 3;

B^1 represents oxygen, sulphur or N-R^{13};

A^{11} and A^{12} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{11}, R^{12} and R^{13} independently represent hydrogen or C_{1-6} alkyl.

3. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

Y^1 represents nitrogen or A^{22}-C;

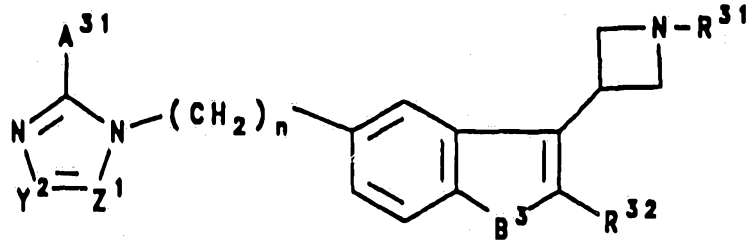
n is zero, 1, 2 or 3;

B^2 represents oxygen, sulphur or N-R^{23};

A^{21} and A^{22} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{21}, R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl.

4. A compound as claimed in claim 1 represented by formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

Y^2 represents nitrogen or A^{32}-C;

Z^1 represents nitrogen or CH;

n is zero, 1, 2 or 3;

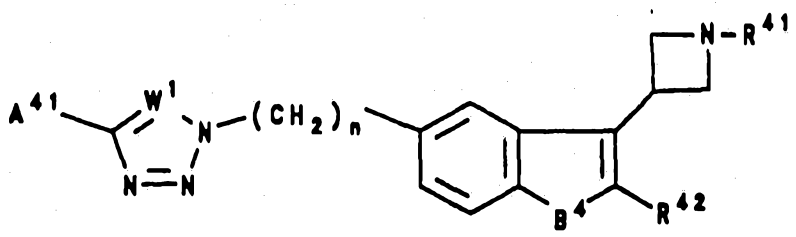
B^3 represents oxygen, sulphur or N-R^{33};

A^{31} and A^{32} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl,

heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{31}, R^{32} and R^{33} independently represent hydrogen or C_{1-6} alkyl.

5. A compound as claimed in claim 1 represented by formula IID, and salts and prodrugs thereof:



(IID)

wherein

W^1 represents nitrogen or C-A^{42};

n is zero, 1, 2 or 3;

B^4 represents oxygen, sulphur or N-R^{43};

A^{41} and A^{42} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R^{41}, R^{42} and R^{43} independently represent hydrogen or C_{1-6} alkyl.

6. A compound as claimed in claim 1 selected from:
N-methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(imidazol-1-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(2-(1-methyltetrazol-5-yl)ethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]azetidine;
N-methyl-3-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]azetidine;
and salts and prodrugs thereof.

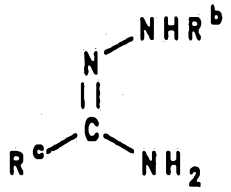
7. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.

8. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated.

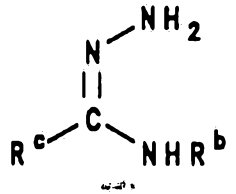
AUSTRALIAN PATENT OFFICE ML

9. A process for the preparation of a compound as claimed in any one of claims 1 to 6 which comprises:

(A) reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with a compound either of formula III or of formula IV, or a salt thereof:



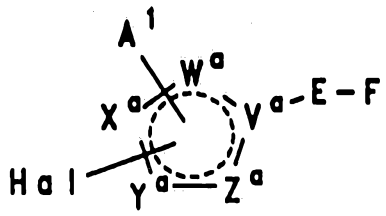
(III)



(IV)

wherein one of R^a, R^b and R^c is a group of formula A^1, another is a group of formula A^2, and the third is a group of formula -E-F, as defined in claim 1; or

(B) reacting a compound of formula XIV:



(XIV)

wherein A^1, E and F are as defined in claim 1, Hal represents halogen, and two of V^a, W^a, X^a, Y^a and Z^a, to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent

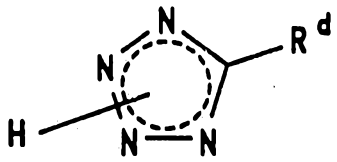
AUSTRALIAN PATENT OFFICE ML

which provides an anion $^{-}A^{2}$, where A^{2} is as defined in claim 1; or

(C) the cycloaddition of an alkyne of formula $R^{a}-C\equiv C-R^{b}$ with an azide of formula $R^{c}-N_{3}$, where R^{a}, R^{b} and R^{c} are as defined above; or

(D) the cycloaddition of a nitrile of formula $N\equiv C-R^{d}$ with an azide of formula $R^{e}-N_{3}$, where one of R^{d} and R^{e} represents a group of formula A^{1} and the other is a group of formula -E-F, as defined in claim 1; or

(E) reacting a compound of formula $R^{e}-L$ with a tetrazole derivative of formula XV:

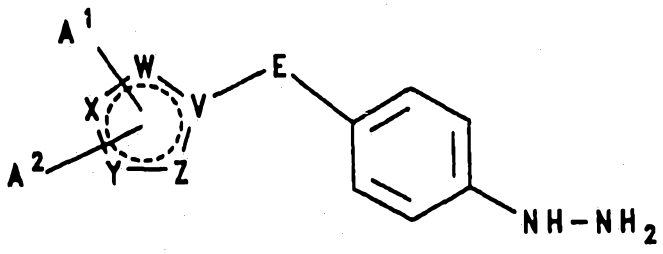


(XV)

wherein one of R^{d} and R^{e} represents a group of formula A^{1} and the other is a group of formula -E-F, as defined in claim 1, and L represents a leaving group; in the presence of a base; or

(F) the cycloaddition of a nitrile of formula $N\equiv C-E-F$, in which E and F are as defined in claim 1, with sodium azide, followed by acidification with a mineral acid; or

(G) reacting a compound of formula XVI:



(XVI)

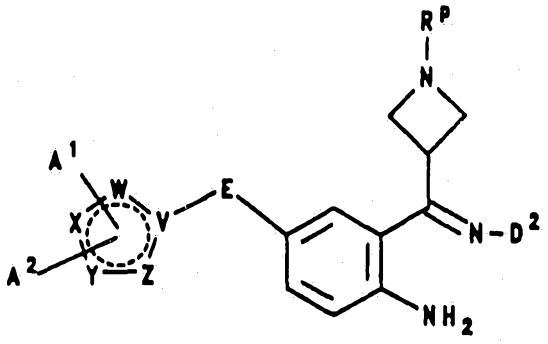
wherein V, W, X, Y, Z, A^1, A^2 and E are as defined in claim 1; with a compound of formula VII or a carbonyl-protected form thereof:



(VII)

wherein R^2 is as defined claim 1 and R^P represents an amino-protecting group; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3; or

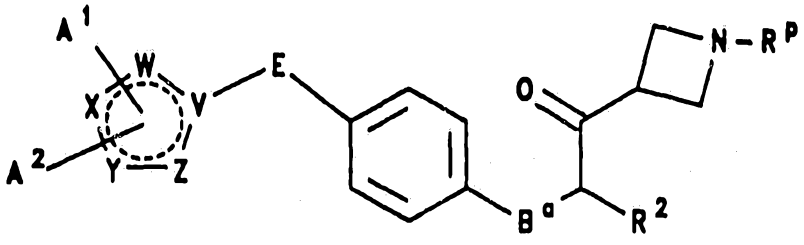
(H) cyclising a compound of formula XXV:



(XXV)

wherein V, W, X, Y, Z, A^1, A^2 and E are as defined in claim 1, R^P is as defined above, and D^2 represents a readily displaceable group; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moieties R^1 and/or R^3; or

(J) cyclising a compound of formula XXVIII:



(XXVIII)

wherein V, W, X, Y, Z, A^1, A^2, E and R^2 are as defined in claim 1, R^P is as defined above, and B^a represents oxygen or sulphur; followed by removal of the protecting group R^P; and subsequently, where required, N-alkylation by standard methods to introduce the moiety R^1; and

(K) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

10. A process for the preparation of an imidazole, triazole or tetrazole derivative of claim 1, substantially as hereinbefore described with reference to any one of the Examples.

11. An imidazole, triazole or tetrazole derivative whenever produced by the process of claim 9 or claim 10.

12. An imidazole, triazole or tetrazole derivative of claim 1 and substantially as hereinbefore described with reference to any one of the Examples.

13. A method for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT_1-like receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in any one of claims 1 to 6, 11 or 12 or a pharmaceutically acceptable salt thereof or a prodrug thereof or of a composition of claim 7.

Dated 22 March, 1996
Merck Sharp & Dohme Limited

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

AUSTRALIAN PATENT OFFICE ML

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00474

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D403/14; A61K31/41

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
Y	WO,A,9 118 897 (THE WELLCOME FOUNDATION LTD.) 12 December 1991 cited in the application see claims	1-11
Y	EP,A,0 313 397 (THE WELLCOME FOUNDATION LTD.) 26 April 1989 cited in the application see claims	1-11
P,Y	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 cited in the application see claims	1-11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 JUNE 1993	- 7. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	CHOULY J.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00474

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

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

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

Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

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

./.

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

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

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

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

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

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

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

Claims searched incompletely: 1 - 10

Lack of conciseness

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

V,W,X,Y,Z,E,F,U,B,A1,A2

The number of theoretically conceivable compounds resultung from the combination of all claimed substituents of above list precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the examples.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300474
SA 71569

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 15/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9118897	12-12-91	AU-A- 7957091	31-12-91
		EP-A- 0486666	27-05-92
EP-A-0313397	26-04-89	AU-A- 2418188	27-04-89
		JP-A- 1146882	08-06-89
EP-A-0497512	05-08-92	AU-A- 1068092	06-08-92
		CN-A- 1064485	16-09-92