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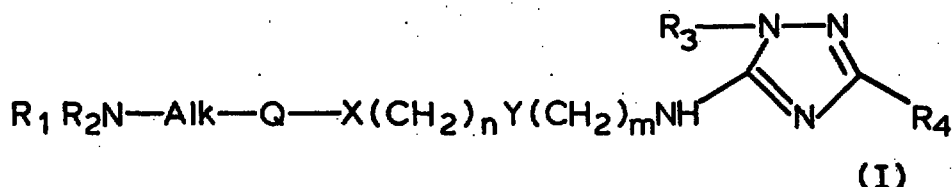
Heterocyclic Derivatives

This invention relates to novel heterocyclic derivatives having action on histamine receptors, to processes for the preparation thereof, to pharmaceutical compositions containing them and to their use in therapeutics.

Certain novel heterocyclic derivatives have now been found which have potent activity as H_2 -antagonists. These compounds, which are more particularly described below, for example show inhibition of the secretion of gastric acid when this is stimulated via histamine receptors (Ash and Schild, Brit. J. Pharmacol. Chemother, 1966, 27, 427). Their ability to do so can be demonstrated in the perfused rat stomach using the method described in German Offenlegungsschrift No. 2,734,070, modified by the use of sodium pentobarbitone (50 mg/kg) as anaesthetic instead of urethane, and in conscious dogs equipped with Heidenhain pouches using the method described by Black et al, Nature 1972 236, 385. Furthermore the compounds antagonise the effect of histamine on the contraction frequency of isolated guinea pig right atrium but do not modify histamine induced contractions of isolated gastrointestinal smooth muscle which are mediated via H_1 -receptors.

Compounds with histamine H_2 -blocking activity may be used in the treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration, as a prophylactic measure in surgical procedures, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator. Thus they may be used for example, either alone or in combination with other active ingredients in the treatment of allergic and inflammatory conditions of the skin.

The present invention provides compounds of the general formula (I).



and physiologically acceptable salts, hydrates and bioprecursors thereof, in which

R_1 represents hydrogen, C_{1-14} alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, trifluoroalkyl or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or C_{1-4} alkyl; or R_1 and R_2 may together with the nitrogen atom to which they are attached form a 5 to 10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl e.g. methyl, groups or a hydroxy group and/or may contain another heteroatom e.g. oxygen or sulphur.

Alk represents a straight or branched alkylene chain of 1 to 6 carbon atoms,

Q represents a furan or thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 5- positions, the furan or thiophen ring optionally bearing a further substituent R_5 adjacent to the group $R_1 R_2 N - Alk -$; or Q represents a thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 4-positions, the thiophen ring optionally bearing a further substituent R_5 adjacent to the group $R_1 R_2 N - Alk$ with the proviso that when the group $R_1 R_2 N - Alk$ is in the 4- position then the group R_5 is in the 5- position; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4-positions;

R_5 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

X represents oxygen, sulphur, $-NH-$, methylene or a bond;

Y represents oxygen, sulphur, methylene or a bond;

n represents zero, 1, 2 or 3, and m is an integer from 2 to 5, with the provisos that (a) the total number of atoms in the chain $X(CH_2)_n Y(CH_2)_m$ is an integer from 3 to 8, (b) when X and Y represent oxygen or sulphur then n is 2 or 3, and (c) when X represents $-NH-$ then Q is a benzene ring and Y represents methylene or a bond;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, or C_{2-8} alkyl substituted by hydroxy or alkoxy;

R_4 represents the group $(CH_2)_p CH = CHR_6$ or $(CH_2)_q R_7$ where p is zero, 1, or 2 and q is zero, 1, 2, 3, 4, 5 or 6 and the alkylene chain $(CH_2)_q$ may be straight or branched, and

R_6 is hydroxymethyl, 1H-tetrazol-5-yl, cyano, or the group $CH_2 NHCOR_{17}$ or $CH_2 NHSO_2 R_{17}$ where R_{17} is alkyl; or the group COR_{18} where R_{18} is hydrogen, hydroxyl, alkyl, alkoxy, amino, alkylamino or dialkylamino; or the group $CR_{19}^a = NR_{20}$ where R_{19}^a is hydrogen or alkyl and R_{20} is hydroxy, alkoxy, aralkyloxy or $-NHC(=A)NH_2$ where A is oxygen or sulphur;

R_7 is nitro, cyano, halomethyl, heteroaryl, arylaminomethyl, aralkylaminomethyl, alkylthioalkyl, arylthioalkyl, 1H-tetrazol-5-yl, aryl $CH = NCH_2 -$ or $CH_2 NHC(=B)NHR_{17}$ where B is NCN, NSO_2 Methyl, NSO_2 Phenyl or $CHNO_2$;

or R_7 is the group $SO_2 R_9$ in which R_9 is hydroxy, alkyl, aryl or the group $NR_9 R_{10}$ where R_9 and R_{10} are the same or different and represent hydrogen, alkyl, aryl or aralkyl;

or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy, alkoxy, aryloxy, aralkyloxy, alkyl, aryl, aralkyl or the group $\text{NR}_{12}\text{R}_{13}$ where R_{12} is hydrogen or alkyl optionally substituted by a hydroxy or alkoxy group, and R_{13} is hydrogen, alkyl (optionally substituted by a hydroxy or alkoxy group), alkenyl, aryl, aralkyl or cycloalkyl, or $\text{NR}_{12}\text{R}_{13}$ forms a 5 to 8 membered ring which may contain another heteroatom e.g. oxygen, or a double bond and/or may be substituted by hydroxy or one or two C_{1-3} alkyl (e.g. methyl) groups; or R_7 is the group $\text{CR}^a_{11}=\text{NR}_{20}$ where R^a_{11} is hydrogen, alkyl, aryl or aralkyl and R_{20} is as defined above;

or R_7 is the group $\text{CH}_2\text{NR}_{18}\text{SO}_2\text{R}_{14}$ where R_{14} is alkyl or aryl and R_{18} is hydrogen or alkyl;

or R_7 is the group $\text{CH}_2\text{NR}_{18}\text{COR}_{15}$ where R_{15} is hydrogen, alkyl, aryl, aralkyl, alkoxy, halomethyl, or the group NHR_{18} where R_{18} is hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

with the proviso that when the group R_7 contains a carbon atom through which it is linked to the alkylene group $(\text{CH}_2)_q$ then the total number of carbon atoms in the resulting chain is not greater than 6 (i.e. q is not greater than 5).

The term "alkyl" as a group or a part of a group means that the group is straight or branched and, unless otherwise stated, has preferably 1 to 6 carbon atoms, and in particular 1 to 4 carbon atoms, e.g. methyl or ethyl, and the terms "alkenyl" and "alkynyl" mean that the group has preferably 3 to 6 carbon atoms. The term "cycloalkyl" means that the group has 3 to 8 carbon atoms. The term "halomethyl" means a mono-, di- or trihalo substituted methyl group, e.g. monochloro or trifluoro. The term "aryl" as a group or part of a group preferably means phenyl or substituted phenyl, for example phenyl substituted with one or more C_{1-3} alkyl or alkoxy groups, or halogen atoms e.g. fluorine. The term "heteroaryl" as a group or part of a group means a 5 or 6 membered monocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, e.g. thienyl, pyridyl, furyl or thiazolyl. The heteroaryl ring may be unsubstituted or substituted by C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl or halogen. The alkyl portion of a heteroaralkyl group is a straight or branched C_{1-4} alkyl chain, and the heteroaryl ring is linked to the alkyl portion through either a carbon or nitrogen atom.

In the compounds according to the invention preferably R_1 represents C_{1-12} alkyl (e.g. methyl, ethyl, propyl, butyl, isobutyl, hexyl, heptyl or undecyl), C_{6-7} cycloalkyl (e.g. cyclohexyl), C_{3-5} alkenyl (e.g. allyl or 3,3-dimethylallyl), phenyl C_{1-3} alkyl (e.g. benzyl), C_{1-4} alkyl substituted by a trifluoromethyl, hydroxy, C_{1-3} alkoxy or di- C_{1-3} alkylamino group (e.g. 2,2,2-trifluoroethyl, 3-hydroxy-propyl, methoxyethyl, ethoxyethyl, dimethylaminoethyl, diethylaminoethyl or dimethylaminopropyl) or a heteroaryl C_{1-3} alkyl group where the heteroaryl ring contains one heteroatom (e.g. furylmethyl, pyridylmethyl, thienylmethyl, pyrrolylmethyl, (5-methylfuran-2-yl)methyl or (5-hydroxymethylfuran-2-yl)methyl; and R_2 represents hydrogen, methyl or ethyl; or $\text{R}_1\text{R}_2\text{N}$ represents a 5 to 8 membered ring optionally containing one double bond and/or substituted by one or two C_{1-3} alkyl (e.g. methyl) groups or a hydroxy group (e.g. pyrrolidino, piperidino, hexamethylenimino, tetrahydropyridino, 4-hydroxypiperidino or 4-methylpiperidino).

More preferably $\text{R}_1\text{R}_2\text{N}$ represents C_{1-8} alkylamino (e.g. hexylamino), di- C_{1-2} alkylamino (e.g. dimethylamino), furylmethylamino or a saturated 5—7 membered ring (e.g. piperidino).

R_3 preferably represents hydrogen, C_{1-4} alkyl (e.g. methyl, ethyl, or propyl), or hydroxy C_{2-4} alkyl (e.g. 2-hydroxyethyl); more preferably hydrogen or C_{1-3} alkyl (e.g. methyl).

Within the definition of R_4 , p is preferably zero and R_6 is preferably hydroxymethyl or the group COR_{18} where R_{18} is hydroxy, amino, C_{1-4} alkylamino or di- C_{1-4} alkylamino; more preferably R_6 is hydroxymethyl or COR_{18} where R_{18} is hydroxy.

q is preferably zero, 1, 2 or 3; and R_7 is preferably nitro, cyano, halomethyl (e.g. chloromethyl or trifluoromethyl), heteroaryl (e.g. pyridyl or thienyl), alkylthioalkyl (e.g. methylthiomethyl), 1H-tetrazol-5-yl, $-\text{CH}_2\text{NHC}(=\text{B})\text{NHR}_{17}$ where B is NCN or CHNO_2 and R_{17} is alkyl (e.g. methyl), or the group SO_2R_8 where R_8 is hydroxy, alkyl e.g. (methyl), or aryl (e.g. phenyl); or the group COR_{11} where R_{11} is hydrogen, hydroxy, alkoxy (e.g. ethoxy), alkyl (e.g. methyl) or the group $\text{NR}_{12}\text{R}_{13}$ where R_{12} and/or R_{13} are hydrogen or alkyl (e.g. methyl), or $\text{NR}_{12}\text{R}_{13}$ forms a 5- or 6- membered ring (e.g. pyrrolidino); or the group $\text{CH}=\text{NR}_{20}$ where R_{20} is hydroxy or alkoxy (e.g. methoxy), or R_7 is the group $\text{CH}_2\text{NHSO}_2\text{R}_{14}$ or $\text{CH}_2\text{NHCOR}_{15}$ where R_{14} is alkyl (e.g. methyl), and R_{15} is alkyl (e.g. methyl), aryl (e.g. phenyl), arylamino (e.g. phenylamino) or halomethyl (e.g. trifluoromethyl).

More preferably R_4 represents nitro, alkylthiomethyl (e.g. methylthiomethyl), heteroarylmethyl (e.g. pyridylmethyl), $\text{CH}=\text{NR}_{20}$ where R_{20} is hydroxy; or the group $(\text{CH}_2)_q\text{R}_7$ where q is zero, 1 or 2, and R_7 is the group $\text{CH}_2\text{NHC}(=\text{B})\text{NHR}_{17}$ where B is NCN or CHNO_2 and R_{17} is alkyl (e.g. methyl); or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy or $\text{NR}_{12}\text{R}_{13}$ where R_{12} and/or R_{13} are hydrogen or alkyl (e.g. methyl), or $\text{NR}_{12}\text{R}_{13}$ forms a 5- or 6- membered ring (e.g. pyrrolidino); or R_7 is the group SO_2R_8 where R_8 is alkyl (e.g. methyl) or aryl (e.g. phenyl); or R_7 is the group $\text{CH}_2\text{NHSO}_2\text{R}_{14}$ or $\text{CH}_2\text{NHCOR}_{15}$ where R_{14} is alkyl (e.g. methyl), and R_{15} is alkyl (e.g. methyl), aryl (e.g. Phenyl) or NHR_{18} where R_{18} is aryl (e.g. phenyl).

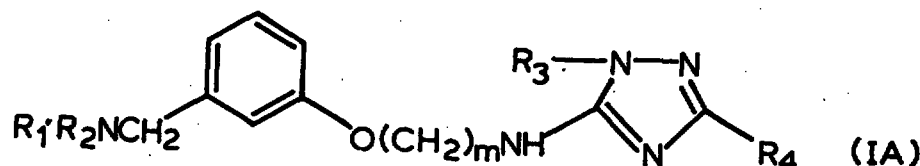
When Q represents a thiophen ring containing a further substituent R_9 , R_9 is preferably bromine, C_{1-3} alkyl (e.g. methyl, ethyl or isopropyl), C_{1-3} alkoxy C_{1-3} alkyl (e.g. methoxymethyl), or hydroxy C_{1-3} alkyl (e.g. hydroxymethyl); more preferably methyl.

The group Alk preferably contains 1—4 carbon atoms and may be for example a methylene,

ethylene or propylene group. More preferably Alk represents methylene.

- The chain $X(CH_2)_nY(CH_2)_m$ preferably contains from 4 to 6 atoms. More particularly when Q is benzene the group $X(CH_2)_nY(CH_2)_m$ preferably represents $-O(CH_2)_{3-5}-$ or $-O(CH_2)_2O(CH_2)_2-$, more preferably $-O(CH_2)_{3-4}-$. When Q is an optionally substituted furan or thiophene ring the group $X(CH_2)_nY(CH_2)_m$ is preferably $-CH_2S(CH_2)_2-$, $-CH_2O(CH_2)_3-$ or $(CH_2)_4-$, more preferably $-CH_2S(CH_2)_2-$. Most preferably Q is a benzene ring incorporated into the rest of the molecule through bonds at the 1- and 3-positions.

A preferred group of compounds are those of the formula (IA)



- where R_1R_2N is pyrrolidino, piperidino or hexamethylenimino (preferably piperidino); m is 3 or 4; R_3 is hydrogen or methyl; and R_4 is the group $(CH_2)_qR_7$, where q is zero, 1 or 2, and R_7 is methylthiomethyl, $CH_2NHC(=B)NHCH_3$ (where B is NCN or $CHNO_2$), SO_2Me , $CH=NOH$; or the group COR_{11} , where R_{11} is hydroxy, amino, dimethylamino or pyrrolidino; or the group CH_2NHSO_2Me ; or the group CH_2NHCOR_{18} , where R_{18} is methyl or phenyl. Within this group of compounds, when q is zero, R_{11} is preferably other than amino.

Particularly preferred compounds are:

- N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]methane-sulphonamide.
 1-Methyl-3-methylsulphonylmethyl-N-[3-[3-(1-piperidinyl-methyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine.
 N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]acetamide.
 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxamide.
 N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]benzamide.
 5-[4-[3-(1-Piperidinylmethyl)phenoxy]butyl]amino-1H-1,2,4-triazole-3-carboxamide.
 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxylic acid.
 1-Methyl-3-methylthiomethyl-N-[3-[3-(1-piperidinyl-methyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine.
 3-Methylsulphonyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-1H-1,2,4-triazole-5-amine.
 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-acetic acid.
 N-Methyl-N'-[[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]-2-nitro-1,1-ethenediamine.
 N,N,1-Trimethyl-5-[[3-[3-(1-piperidinyl)methyl]phenoxy]propyl]amino-1H-1,2,4-triazole-3-propanamide.
 1-[3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-1-oxopropyl]pyrrolidine.
 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde oxime.
 N-[3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]propyl]methanesulphonamide.
 N-Cyano-N'-methyl-N'-[[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]guanidine and their physiologically acceptable salts.
- According to one aspect the invention provides compounds of formula (I) in which R_1 represents hydrogen, C_{1-10} alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, trifluoroalkyl, or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or C_{1-4} alkyl; or R_1 and R_2 may together with the nitrogen atom to which they are attached form a 5 to 10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl groups or a hydroxy group and/or may contain another heteroatom;

Alk represents a straight or branched alkylene chain of 1 to 6 carbon atoms;

- Q represents a furan or thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 5- positions, the furan ring optionally bearing a further substituent R_8 adjacent to the group R_1R_2N-Alk ; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4-positions;

R_8 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

X represents a bond or, when Q is a benzene ring and Y is methylene or a bond, $-NH-$;

Y represents oxygen, sulphur or methylene;

n represents zero, 1 or 2;

m represents 2, 3 or 4;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, or C_{2-6} alkyl substituted by hydroxy or alkoxy; and

5 R_4 represents the group $(CH_2)_q R_7$, where q is zero, 1, 2, 3, 4, 5 or 6 and the alkylene chain $(CH_2)_q$ may be straight or branched, and

R_7 is nitro, cyano, halomethyl, heteroaryl, arylaminomethyl, aralkylaminomethyl, or Aryl $CH=NCH_2-$;

10 or R_7 is the group $SO_2 R_9$ in which R_9 is alkyl, aryl or the group $NR_9 R_{10}$ where R_9 and R_{10} are the same or different and represent hydrogen, alkyl, aryl or aralkyl;

or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy, alkoxy, aryloxy, aralkyloxy, alkyl, aryl, aralkyl or the group $NR_{12} R_{13}$ where R_{12} is hydrogen or alkyl optionally substituted by a hydroxy or alkoxy group, and R_{13} is hydrogen, alkyl optionally substituted by a hydroxy or alkoxy group, alkenyl, aryl, aralkyl or cycloalkyl, or $NR_{12} R_{13}$ forms a 5 to 8 membered ring which may contain another heteroatom,

15 or a double bond and/or may be substituted by hydroxy or one or two C_{1-3} alkyl groups;

or R_7 is the group $CR^{*}_{11}=NR_{20}$ where R^{*}_{11} is hydrogen, alkyl, aryl or aralkyl, and R_{20} is hydroxy, alkoxy or $-NHC(=A)NH_2$ where A is oxygen or sulphur.

or R_7 is the group $CH_2 NR_{18} SO_2 R_{14}$ where R_{14} is alkyl or aryl and R_{18} is hydrogen or alkyl;

20 or R_7 is the group $CH_2 NR_{18} COR_{15}$ where R_{15} is hydrogen, alkyl, aryl, aralkyl, alkoxy or the group NHR_{16} where R_{16} is hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

With the proviso that when the group R_7 contains a carbon atom through which it is linked to the alkylene group $(CH_2)_q$ then the total number of carbon atoms in the resulting chain is not greater than 6 (i.e. q is not greater than 5). Preferably when q is zero, R_7 does not represent heteroaryl or COR_{11} where R_{11} is alkoxy or $NR_{12} R_{13}$ where R_{12} and R_{13} are both hydrogen.

25 According to a further aspect the invention provides compounds of formula (I) in which R_4 represents $(CH_2)_q R_7$, where R_7 is $-CH_2 NHC(=B)NHR_{17}$.

According to another aspect the invention provides compounds of formula (I) in which R_4 represents $(CH_2)_p CH=CHR_6$ where R_6 and p are as defined above or R_4 represents $(CH_2)_q R_7$, where q is zero, 1, 2, 3, 4, 5 or 6 and the alkylene chain may be straight or branched and R_7 is alkylthioalkyl,

30 arylthioalkyl, 1H-tetrazol-5-yl, or R_7 is the group $SO_2 R_8$ where R_8 is hydroxy, or R_7 is the group $CH_2 NR_{18} COR_{15}$ where R_{18} is halomethyl.

The invention includes the compounds of formula (I) in the form of physiologically acceptable salts with inorganic and organic acids. Particularly useful salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, acetates, maleates, succinates, citrates, tartrates, fumarates and benzoates. The compounds of formula (I) and their salts may also form hydrates, which hydrates are also to be considered as part of the invention. The compounds of formula (I) can exhibit tautomerism and the formula is intended to cover all tautomers. Where optical isomers may exist the formula is intended to cover all diastereoisomers and optical enantiomers. The term bioprecursors as used herein means compounds which have a structure different to that of the compounds of formula (I) but which, upon administration to the animal or human being, are converted in the body into a compound of formula (I).

40 The compounds according to the invention, preferably in the form of a salt, may be formulated for administration in any convenient way and the invention includes within its scope pharmaceutical compositions containing at least one compound according to the invention adapted for use in human or veterinary medicine. Such compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Such compositions may also contain if required other active ingredients e.g. H_1 -antagonists.

Thus the compounds according to the invention may be formulated for oral, buccal, topical, parenteral or rectal administration. Oral administration is preferred.

50 For oral administration, the pharmaceutical composition may take the form of for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients. For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

55 The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be present in unit dosage form in ampoules, or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a soluble vehicle e.g. sterile pyrogen-free water before use.

60 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

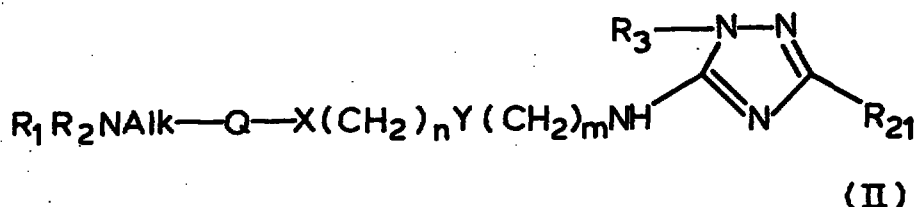
65 For topical application, the compounds of the invention may be formulated as ointments, creams, gels, lotions, powders or sprays in a conventional manner.

For internal administration a convenient daily dosage regime of the compounds according to the invention would be 1 to 4 doses to the total of some 5 mg. to 1 g per day, preferably 5 to 250 mg. per day, dependent upon the condition of the patient.

- 5 It will be appreciated that in the methods for the preparation of compounds of formula (I) given below, for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where R_1 and R_2 in intermediates used to prepare compounds of formula (I) are hydrogen atoms and/or when R_3 in intermediates is an alkyl group bearing a hydroxy substituent and/or when R_4 contains an amino group. Standard protection and deprotection procedures can be employed, for example amines may be protected by formation of a phthalimide group which may subsequently be cleaved by treatment with a hydrazine e.g. hydrazine hydrate or a primary amine, for example methylamine.

- 10 In describing the processes which may be used for preparing the compounds of formula (I) or intermediates useful in the preparation thereof, any of R_1 to R_{20} , A, B, Alk, Q, X, Y, n, m, p and q in the various formulae are as defined in formula (I) unless otherwise stated.

15 Compounds of formula (I) in which R_7 is the group $\text{CH}_2\text{NR}_{18}\text{COR}_{15}$, $\text{CH}_2\text{NR}_{18}\text{SO}_2\text{R}_{14}$, $\text{CH}_2\text{NHC}(=\text{B})\text{NHR}_{17}$ or $-\text{CH}_2\text{N}=\text{CH}$ Aryl, or R_8 is the group $\text{CH}_2\text{NHCOR}_{17}$ or $\text{CH}_2\text{NHSO}_2\text{R}_{17}$ may be prepared by treating an aminoalkyltriazole of formula (II)



- 20 in which R_1 , R_2 and R_3 are as defined in formula (I) or are groups readily convertible thereto, and R_{21} is the group $(\text{CH}_2)_{q+1}\text{NHR}_{18}$ or the group $(\text{CH}_2)_p\text{CH}=\text{CHCH}_2\text{NH}_2$, with a compound capable of replacing the hydrogen atom in the group NHR_{18} by the group COR_{15} , SO_2R_{14} or $\text{C}(=\text{B})\text{NHR}_{17}$, or the hydrogen atom in the group NH_2 by the group COR_{17} or SO_2R_{17} , or both hydrogen atoms in the group NHR_{18} where R_{18} is hydrogen by $=\text{CH}$ Aryl.

- 25 Thus for example the aminoalkyltriazole (II) in which R_{21} is the group $(\text{CH}_2)_{q+1}\text{NHR}_{18}$ may be reacted with an isocyanate $\text{R}'_{18}\text{NCO}$ in which R'_{18} has any of the meanings defined for R_{18} in formula (I) except hydrogen or represents an alkali metal atom such as potassium or sodium, or with an activated derivative of either a carboxylic acid R_{15}COOH (in which R_{15} is other than the group NHR_{18}) or a sulphonic acid $\text{R}_{14}\text{SO}_3\text{H}$ to give a compound of formula (I) in which R_7 is respectively the group $\text{CH}_2\text{NR}_{18}\text{CONHR}_{18}$, $\text{CH}_2\text{NR}_{18}\text{COR}_{15}$ (in which R_{18} is other than NHR_{18}), or $\text{CH}_2\text{NR}_{18}\text{SO}_2\text{R}_{14}$. Similarly an aminoalkyltriazole (II) in which R_{21} is the group $(\text{CH}_2)_p\text{CH}=\text{CHCH}_2\text{NH}_2$ may be treated with an activated derivative of either a carboxylic acid R_{17}COOH or a sulphonic acid $\text{R}_{17}\text{SO}_3\text{H}$ to give a compound of formula (I) in which R_8 is respectively the group $\text{CH}_2\text{NHCOR}_{17}$ or $\text{CH}_2\text{NHSO}_2\text{R}_{17}$.

- 30 Suitable activated derivatives include acid halides e.g. acid chlorides, alkylchloroformates, acid anhydrides including mixed anhydrides (e.g. acetic formic anhydride), esters such as alkyl esters, ortho esters and (1-alkyl-2-pyridinyl) esters, or derivatives formed from a coupling agent such as carbonyldiimidazole or a carbodiimide such as dicyclohexylcarbodiimide.

- 35 The reaction with an acid halide is preferably carried out in the presence of a base e.g. an inorganic base such as sodium hydroxide or an organic base such as triethylamine or pyridine. The reaction with an alkylchloroformate is preferably carried out in the presence of a base, e.g. potassium carbonate or triethylamine, in a solvent such as dimethylformamide. The reaction with an acid anhydride may be carried out in the absence of presence of solvent such as pyridine.

- 40 In the reaction with an isocyanate compounds of formula (I) in which R_{18} is other than hydrogen are conveniently prepared by carrying out the reaction in a solvent such as acetonitrile at temperatures from ambient to reflux. Compounds of formula (I) in which R_{18} is hydrogen may be prepared by heating a salt e.g. hydrochloride of the aminotriazole (II) with an aqueous solution of an appropriate cyanate eg. potassium cyanate.

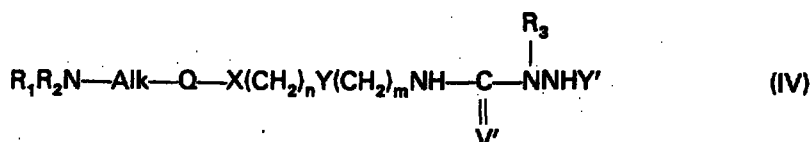
- 45 As a further embodiment of this process an aminoalkyltriazole (II) in which R_{21} is the group $(\text{CH}_2)_{q+1}\text{NHR}_{18}$ where R_{18} is hydrogen may be treated with a compound of formula $\text{LC}(=\text{B})\text{NHR}_{17}$ where L is a leaving group (e.g. methylthio) to give a compound of formula (I) in which R_7 is $\text{CH}_2\text{NHC}(=\text{B})\text{NHR}_{17}$. The reactants may for example be mixed in an aqueous solution at room temperature.

- 50 In yet another embodiment of this process an aminoalkyltriazole (II) in which R_{21} is the group $(\text{CH}_2)_{q+1}\text{NHR}_{18}$ where R_{18} is hydrogen is treated with an appropriate aromatic aldehyde, e.g. benzaldehyde to give a product in which R_7 is $\text{CH}_2\text{N}=\text{CH}$ Aryl.

55 Aminoalkyltriazoles of formula (II) may be prepared by method described in or analogous to those described in British Patent Specification No. 2047238A.

In an alternative method for preparing compounds of formula (I) in which R_7 is the group $\text{CH}_2\text{NHC}(=\text{B})\text{NHR}_{17}$, a diamine of formula (II) in which R_{21} is the group $(\text{CH}_2)_{q+1}\text{NH}_2$ may be treated with a compound of formula $\text{LC}(=\text{B})\text{L}$ in which L is a leaving group (e.g. methylthio), followed by reaction with an appropriate alkylamine R_1NH_2 . The diamine (II) in which R_{21} is the group $(\text{CH}_2)_{q+1}\text{NH}_2$ may be treated with the compound of formula $\text{LC}(=\text{B})\text{L}$ in a suitable solvent (e.g. diethyl ether) optionally with heating and the reaction with the amine R_1NH_2 may be carried out in a solvent such as ethanol again optionally with heating.

Compounds of formula (I) in which R_4 is other than nitro, cyano, mono- or dihaloalkyl, 1H-tetrazol-5-yl, the group SO_2R_8 , the group COR_{11} where R_{11} is hydrogen, alkyl, aryl or aralkyl, or the group $\text{CR}_{11}^a=\text{NR}_{20}$ may be prepared by cyclisation of a compound of formula (IV)



in which V' is



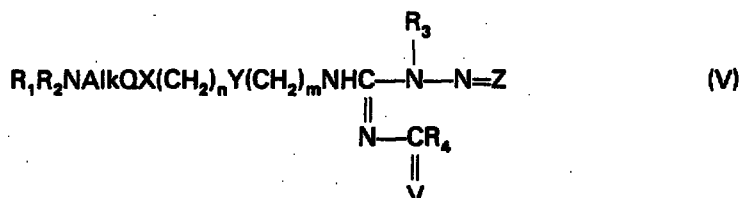
and Y' is hydrogen where V is oxygen or sulphur and R'_4 is a group as defined for R_4 above or a group convertible thereto under the conditions of the cyclisation reaction or V' is NH and Y' is



where Y'' is sulphur, oxygen or NH; or V' is sulphur or oxygen and Y' is



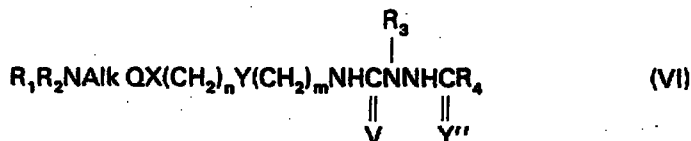
Thus for example compounds according to formula (I) may be prepared by cyclisation of a compound of formula (V)



where V represents sulphur or more preferably oxygen and Z represents two hydrogen atoms, in the absence or presence of a solvent, e.g. acetone or water, and optionally with heating.

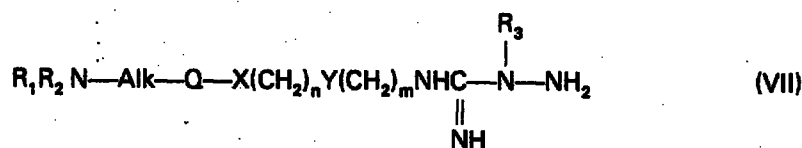
It may be convenient to prepare *in situ* compounds of formula (V) in which Z represents two hydrogen atoms by treating a compound of formula (V) where Z represents a divalent protecting group which can readily be removed to yield two hydrogen atoms, for example a benzylidene group, with an acid, e.g. hydrochloric acid, preferably with heating and under such conditions cyclisation to give compounds of formula (I) will normally occur.

In a further embodiment of the cyclisation of compounds of formula (IV) compounds of formula (I) may also be prepared by cyclisation of a compound of formula (VI)



where V is NH and Y'' is sulphur, oxygen or NH, or V is sulphur or oxygen and Y'' is NH. The reaction is preferably carried out by heating the compound (VI) in a suitable solvent such as acetonitrile or dimethylformamide.

In a convenient embodiment of this process an intermediate of formula (VI) in which V is NH and Y'' is oxygen may be prepared *in situ* by the reaction of an aminoguanidine (VII)



with an acid R_4COOH or with an activated derivative thereof as defined above.

The acid and the aminoguanidine (VII) may be heated together, under which conditions cyclisation of the intermediate (VI) takes place directly to give a compound of formula (I). In the case of an activated derivative an aprotic solvent, e.g. tetrahydrofuran may be used at temperatures from ambient to reflux. When using an acyl chloride as the activated derivative the reaction may also be carried out in the presence of a base e.g. a tertiary amine such as pyridine, which may also be used as the solvent.

In general intermediates of formulae (V) and (VI) may be prepared from diamines of the formula

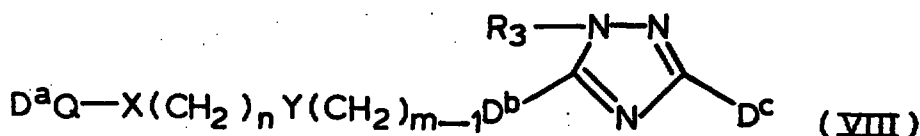


by methods analogous to those described in British Patent Specifications Nos. 2047238A and 2023133A respectively.

The aminoguanidines (VII) may be prepared as described in British Patent Specification No.

2023133A.

Compounds of formula (I) may be prepared by reducing a compound of formula (VIII)



in which at least one of D^a , D^b and D^c represents a reducible group and the other(s) take the appropriate meaning corresponding to formula (I), where

D^a may represent R_1R_2NAlk or a group convertible thereto under reducing conditions;

D^b represents $-CH_2NH-$, $-CONH-$ or $-CH=N-$; and

D^c represents R_4 or a group convertible thereto under reducing conditions.

Thus for example compounds of formula (I) in which R_4 is hydroxymethyl or 1H-tetrazol-5-yl, and R_7 is 1H-tetrazol-5-yl, trifluoromethyl, heteroaryl, arylaminomethyl, alkylaminomethyl, alkylthioalkyl, arylthioalkyl or the group SO_2R_8 or $CH_2NR_8SO_2R_{14}$ may be prepared by reducing an amide of formula (VIII) in which either D^a represents R_1R_2NAlk and D^b represents $-CONH-$, or D^a represents R_1R_2NCO and D^b represents $-CH_2NH-$, and D^c represents R_4 or a group convertible thereto under the conditions of the reaction. Reduction may be effected using for example lithium aluminium hydride or aluminium hydride in a solvent such as tetrahydrofuran, dioxan or diethyl ether.

In another embodiment of the reduction process an imine of formula (VIII) in which D^a represents R_1R_2NAlk , D^b represents $-CH=N-$ and D^c represents R_4 or a group convertible thereto under the conditions of the reaction may be reduced using for example a metal hydride such as an alkali or alkaline earth metal borohydride e.g. sodium borohydride in a solvent such as an alkanol e.g. methanol or ethanol, or aluminium hydride or lithium aluminium hydride in a solvent such as tetrahydrofuran or dioxan. Reduction of the imine (VIII) may also be effected using hydrogen and a suitable metal catalyst such as platinum, palladium or Raney nickel, in a solvent such as an alkanol e.g. methanol or ethanol.

In a further embodiment of the reduction process a compound of formula (I) in which R_4 is the group $(CH_2)_pCH=CHR_8$ where R_8 represents hydroxymethyl may be prepared by reduction of an ester of formula (VIII) in which D^a represents R_1R_2NAlk , D^b represents $-CH_2NH-$ and D^c represents $(CH_2)_pCH=CHCOR_{19}$ where R_{19} represents alkoxy. Reduction may be effected using for example lithium aluminium hydride or sodium bis (2-methoxyethyl)-aluminium hydride.

In yet another embodiment of the reduction process a compound of formula (I) in which Alk is methylene may be prepared by treating an aldehyde of formula (VIII) in which D^a represents CHO , D^b represents $-CH_2NH-$ and D^c represents R_4 with ammonia or an amine R_1R_2NH in a solvent such as tetrahydrofuran or an alkanol e.g. methanol or ethanol, followed by reduction using for example a hydride reducing agent such as an alkali or alkaline earth metal borohydride e.g. sodium borohydride, or aluminium hydride or lithium aluminium hydride, or with hydrogen and a metal catalyst such as palladium or platinum.

In the above embodiments it will be appreciated that in a process involving reductive alkylation of a compound of formula (VIII) in which D^a represents CHO , or reduction of an imine (VIII) in which D^b represents $-CH=N-$, the choice of reducing agent depends upon the nature of the group R_4 , and the process may not be used for preparing compounds in which R_4 is COR_{19} where R_{19} represents hydrogen

or alkyl, or where R_7 is $-\text{CH}_2\text{N}=\text{CHAr}_1$ or COR_{11} , where R_{11} represents hydrogen, alkyl, aryl or aralkyl.

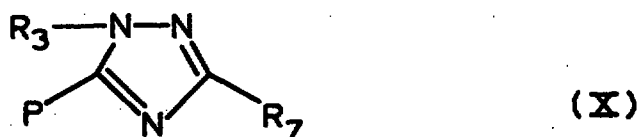
Amides and imines of formula (VIII) where D^b is $-\text{CONH}-$ or $-\text{CH}=\text{N}-$, D^a is $\text{R}_1\text{R}_2\text{NAlk}$ or $\text{R}_1\text{R}_2\text{NCO}$ and D^c is R_4 or a group convertible thereto may be prepared by methods analogous to those described in British Patent Specification No. 2047238A.

- 5 The compounds of formula (VIII) in which D^a represents CHO , D^b represents $-\text{CH}_2\text{NH}$ and D^c represents R_4 or a group convertible thereto may be prepared from an amine of formula (IX) 5



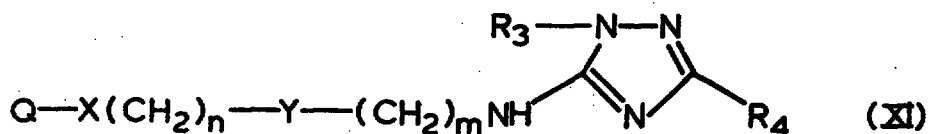
- 10 in which W represents a protected aldehyde group e.g. a cyclic acetal such as an ethylene acetal, by methods analogous to those described herein for preparing the corresponding compounds of formula (I). 10

Compounds of formula (I) in which q is zero and R_7 is an activating group such as nitro may be prepared by heating a diamine of formula (III) with a triazole of formula (X)



- 15 in which P is leaving group such as halogen e.g. bromine, and R_7 is as defined above, in the absence or presence of a solvent such as acetonitrile. 15

- Compounds of formula (I) may also be prepared by introducing the group $\text{R}_1\text{R}_2\text{NCH}_2-$ into the group Q present in a suitable intermediate. Thus compounds of formula (I) in which Alk represents a methylene group, Q represents a furan or substituted furan ring as defined in formula (I), and R_4 does not contain the group $\text{CH}_2\text{NHC}(=\text{CHNO}_2)\text{NHR}_{17}$, $\text{CH}_2\text{N}=\text{CHAr}_1$, COR_{11} (where R_{11} is hydrogen, alkyl, aryl or aralkyl), or COR_{18} (where R_{18} is hydrogen or alkyl) may be prepared from a corresponding compound of formula (XI) 20



- by a Mannich reaction using for example formaldehyde and an amine $\text{R}_1\text{R}_2\text{NH}$ or a salt thereof. The reaction may be carried out by reacting the amine salt with aqueous formaldehyde and the compound (XI) or by refluxing the amine salt with paraformaldehyde and the compound (XI) in a suitable solvent such as ethanol. 25

- Compounds of formula (I) in which R_4 is the group $(\text{CH}_2)_q\text{R}_7$ in which R_7 is COR_{11} , where R_{11} is hydrogen, hydroxy, alkyl, aryl or aralkyl, or SO_2R_8 may be prepared by oxidation of the corresponding compound in which R_4 is the group $(\text{CH}_2)_q\text{CHR}_{11}\text{OH}$, $(\text{CH}_2)_q\text{CHO}$, $(\text{CH}_2)_q\text{SR}_8$ (where R_8 is other than hydroxy) or $(\text{CH}_2)_q\text{SH}$. 30

Thus aldehydes and ketones of formula (I) in which R_4 is the group $(\text{CH}_2)_q\text{COR}_{11}$, where R_{11} is hydrogen, alkyl, aryl or aralkyl may be prepared by oxidising the corresponding hydroxyalkyl compound in which R_4 is $(\text{CH}_2)_q\text{CHR}_{11}\text{OH}$ using for example oxalyl chloride and dimethylsulphoxide, or activated manganese dioxide in a solvent such as dichloromethane.

- Carboxylic acids of formula (I) in which R_4 is the group $(\text{CH}_2)_q\text{CO}_2\text{H}$ may be prepared by oxidising the corresponding aldehyde with e.g. silver oxide, in a solvent such as methanol. 35

- Compounds of formula (I) in which R_4 is the group $(\text{CH}_2)_q\text{SO}_2\text{R}_8$ may be prepared by oxidising the corresponding compound in which R_4 is either $-(\text{CH}_2)_q\text{SR}_8$ (where R_8 is other than hydroxy) or $(\text{CH}_2)_q\text{SH}$ with for example peracetic acid or nitric acid. The reaction may be carried out in a solvent such as acetic acid, at room temperature. 40

The starting material in which R_4 is $(\text{CH}_2)_q\text{SH}$ where q is other than zero may be obtained by alkaline hydrolysis of the corresponding isothioureia, which may in turn be prepared by alkylating thioureia with an appropriate compound of formula (I) in which R_7 is a leaving group e.g. halo.

- The thiol starting material in which R_4 is SH may be prepared by diazotisation of the corresponding aminotriazole followed by treatment with an alkali metal (e.g. potassium) salt of ethyl xanthate to give a xanthate in which R_4 is the group $-\text{SC}(=\text{S})\text{OEt}$, which is subsequently hydrolysed (for example by heating with ethanolic potassium hydroxide) to give the starting thiol in which R_4 is the group SH . 45

- The above oxidation process is particularly applicable to the preparation of compounds of formula (I) in which Q is a benzene or furan ring, X and Y are each oxygen, methylene or a bond, and there is no unsaturation within the groups R_1 , R_2 , R_3 and R_4 . 50

Compounds of formula (I) in which R_8 is $\text{CR}^a_{19}=\text{NR}_{20}$ or R_7 is $\text{CR}^a_{11}=\text{NR}_{20}$ may be prepared by

reacting the corresponding carbonyl compound with an appropriate reagent H_2NR_{20} in a suitable solvent such as ethanol, optionally with heating.

Compounds of formula (I) in which R_4 is the group $CH=CHCOR_{19}$ where R_{19} is alkyl or alkoxy may be prepared by treating the corresponding aldehyde in which R_4 is CHO with an appropriate compound containing an activated methylene group, for example by heating with a compound of formula $R_{19}COCH_2CO_2R_{22}$ (in which R_{19} is alkyl or alkoxy and R_{22} is alkyl e.g. ethyl) in a solvent such as pyridine or piperidine to give an intermediate of formula (I) in which R_4 is the group $CH=C(COR_{19})CO_2R_{20}$. Subsequent hydrolysis and decarboxylation for example by heating with methanolic potassium hydroxide, affords a product of formula (I) in which R_4 is $CH=CHCOR_{19}$ where R_{19} is alkyl or alkoxy.

In a modification of the above process a compound of formula (I) in which R_4 is the group $CH=CHCOR_{19}$ where R_{19} is hydroxy may be prepared by heating an aldehyde of formula (I) in which R_4 is CHO with malonic acid in a solvent such as pyridine or piperidine.

Compounds of formula (I) in which R_4 is the group $(CH_2)_pCH=CHCOR_{19}$ where R_{19} is amino, alkylamino or dialkylamino, or R_4 is the group $(CH_2)_qR_7$ where R_7 is $SO_2NR_9R_{10}$ or $CONH_{12}R_{13}$ may be prepared by reacting an activated derivative of the corresponding carboxylic or sulphonic acid with ammonia or an appropriate amine HNR_9R_{10} or $HNR_{12}R_{13}$. Suitable activated derivatives include those referred to previously e.g. acid chlorides or esters.

Amides and carboxylic acids of formula (I) in which R_7 is respectively $-CONH_2$ or $-CO_2H$ may be prepared by hydrolysis of the corresponding nitrile or ester.

Compounds of formula (I) in which R_7 is cyano and q is other than zero may be prepared by treating the corresponding compound in which R_7 is a leaving group such as a methanesulphonyloxy group with for example an alkali metal cyanide under aqueous conditions. The required methanesulphonate starting material may be prepared by treating the corresponding hydroxyalkyl derivative with an appropriate acid chloride such as methanesulphonyl chloride.

Compounds of formula (I) in which R_7 is cyano may be prepared by heating an oxime of formula (I) in which R_7 is the group $-CH=NOH$ with a dehydrating agent such as acetic anhydride.

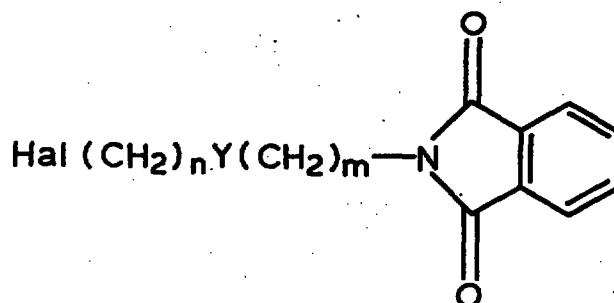
Compounds of formula (I) in which R_6 or R_7 is a 1H-tetrazol-5-yl group may be prepared by treating the corresponding compound of formula (I) in which R_6 or R_7 is a cyano group with an alcohol (e.g. ethanol) in a concentrated mineral acid (e.g. hydrochloric acid) to give an intermediate imidate which may then be treated with sodium azide in a suitable solvent such as dimethylformamide.

Compounds of formula (I) in which R_7 is a monohalomethyl group may be prepared by treating the corresponding hydroxyalkyl compound with an appropriate acid halide, for example thionyl chloride.

Amines of formula (III) may be made by methods described in German Offenlegungsschrifts No. 2,734,070, 2,821,409 and 2,821,410 and British Patent Specification No. 2006771A or by methods analogous to those described therein. For example, amines of formula (III) in which X is oxygen or sulphur and Q is preferably a benzene ring may be prepared by reacting a compound of formula (XII)



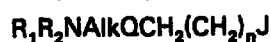
with the phthalimide derivative (XIII)



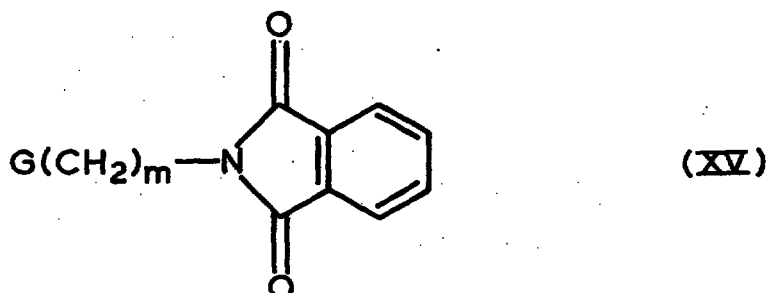
(XIII) 40

where Hal is chlorine or bromine, in the presence of a base followed by removal of the phthalimide protecting group.

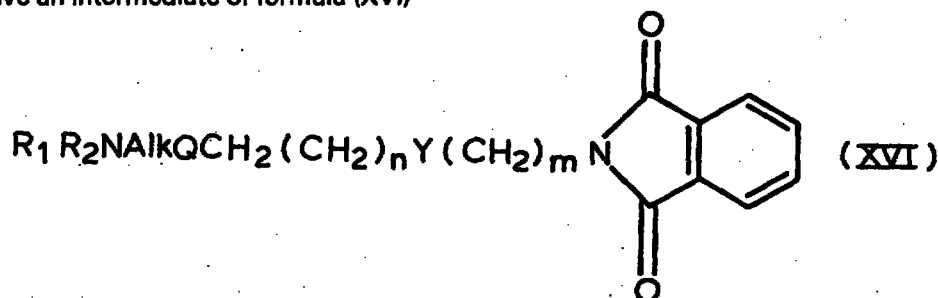
Amines of formula (III) in which X is $-CH_2-$ may be prepared by reacting a compound of formula (XIV) with a compound of formula (XV)



(XIV) 45



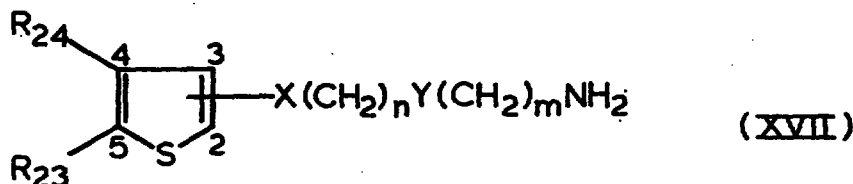
where either J is a leaving group e.g. halogen and G is a hydroxyl or thiol group, or J is a hydroxyl or thiol group and G is a leaving group e.g. halogen. The reaction is carried out in the presence of a base e.g. sodium hydride or potassium carbonate, in a solvent such as dimethylformamide or acetone respectively, to give an intermediate of formula (XVI)



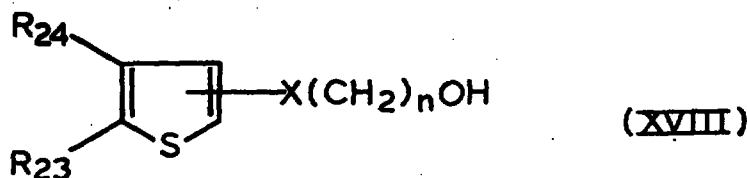
from which the amine (III) in which X is —CH₂— may be formed by cleavage of the phthalimide protecting group.

Amines of formula (III) in which Q is a thiophen ring incorporated into the rest of the molecule through bonds at the 2- and 5- positions with an additional substituent R_s adjacent to the group R₁R₂NAIk, or Q is a thiophen ring incorporated into the rest of the molecule through bonds at the 2- and 4- positions with an optional substituent R_s adjacent to the group R₁R₂NAIk (with the proviso that when the group R₁R₂NAIk is in the 4-position then R_s is in the 5-position), may be made by a number of methods depending on the precise structure of the compound.

Thus for example amines of formula (XVII)



in which one of R₂₃ and R₂₄ represents the group R_s and the other represents the group R₁R₂NAIk, X is a bond, n is 1 or 2, and Y is oxygen or sulphur may be prepared from the corresponding alcohol of formula (XVIII)



in which X is a bond and n is 1 or 2.

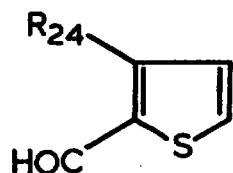
Thus amines of formula (XVII) in which X is a bond, n is 1 and Y is sulphur may be prepared by reacting an alcohol of formula (XVIII) in which X is a bond and n is 1 with an appropriate aminoalkane thiol salt (e.g. cysteamine hydrochloride) in a concentrated mineral acid (e.g. hydrochloric acid).

Amines of formula (XVII) in which X is a bond, n is 2 and Y is sulphur may be prepared by converting an alcohol of formula (XVIII) in which X is a bond and n is 2 into the corresponding haloalkyl compound using for example thionyl chloride or phosphorus tribromide, or mesylate by reaction with methane-sulphonylchloride, followed by treatment with an appropriate aminoalkylthiol (e.g. cysteamine) in a solvent such as ethanol and in the presence of a base (e.g. sodium ethoxide).

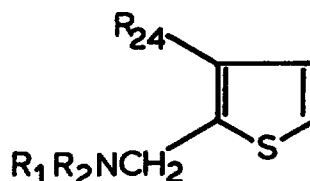
Amines of formula (XVII) in which X is a bond, n is 1 or 2 and Y is oxygen may be prepared by treating an alcohol of formula (XVIII) in which X is a bond and n is 1 or 2 with a suitable base (e.g. potassium t-butoxide) in a solvent (e.g. dimethylformamide) followed by the addition of an appropriate haloalkylamine (e.g. chloropropylamine).

The alcohols of formula (XVIII), as well as the intermediates (XXX) and (XXXI) below, may be made by a variety of processes based on conventional methods in thiophene chemistry (Advances in Heterocyclic Chemistry Volume 1, 1963, page 2—116, Ed. A. R. Katritzky, Academic Press, London and New York; and Comprehensive Chemistry Volume 4, page 787, Ed. PG. Sammes, Pergamon Press, Oxford). Some representative routes and reagents are given in each case.

Alcohols of formula (XVIII) in which R_{23} is the group $R_1R_2NCH_2$, X is a bond, n is 1 and the hydroxymethyl substituent is in either the 2- or 3- position may be prepared by treating a compound of formula (XIX)



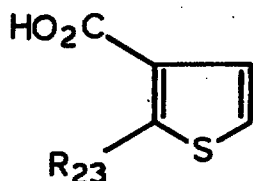
(XIX)



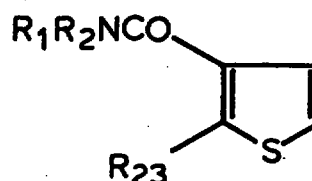
(XX)

- 10 with an amine R_1R_2NH under reducing conditions as described previously for the preparation of compounds of the invention, to give a thiophenemethanamine of formula (XX) which may be subsequently reacted with paraformaldehyde in a concentrated mineral acid (e.g. hydrochloric acid) and acetic acid to introduce the hydroxymethyl group at either the 2- or 3- position.

- 15 Alcohols of formula (XVIII) in which R_{24} is the group $R_1R_2NCH_2$, X is a bond, n is 1 and the hydroxymethyl substituent is at the 2- position may be prepared by reacting a compound of formula (XXI)

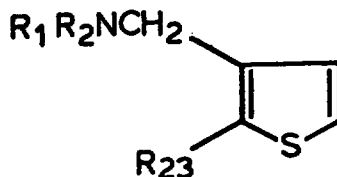


(XXI)



(XXII)

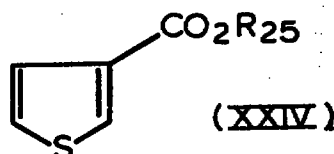
- with for example oxalyl chloride in a solvent (e.g. benzene) and preferably in the presence of a catalyst (e.g. pyridine) followed by treatment with an amine R_1R_2NH to give an amide of formula (XXII) which is subsequently reduced with a complex metal hydride e.g. lithium aluminium hydride in a solvent such as tetrahydrofuran to give a compound of formula (XXIII).



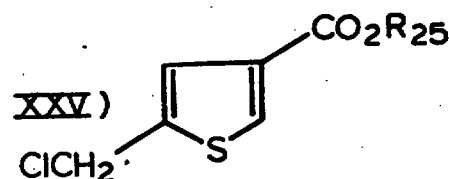
(XXIII)

- 25 The 2-hydroxymethyl group is then introduced by reacting the compound of formula (XXIII) with formaldehyde or a precursor of formaldehyde such as paraformaldehyde, in a concentrated mineral acid, e.g. hydrochloric acid or acetic acid.

Alcohols of formula (XVIII) in which R_{23} is the group $R_1R_2NCH_2$, R_{24} is hydrogen, X is a bond, n is 1 and the hydroxymethyl substituent is in the 3-position may be prepared from a thiophene 3-carboxylate of formula (XXIV)

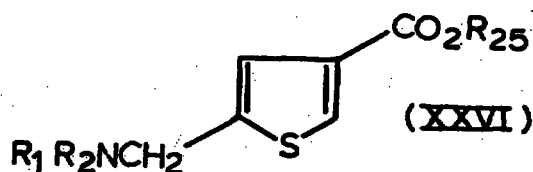


(XXIV)



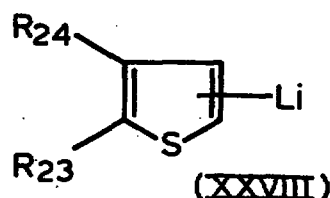
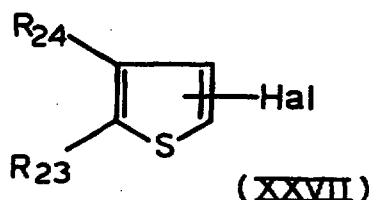
(XXV)

- 30 where R_{25} is an alkyl group. This compound is halomethylated e.g. chloromethylated using for example formaldehyde, or a precursor of formaldehyde such as paraformaldehyde, and gaseous hydrogen chloride in a solvent such as chloroform and in the presence of zinc chloride to give a compound of formula (XXV). The amino group R_1R_2N is then introduced into the compound of formula (XXV) by reaction with an amine R_1R_2NH , in a suitable solvent such as ether, to give a compound of formula (XXVI)



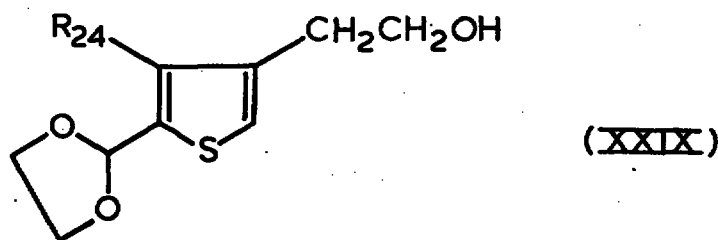
which is then reduced using for example lithium aluminium hydride in a suitable solvent such as ether.

Alcohols of formula (XVIII) in which X is a bond and n is 2 may be prepared by lithiating a halothiophene of formula (XXVII)



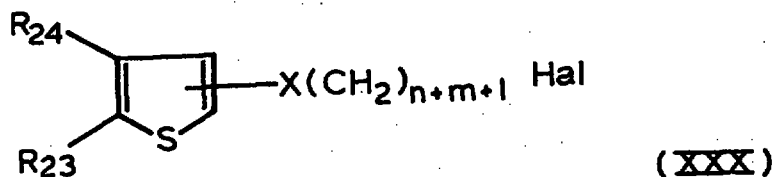
(where Hal is halogen e.g. bromine) using n-butyl lithium in a suitable solvent (e.g. tetrahydrofuran) at a low temperature (e.g. -78°), followed by treatment of the resulting lithio derivative (XXVIII) with ethylene oxide in a solvent such as tetrahydrofuran, to give the desired hydroxyethyl compound (XVIII, X=bond and n=2).

In a modification of this process a halothiophene of formula (XXVII) in which R₂₃ is a group convertible to R₁R₂NCH₂- (e.g. an aldehyde grouping protected as an acetal) and the group Hal is at the 3-position may be lithiated and treated with ethylene oxide as described above to give a hydroxyethyl compound of formula (XXIX).



Subsequent treatment with an amine R₁R₂NH under reducing conditions as described previously for preparing compounds of the invention affords an alcohol of formula (XVIII) in which R₂₃ is the group R₁R₂NCH₂, X is a bond, n is 2 and the hydroxyethyl substituent is at the 3-position.

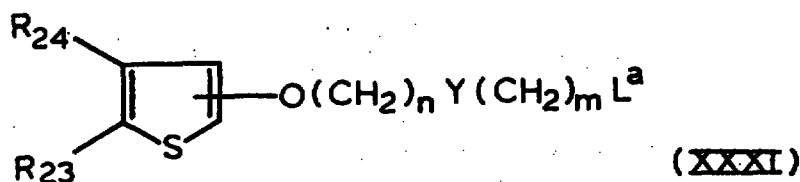
Amines of formula (XVII) in which X is a bond and Y is CH₂ may be prepared from an appropriate haloalkylthiophene of formula (XXX)



(in which X is a bond and Hal is halogen) by treatment with for example potassium phthalimide in a solvent (e.g. dimethylformamide), followed by deprotection of the phthalimido derivative using for example hydrazine hydrate.

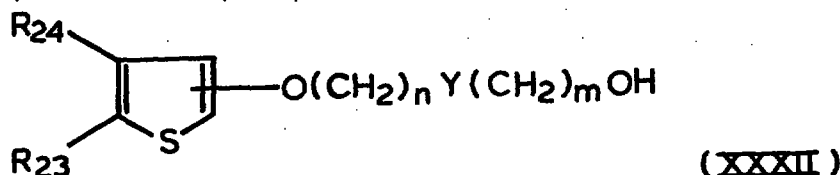
The haloalkylthiophenes of formula (XXX) wherein X is a bond may be prepared for example by treating a lithio derivative of formula (XXVIII) with an α, ω -dihaloalkane (e.g. Br(CH₂)_{n+m+1}Br) in a solvent such as tetrahydrofuran to give an intermediate of formula (XXX).

Amines of formula (XVII) in which X is oxygen and n is 2 or 3 may be prepared from an appropriate alkoxythiophene (XXXI)



where L^a is a halogen atom (e.g. chlorine or bromine) or a leaving group (e.g. mesylate), by similar method to that described above for the preparation of amines of formula (XVII) in which X is a bond and Y is CH₂ from the corresponding haloalkyl thiophene.

- Alkoxythiophenes of formula (XXXI) may be prepared for example by treating a halo (e.g. bromo) thiophene of formula (XXVII) with a diol HO(CH₂)_nY(CH₂)_mOH where n is 2 or 3 in the presence of a base (e.g. sodium hydride) and cuprous oxide, and preferably with the addition of potassium iodide, to give a hydroxy-alkoxy compound of formula (XXXII)



- (wherein n is 2 or 3) which may be treated with for example, thionyl chloride, phosphorus tribromide or methanesulphonyl chloride to give the alkoxythiophene of formula (XXXI).

- Amines of formula (XVII) in which X is sulphur, and n is 2 or 3 may be prepared by treating a lithio derivative of formula (XXVIII) with elemental sulphur, followed by reaction with an appropriate haloalkylamine Hal(CH₂)_nY(CH₂)_mNH₂ wherein n is 2 or 3 preferably in protected form, e.g. as a phthalimide with subsequent cleavage of the phthalimide group using for example hydrazine hydrate.

- Where the product of any of the above processes is a free base and a salt is required, the salt may be formed in a conventional manner. Thus, for example, a generally convenient method of forming the salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent(s) e.g. an alcohol such as ethanol or an ester such as ethyl acetate.

- The invention is illustrated but not limited by the following Examples and Preparations.

- In the following Examples and Preparations temperatures are in °C. "T.l.c." refers to thin layer chromatography and this and preparative chromatography where carried out on silica using, unless otherwise stated, one of the following solvent systems:

- System A ethyl acetate:water:isopropanol:0.88 ammonia (25:4:15:1)

- System B ethyl acetate:ethanol:0.88 ammonia (20:3:2)

- System C Dichloromethane:ethanol:0.88 ammonia (50:8:1)

- System D Methanol:0.88 ammonia (79:1)

- System E ethyl acetate:water:isopropanol:0.88 ammonia (25:8:15:2).

Preparation 1

- Methyl N[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]-1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate**

- Methyl 1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate hydroiodide (13.4 g) was suspended in a saturated aqueous solution of sodium carbonate and extracted with ethyl acetate. The organic extract was evaporated to leave a yellow oil (5.7 g) which was dissolved in acetone (180 ml) and treated with potassium carbonate (3.86 g) and 1,3-dioxo-2-isoindoline acetyl chloride (7.4 g). The suspension was stirred at room temperature for 18h, heated at reflux for 3h, and evaporated under reduced pressure. The residue was dissolved in water, saturated with sodium chloride, and the solution was washed with cyclohexane and ether, extracted with ethyl acetate and dichloromethane, and the organic extracts were evaporated to leave a pale yellow solid which was recrystallised from ethyl acetate to give the *title compound* (3.4 g) m.p. 182°.

Preparation 2

- (a) Methyl N-[2-(methylthio)acetyl]-1-methyl-2-(phenylmethylene)hydrazine carboximidothioate**

- (Methylthio)acetyl chloride (5.6 g) was added portionwise to a solution of methyl 1-methyl-2-(phenylmethylene)hydrazine carboximidothioate hydroiodide (A) (10.4 g) in triethylamine (7.08 g) and dichloromethane (55 ml) and the mixture stirred at room temperature for 2h. The mixture was washed with water and evaporated to give an oil which was chromatographed using 1:1 ether-petroleum ether (b.p. 60—80°) followed by ether to give the *title compound* (4.6 g) as a cream solid, m.p. 68—70°.

- (b) Similarly prepared from pyridine-2-carbonyl chloride hydrochloride (6 g) and methyl 1-methyl-2-(phenylmethylene) hydrazinecarboximidothioate hydrochloride (B) (10 g) in triethylamine (13 ml) and dichloromethane (50 ml), except that the crude product was crystallized from methyl acetate and petroleum ether (b.p. 60—80°) was methyl 1-methyl-2-(phenylmethylene)-N-[2-(pyridinyl)carbonyl]-hydrazinecarboximidothioate (1.6 g) as an off-white solid, m.p. 103°C.

- (c) Similarly prepared from (phenylsulphonyl)acetyl chloride (4.4 g) and A (5.2 g) in triethylamine (6 ml) and dichloromethane (25 ml), except that the crude product was chromatographed using dichloromethane:methanol (50:1) and then triturated with methyl acetate, was methyl 1-methyl-2-(phenylmethylene)-N-[2-(phenylsulphonyl)acetyl]-hydrazine carboximidothioate (1.1 g), m.p. 129.5—130.5°.

- (d) Similarly prepared from ethyl succinyl chloride (10.2 g) and A (17.25 g) in triethylamine (17

ml) and dichloromethane (50 ml), except that the crude product was triturated with ether and petroleum ether b.p. 60—80° and recrystallised from ether, was ethyl-4-[[[1-methyl-2-(phenylmethylene)hydrazino][methylthio)methylene]amino]-4-oxobutanoate (9.6 g) m.p. 51—53°

(e) Similarly prepared from 2-(acetoxy)propionyl chloride (5.25 g) and B (8 g) in triethylamine (10 ml) and dichloromethane (40 ml), except that the crude product was chromatographed using ethyl acetate:petroleum ether (b.p. 60—80°) (1:1) and then crystallized from methyl acetate and petroleum ether (b.p. 60—80°) was methyl N-[2-(acetyloxy-1-oxo-propyl)]-1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate (2.5 g) as a white solid, m.p. 89°.

(f) Similarly prepared from B (48.8 g) and 4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)butyryl chloride (53.4 g) was methyl N-[4-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-butyryl]]-1-methyl-2-(phenylmethylene)hydrazine carboximidothioate (44.7 g) as colourless plates from ethanol, m.p. 128—129.5°C.

Preparation 3

(a) N-Amino-N'-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]guanidine Hydrogen Carbonate Hemihydrate

3-[3-(1-Piperidinylmethyl)phenoxy]propanamine (A) (9.92 g) and methyl hydrazine carboximidothioate hydroiodide (B) (10.25 g) were heated together as a melt for 7h at 80° then dissolved in toluene (50 ml) and heated for a further 2h at 80°. The solution was cooled and washed with water. The aqueous layer was basified with 2N sodium bicarbonate resulting in a precipitate which was filtered off to give the *title compound* (4.2 g) as a buff coloured solid m.p. 115°.

(b) Similarly prepared from A (9.9 g) and B (9.3 g), but with the omission of the basification step and formation of the hemi-tartrate salt in a ethyl acetate-ethanol solution, was N-Amino-N'-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]guanidine hydroiodide hemi-tartrate (13.9 g), m.p. 55°.

Preparation 4

1-Methyl-3-trifluoromethyl-1H-1,2,4-triazole-5-amine

1-Amino-1-methyl guanidine sulphate (12.3 g) and trifluoroacetic acid (16 ml) were heated at reflux for 96h. Excess trifluoroacetic acid was removed by distillation and the residue was basified with sodium bicarbonate and extracted with ethyl acetate. The extract was dried and evaporated to give a white solid (7.2 g) which was recrystallised from a mixture of methyl acetate (8 ml) and petroleum ether (b.p. 60—80°) (20 ml) to give the *title compound* as a white powder (5.1 g) m.p. 165—166°.

Preparation 5

(a) 1-Methyl-5[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]1H-1,2,4-triazole-3-methanamine

N-[[1-Methyl-2-(phenylmethylene)hydrazino][[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]methylene](1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetamide

A solution of 3-[3-(1-piperidinylmethyl)phenoxy]propanamine (A) (1.96 g) and methyl N-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]-1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate (B) (3.1 g) in acetonitrile (20 ml) was stirred at room temperature for 18h. The solvent was evaporated to leave a yellow oil (5 g) which was crystallised from ether (600 ml), to give the *title compound* as a white solid (3.5 g), m.p. 84.5°.

1-Methyl-5[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]1H-1,2,4-triazole-3-methanamine

A solution of the above acetamide (3.4 g) in acetone (100 ml) and 2N hydrochloric acid (15 ml) was heated at reflux for 17h. The solution was diluted with water (20 ml) and evaporated under reduced pressure to a volume of 50 ml. The aqueous solution was washed with ethyl acetate, basified with sodium carbonate, and extracted with ethyl acetate. The organic extracts were evaporated to leave a yellow oil (2.7 g) which was used without further purification. The oil (1.2 g) was dissolved in ethanol (15 ml), and stirred at room temperature with hydrazine hydrate (0.5 g) for 24h. The solvent was removed under reduced pressure, and the residue was dissolved in aqueous sodium carbonate. The aqueous solution was washed with ether treated with 2N sodium hydroxide and extracted with ethyl acetate. The organic extracts were evaporated to leave the *title compound* as pale yellow oil (0.51 g). T.l.c. System B (20:3:2) R_f 0.25.

(b) Similarly prepared from methyl N-[4-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)butyryl]]-1-methyl-2-(phenylmethylene)hydrazine carboximidothioate (21.1 g) and A (15.3 g), but using ethanolic methylamine instead of hydrazine (as in Preparation 8), was 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-propanamine as a gum (1.8 g). T.l.c. System C, R_f 0.06.

(c) Similarly prepared from B (1.5 g) and 5-[[2(amino)-ethyl]thio]methyl-N,N-3-trimethylthiophenemethanamine (1.0 g) was 2-[[5-[[[5-[[[5-(dimethylamino)methyl]-4-methyl-2-thienyl]methyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]-1H-isoindole-1,3(2H)-dione (1.2 g) with the exceptions that the cyclisation was effected by heating the reaction mixture in acetone

at 80° for 1h with 2N hydrochloric acid and the crude product was purified by column chromatography (System C). T.l.c. System C Rf 0.85.

The above 1*H*-isoindole-1,3(2*H*)-dione (1.1 g) gave 1-methyl-5-[[2-[[5-[[dimethylamino)methyl]-4-methyl-2-thienyl]methyl]thio]ethyl]amino]-1*H*-1,2,4-triazole-3-methanamine (0.6 g) except that ethanolic methylamine was used instead of hydrazine (as in Preparation 8) and the crude product was purified by column chromatography (dichloromethane:ethanol:0.88 ammonia 40:8:1). T.l.c. System C Rf 0.35.

Preparation 6

(a) 2-[[1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino-N-[[[2-[[5-[[dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino][1-methyl-2-(phenylmethylene)hydrazino]methylene]acetamide 10

A solution of 2[[5-[[Dimethylamino)methyl]-2-furanylmethyl]thio]ethylamine (2.1 g) and methyl N-[[1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl]acetyl]-1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate (B) (3.9 g) in acetonitrile (30 ml) was stirred at 25°C for 18h. The white solid which resulted was filtered off and washed with acetonitrile (2x10 ml) to give the title compound (3.0 g) as a white solid, m.p. 115°. 15

The following compounds were similarly prepared from Compound B and the appropriate amine.

(b) Compound B (2 g) and 3[[3-[[dimethylamino)methyl]phenoxy]propanamine (1 g) gave 2-[[1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino]-N-[[[3-[[dimethylamino)methyl]phenoxy]propyl]amino][1-methyl-2-(phenylmethylene)hydrazino]methylene]acetamide (2.5 g) as a pale yellow foam. T.l.c. System E. Rf 0.7 20

(c) Compound B (2.0 g) and 2[[2-[[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amine (1.4 g) gave 2-[[1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino]-N-[[1-methyl-2-(phenylmethylene)hydrazino][2-[[2-[[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]methylene]acetamide (3.1 g) as a pale yellow gum. T.l.c. System B Rf 0.65. 25

(d) Compound B (2.0 g) and 3-[[N,N-dimethylamino)methyl]benzenebutanamine (1.1 g) gave N-[[[4-[[3-(dimethylaminomethyl)phenyl]butyl]amino]methylene][1-methyl-2-(phenylmethylene)hydrazino](1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)]acetamide (2.8 g) as a white solid mp 123—126°. 25

Preparation 7

(a) 2-[[5-[[2-[[5-[[Dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1*H*-1,2,4-triazol-3-yl]methyl]-1*H*-isoindole-1,3(2*H*)-dione 30

2-[[1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino]-N-[[[2-[[5-[[dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino][1-methyl-2-(phenylmethylene)hydrazino]methylene]acetamide (2.82 g) was dissolved in 2N hydrochloric acid (9 ml) and toluene (5 ml) and stirred at 40—50° for 18h. The phases were separated and the aqueous phase washed with toluene, basified with sodium carbonate solution and extracted with ethyl acetate. The extract was evaporated to give the title compound (2.28 g) as a pale yellow oil. T.l.c. System A, Rf 0.55. 35

The following triazoles were similarly prepared from the corresponding acetamides.

(b) 2-[[1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino]-N-[[[3-[[3-[[dimethylamino)methyl]phenoxy]propyl]amino][1-methyl-2-(phenylmethylene)hydrazino]methylene]acetamide (2.5 g) gave 2[[5-[[3-[[3-[[dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1*H*-1,2,4-triazol-3-yl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (1.85 g) as an off white foam. T.l.c. System A, Rf 0.6. 40

(c) 2-[[1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl]amino]-N-[[1-methyl-2-(phenylmethylene)hydrazino][2-[[2-[[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]methylene]acetamide (3.1 g) gave 2-[[1-methyl-2-[[2-[[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]-1*H*-1,2,4-triazol-3-yl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (2.4 g) as a pale yellow solid. T.l.c. System B Rf 0.55. 45

(d) N-[[[4-[[3-(dimethylaminomethyl)phenyl]butyl]amino]methylene][1-methyl-2-(phenylmethylene)hydrazino](1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)]acetamide (2.8 g) gave 3-[[1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl]methyl]-N-[[4-[[3-(dimethylaminomethyl)phenyl]butyl]-1-methyl-1*H*-1,2,4-triazol-5-amine as a brown gum (1.45 g) T.l.c. System D Rf 0.47. 50

Preparation 8

(a) 5-[[2-[[5-[[Dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1*H*-1,2,4-triazole-3-methanamine 55

2-[[5-[[2-[[5-[[Dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1*H*-1,2,4-triazol-3-yl]methyl]-1*H*-isoindole-1,3(2*H*)-dione (2.2 g) in ethanol (25 ml) was treated with ethanolic methylamine (33% w/v, 7 ml) and the mixture was stirred at room temperature for 3 h. The mixture was evaporated and the residue partitioned between 2N sodium hydroxide and ethyl acetate. The organic phase was washed with 5N sodium hydroxide and evaporated to give the title compound (1.5 g) as a pale brown oil. T.l.c. System A, Rf 0.3. 60

The following 3-aminomethyl triazoles were similarly prepared from the corresponding isoindole-1,3(2*H*)-diones.

(b) 2-[[5-[[3-[(Dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]-1H-isoindole-1,3 (2H) dione (1.8 g) gave 5-[[3-[[3-[(dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (1.1 g) as a pale yellow oil. T.l.c. System B, Rf 0.4.

5 (c) 2-[1-Methyl-5-[2[[2-[(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]-1H-1,2,4-triazol-3-yl]methyl]-1H-isoindole-1,3 (2H)-dione (2.4 g) gave 1-methyl-5-[2-[[2-[(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]-1H-1,2,4-triazole-3-methanamine (1.37 g) as a pale yellow oil. T.l.c. System B Rf 0.25.

10 (d) 3-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]-N-[4-[3-(dimethylaminomethyl)phenyl]butyl]-1-methyl-1H-1,2,4-triazol-5-amine (1.45 g) gave 5-[[4-[3-[(dimethylamino)methyl]phenyl]butyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (1.1 g) as a brown gum. T.l.c. System D Rf. 0.25.

Preparation 9

15 3-[3-[[1-Methyl-3-[(phenylsulphonyl)methyl]-1H-1,2,4-triazol-5-yl]amino]propoxy]benzaldehyde
A mixture of 3-[3-(1,2-dioxolan-2-yl)phenoxy]propanamine (2.3 g) and methyl-1-methyl-2-(phenylmethylene)N-[2-(phenylsulphonyl)acetyl]hydrazine carboximidothioate (4.0 g) was heated at 60° under water pump vacuum for 3h. The reaction mixture was dissolved in toluene (100 ml), 5N hydrochloric acid (100 ml) and acetone (50 ml) and stirred at room temperature for 18h. The aqueous layer was basified to pH 9 with potassium carbonate and extracted with ethyl acetate. The organic
20 extract was evaporated to give the *title compound* as an amber gum (3.0 g) T.l.c. Methanol; Rf 0.8.

Preparation 10

4-[[2-(Amino)ethyl]thio]methyl-N,N-dimethyl-2-thiophene-methanamine
Methyl 5-(dimethylaminomethyl)-3-thiophene Carboxylate

25 A solution of methyl 5-(chloromethyl)-3-thiophene-carboxylate (1.9 g) in a dry diethylether (100 ml) was treated with anhydrous dimethylamine (5 ml). After 6 hours the solvent was removed *in vacuo* and the residue was dissolved in 5M hydrochloric acid (20 ml). The aqueous solution was washed with diethylether, basified with 5M sodium hydroxide (30 ml) and extracted with ether. The ethereal extracts were evaporated to give an oily residue which was distilled to yield the *title compound* as a colourless oil (1.6 g) b.p. 120—130°/0.5 mm.

30 5-(Dimethylaminomethyl)-3-thiophenemethanol

A solution of the above thiophenecarboxylate (1.5 g) in diethylether (50 ml) was treated with lithium aluminium hydride (0.21g). After 1 hour water (2 ml) was added and the solution was filtered through diatomaceous earth. Evaporation of the filtrate gave an oily residue which distilled to give the *title compound* as an oil (1.2 g) b.p. 120°/0.1 mm.

35 4-[[2-(Amino)ethyl]thio]methyl-N,N-dimethyl-2-thiophenemethanamine

A mixture of the above thiophenemethanol (1 g) and 2-aminoethanethiol hydrochloride (0.67 g) was stirred in concentrated hydrochloric acid (7 ml) at 0°C for 2 hours; and then at room temperature for 48 hours. Solid anhydrous sodium carbonate was added and the product was extracted into ethyl acetate.

40 The organic extract was distilled to give the *title compound* as a colourless oil (0.75 g) b.p. 130°/0.05 mm.

Preparation 11

5-[[2-(Amino)ethyl]thio]methyl-N,N,3-trimethylthiophene-methanamine
5-(Dimethylaminomethyl)-4-methyl-2-thiophene-methanol

45 A solution of N,N,3-trimethyl-2-thiophenemethanamine (1.5 g) in dry tetrahydrofuran (50 ml) was treated with a solution of n-butyl lithium (1.6 M; 7 ml) at room temperature, under nitrogen. After 4h, gaseous formaldehyde (excess) was added and the mixture was heated at 40°C for 20h.

Water (100 ml) and chloroform (100 ml) were added and the organic solution evaporated *in vacuo* to leave an oily residue which was dissolved in ethanol (50 ml) and treated with sodium borohydride (0.1 g), followed by acetic acid (10 ml). The reaction mixture was evaporated to dryness and the residue was dissolved in sodium carbonate solution (8%, 50 ml) and extracted with chloroform. The organic extract was distilled to give the *title compound* as a colourless oil (0.65 g) b.p. 120°/0.1 mm.

55 Following the method of Preparation 10, 2-amino-ethanethiol hydrochloride (0.6 g) and the above thiophenemethanol (0.6 g) gave 5-[[2-(amino)ethyl]-thio]methyl-N,N,3-trimethylthiophenemethanamine as a colourless oil (0.69 g) b.p. 150°/0.1 mm.

Preparation 12

2-[2-[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethylamine

A solution of 3-[1-piperidinylmethyl]phenol (2.7 g) and sodium hydride (0.34 g) in dry

dimethylformamide (100 ml) was stirred at 25° during 6h under nitrogen. 2-[2-(2-Chloroethoxy)ethyl]-1H-isoindole-1,3-(2H)-dione (3.6 g) was added and the mixture was stirred at 25° during 12h and at 80° during 2h. The cooled mixture was poured onto water and extracted with ether. The solvent was evaporated to leave a crude oil (5.1 g) which was used without further purification.

- 5 This oil and hydrazine hydrate (1.0 g) were heated under reflux in ethanol (100 ml) for 2h and then cooled to 25°. Ether was added and the precipitate which formed was removed by filtration. The filtrate was concentrated *in vacuo* to give the *title compound* (2 g) b.p. 180° (0.1 mm). 5

Preparation 13

Methyl 1-methyl-N-[(methylsulphonyl)acetyl]-2-(phenylmethylene)hydrazinecarboximidothioate

- 10 To a stirred solution of methyl 1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate hydrochloride (5.71 g) and triethylamine (5.2 g) in dichloromethane (100 ml) was added methylsulphonylchloride (4.9 g) in dichloromethane (20 ml) dropwise during 0.5h at 20°. The mixture was stirred at 20° during 18h, water (100 ml) added and the phase separated. The dichloromethane layer was washed with water, dried, and evaporated. The residue was crystallised from ethanol to give the *title compound* (2.7 g) as off white needles. m.p. 149.5—150.5°. 15

Example 1

(a) 1-Methyl-3-methylthiomethyl-N-[3-[3-(1-piperidiny-methyl)phenoxy]propyl]-1H-1,2,4-triazole Dihydro Chloride Hemihydrate

- 20 Methyl N-[2-(methylthio)acetyl]-1-methyl-2-(phenylmethylene)hydrazine carboximidothioate (2.95 g) and 3-[3-(1-piperidiny-methyl)phenoxy]propanamine (2.48 g) were heated at 55° under water vacuum for 1 h. Additional carboximidothioate (0.3 g) was then added and the mixture heated for a further 0.5h. The reaction mixture was dissolved in toluene (15 ml) and 5N hydrochloric acid (12 ml), and stirred at room temperature for 18h and the phases separated. The aqueous phase was basified to pH 8 with sodium bicarbonate solution, washed with toluene, basified to pH 10 with sodium carbonate and extracted with ethyl acetate to give an oil, which was chromatographed using 3:1 ethyl acetate-methanol to give an oil (3.1 g). This oil (1.27 g) was dissolved in ether and treated with ethereal hydrogen chloride to give a white solid which was recrystallised from ethyl acetate-methanol to give the *title compound* (0.37 g) as white crystals m.p. 158—160°. 25

- 30 Found: C, 50.9; H, 7.1; N, 14.6;
C₂₀H₃₁N₅OS₂HCl.½H₂O requires: C, 50.9; H, 7.3; N, 14.6% 30

(b) Similarly prepared from 3-[3-(1-piperidiny-methyl)phenoxy]propanamine (0.58 g) and methyl 1-methyl-2-(phenylmethylene)-N-[2-(phenylsulphonyl)acetyl]hydrazine carboximidothioate (A), (1.1 g) was 1-methyl-3-phenylsulphonylmethyl-N-[3-[3-(1-piperidiny-methyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine dihydrochloride hydrate (1.0 g), m.p. 120—123°.

- 35 Found: C, 52.3; H, 6.2; N, 11.7;
C₂₅H₃₃N₅O₃S₂HCl.H₂O requires: C, 52.3; H, 6.5; N, 12.2% 35

- (c) Similarly prepared from 3-[3-(1-piperidiny-methyl)phenoxy]propanamine (0.50 g) and methyl 1-methyl-2-(phenylmethylene)-N-[2-(pyridiny)carbonyl]hydrazine carboximidothioate (0.69 g), except that column chromatography was not necessary, was 1-methyl-2-[3-(1-piperidiny-methyl)phenoxy]propyl]-3-(2-pyridiny)-1H-1,2,4-triazole-5-amine (0.7 g). T.l.c. system A, Rf 0.75. 40

Nmr (CDCl₃): 2.28, dd, (1H); 2.9, dd, (1H); 2.23 dt, (1H); 2.75; dt+t, (2H); 2.9—3.0, m, (3H); 5.35, brt, (1H); 5.82, t, (2H); 6.30—6.33, q+s, (5H); 6.57, s, (2H); 7.5—7.8, m, (6H); 8.5, m, (6H).

- 45 (d) Similarly prepared from 4-[[2-(aminoethyl)thio]methyl]-N,N-dimethyl-2-thiophenemethanamine (0.54 g) and A (1 g) was 1-methyl-3-(phenylsulphonyl)methyl-N-[2-[[5-(dimethylamino)methyl-3-thienylmethyl]thio]ethyl]-1H-1,2,4-triazole-5-amine (1.0 g) as a pale orange-brown oil. 45

- 50 Nmr (CDCl₃): 2.1, m, (2H); 2.3—2.6, m, (3H); 3.0, s, (1H); 3.15, s, (1H); 5.7, s, (2H), ca. 5.7, br t, (1H); 6.4, s, (2H); 6.47, s, (2H); 6.54, s, (3H); 6.64, q, (2H); 7.42, t, (2H); 7.78, s, (6H). 50
Ir (smear): 3380cm⁻¹, 1318, 1158.

Example 2

(a) N-[[1-methyl-5-[[3-[3-(1-piperidiny-methyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-yl]methyl]acetamide

- 55 A solution of acetic anhydride (0.089 g) in dry pyridine (1 ml) was added dropwise to a solution of 1-methyl-5-[[3-[3-(1-piperidiny-methyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanamine (A) (0.31 g) at 5°. The solution was stirred at room temperature for 0.5h, and the solvent was removed under reduced pressure to leave a yellow oil which was triturated with light petroleum b.p. 60—80° to give the *title compound* as a white solid (0.27 g), m.p. 123°. 55

Analysis Found: C, 63.1; H, 8.1; N, 20.7;
 $C_{21}H_{32}N_6O_2$ requires: C, 63.0; H, 8.05; N, 21.0%

The following compounds were similarly prepared:

- (b) A (0.5 g) and trifluoroacetic anhydride (0.29 g) gave 2,2,2-trifluoro-N-[[1-methyl-5-[[3-[3-(1-piperidinyl-methyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]acetamide (260 mg). T.l.c. System A Rf 0.7. 5
- Nmr ($CDCl_3$): 2.77—3.3, m+t, (5H); 5.49—5.62, d, (3H); 5.90, t, (2H); 6.45—6.60, q+s+s, (7H); 7.67—7.90, m+m, (6H); 8.6, m, (6H).
- (c) 5-[[2-[[5-[(dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (0.75 g) and acetic anhydride (0.23 ml) gave N-[[5-[[2-[[5-[(dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]acetamide (0.6 g) as a brown gum. T.l.c. System D. Rf 0.48. 10
- Nmr ($CDCl_3$): 3.8—3.9, brs, (3H); 5.3, brt, (1H); 6.3, s, (2H); 6.49—6.60, s+q, (7H); 7.2, t, (2H); 7.8, s, (6H); 8.0, s, (3H).
- (d) 5-[[4-[3-[(dimethylamino)methyl]phenyl]butyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (1.1 g) and acetic anhydride (0.35 ml) gave N-[[5-[[4-[3-[(dimethylamino)methyl]phenyl]butyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]acetamide (1.0 g). T.l.c. System D. Rf 0.44. 15
- Nmr ($CDCl_3$): 2.7—3.0, m, (4H); 3.60, br, (1H); 5.67, d, (2H); 5.77, t, (1H); 6.50—6.60, 2xs+q, (7H); 7.32, t, (2H); 7.74, s, (6H); 8.00, s, (3H); 8.30, m, (4H). 20
- (e) 1-Methyl-5-[[2-[[5-[(dimethylamino)methyl]-4-methyl-2-thienyl]methyl]thio]ethyl]amino]-1H-1,2,4-triazole-3-methanamine (0.55 g) and acetic anhydride (1.6 g) gave N-[[1-methyl-5-[[2-[[5-[(dimethylamino)methyl]-4-methyl-2-thienyl]methyl]thio]ethyl]amino]-1H-1,2,4-triazol-3-yl]methyl]acetamide (0.32 g). T.l.c. System C. Rf 0.42. 25
- Nmr ($CDCl_3$): 3.35, s, (1H); 3.80, s, (1H); 5.50, t, (1H); 5.65, d, (2H); 6.12, s, (2H); 6.4—6.6, m, (7H); 7.20, t, (2H); 7.73, s, (6H); 7.90, s, (3H); 7.98, s, (3H). 25

Example 3

1-Methyl-3-nitro-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine 5-Bromo-1-methyl-3-nitro-1H-1,2,4-triazole

- A stirred solution of 3-bromo-5-nitro-1H-1,2,4-triazole (13.1 g) in acetone (100 ml) was cooled to 0° and treated with 10% sodium hydroxide solution (30 ml), followed by dimethyl sulphate (9.5 g). After 18h at room temperature, the mixture was evaporated *in vacuo*; the residue was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 2N sodium hydroxide solution, water, and evaporated *in vacuo*. The resulting solid was recrystallised from a mixture of ethyl acetate and cyclohexane to yield the *title compound* (6.0 g), m.p. 90.5—91.5°. 30 35

1-Methyl-3-nitro-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine

The above triazole (0.414 g) and 3-[3-(1-piperidinyl-methyl)phenoxy]propanamine (1.0 g) were heated together under nitrogen at 80° for 1h. The resulting oil was chromatographed using methanol as eluant to give the *title compound* as an oil (0.6 g). T.l.c. System E. R_f 0.8.

- Nmr ($CDCl_3$): 2.72, m, (1H); 3.0—3.3, m, (3H); 4.72, t, (1H); 5.83, t, (2H); 6.28, s+q (5H); 6.50, s, (2H); 7.4—7.7 and 7.83, m, (total 6H); 8.2—8.7, m, (6H). 40

Example 4

(a) 1-Methyl-5-[[4-[3-(1-piperidinylmethyl)phenoxy]butyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde

- Dimethyl sulphoxide (304 mg) was added to a solution of oxalyl chloride (254 mg) in dichloromethane (20 ml) at -60° under nitrogen for 2 min. and a solution of 1-methyl-5-[[4-[3-(1-piperidinylmethyl)phenoxy]butyl]amino]-1H-1,2,4-triazole-3-methanol (0.5 g) in dichloromethane (10 ml) was added. The mixture was stirred at -50 to -60° for 15 min. and then quenched with triethylamine (657 mg). The solution was allowed to warm to 25° and was diluted with water. The aqueous phase was extracted with dichloromethane and the combined organic extracts were dried and evaporated to leave the *title compound* as a pale yellow oil (0.4 g). 45 50

Nmr ($CDCl_3$): 0.2, s, (1H); 2.78, t, (1H); 3.0—3.3, m, (3H); 5.25, br, t, (1H); 6.06, br, t, (2H); 6.40, s, (3H); 6.5, q, (2H); 6.60, s, (2H); 7.68, br, (4H); 8.0—8.6, m, (10H). T.l.c. System D R_f 0.55.

- (b) Similarly 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol (4 g), oxalyl chloride (2.03 g) and dimethyl sulphoxide (2.43 g) gave 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde (2.54 g), m.p. 91—2°. 55

Found: C, 63.5; H, 7.5; N, 19.3;
 $C_{19}H_{27}N_5O_2$ requires: C, 63.8; H, 7.6; N, 19.6%

Example 5**Ethyl 5-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]amino-1H-1,2,4-triazole-3-carboxylate**

Methyl 5-amino-1H-1,2,4-triazole-3-carboxylate (0.568 g) and 4-[3-(1-piperidinylmethyl)phenoxy]butanal in ethanol (40 ml) were heated at reflux for 2h. The cooled reaction mixture was treated with sodium borohydride (0.4 g) and stirred at room temperature for 15h. The solvent was evaporated and the residue was dissolved in 2N hydrochloric acid which was washed with ethyl acetate, basified with sodium carbonate and extracted with ethyl acetate. The combined organic extracts were evaporated to yield the *title compound* as a white solid which was recrystallised from a mixture of ethyl acetate and ethanol (1:1) (0.5g) m.p. 170—1° dec.;

10

Found: C, 62.6; H, 7.6; N, 17.2;
 $C_{21}H_{31}N_5O_3$ requires: C, 62.8; H, 7.8; N, 17.4%

10

Example 6**5-[4-[3-(1-Piperidinylmethyl)phenoxy]butyl]amino-1H-1,2,4-triazole-3-carboxamide**

A suspension of ethyl 5-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]amino-1H-1,2,4-triazole-3-carboxylate (867 mg) in 0.88 ammonia (25 ml) was stirred at room temperature for 18h. The mixture was evaporated and the residual solid was washed with boiling methanol to leave the *title compound* as a white solid (255 mg) m.p. 212—4° dec.

Found: C, 61.3; H, 7.6; N, 22.3;
 $C_{19}H_{28}N_6O_2$ requires: C, 61.3; H, 7.6; N, 22.6%

Example 7**1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxylic Acid Hemitartrate Sesquihydrate**

A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde (1.07 g) in methanol was treated with silver oxide (3 g). The mixture was stirred for 19h at room temperature, and then chromatographed using methanol. The crude acid was dissolved in water (charcoaled), filtered and evaporated. The solid residue was dissolved in hot methanol and isopropanol. The cooled solution was purified by filtration and the filtrate was evaporated. The residue was dissolved in ethanol and treated with a solution of tartaric acid in ethanol. The resulting solid was collected by filtration to give the *title compound* (0.43 g), m.p. 130° (softens).

30

Found: C, 53.4; H, 6.60; N, 14.8;
 $C_{19}H_{27}N_5O_3 \cdot \frac{1}{2}C_4H_6O_6 \cdot \frac{1}{2}H_2O$ requires: C, 53.1; H, 6.98; N, 14.7%

30

Example 8**(a) 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxamide Tartrate Dihydrate**

A mixture of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxylic acid (0.5 g), dimethylformamide (0.05 g), thionyl chloride (0.5 ml) and dry dichloromethane (10 ml) was stirred at room temperature for 2 hours. Ammonia gas was passed through the reaction mixture for 1 hour. Water was added and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by thin layer chromatography. Solvent System E. The resulting oil was dissolved in ethyl acetate and treated with a solution of tartaric acid in ethyl acetate. The white precipitates was collected by filtration to give the *title compound* (0.326 g)

Nmr (CDCl₃): 2.5, t, (1H); 2.8 to 3, m, (3H) 5.4, s, (2H); 5.7 to 5.8, s+t, (4H); 6.4 to 6.5, s+t+m, (7H); 7.05, t, (2H); 7.7 to 8.5, m, (8H).

45

Found: C, 49.8; H, 6.3; N, 14.9;
 $C_{19}H_{26}N_6O_2 \cdot C_4H_6O_6 \cdot 2H_2O$ requires: C, 49.5; H, 6.8; N, 15.0%

45

The following compounds were similarly prepared from 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-propanoic acid (A), by the above method except that the excess thionyl chloride was removed under reduced pressure to leave a residue which was dissolved in dichloromethane (15 ml) before adding the appropriate amine.

(b) (A) (0.32 g) and dimethylamine (0.27 g) gave N,N,1-Trimethyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-propanamide (0.05 g) as a yellow solid, m.p. 62—4°.

Found: C, 64.2; H, 8.5; N, 19.4;
 $C_{23}H_{28}N_6O_2$ requires: C, 64.4; H, 8.5; N, 19.6

(c) (A) (0.5 g) and pyrrolidine (0.2 g) gave 1-[3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-1-oxopropyl]pyrrolidine (0.13 g) as a brick-red solid. T.l.c. System E Rf 0.5.

55

Nmr (CDCl₃): 2.74, m, (1H); 3.0—3.3, m, (3H); 5.4, t, (1H), 5.89, t, (2H); 6.2—6.6, m, (6H); 6.49, s, (3H); 6.53, s, (2H); 6.8—7.15, t, (2H); 7.15—7.4, t, (2H); 7.56, m, (4H); 7.7—8.3, m, (6H); 8.2—8.6, m, (6H).

Example 9

5 N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-3-(2-thienyl)-1H-1,2,4-triazole-5-amine Hemi-hydrate 5

A mixture of N-amino-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]guanidine hydrogen carbonate, hemi-hydrate (1.0 g) and 2-thiophene carbonyl chloride (0.63 g) in pyridine (5 ml) was stirred at 24° for 12h and then heated under reflux for 3h. The mixture was dissolved in water (50 ml), basified with potassium carbonate, washed with cyclohexane and extracted with ether and ethyl acetate. The combined organic extracts were evaporated to leave a brown gum (1.0 g) which was chromatographed using methanol as eluent, to give a solid (0.20 g). Recrystallisation of the solid from a mixture of light petroleum (b.p. 60—80°) and methyl acetate gave the *title compound* as a white powder (0.12 g), m.p. 157°.

15 Nmr (CDCl₃): 2.5, m, (1H); 2.7—3.3, m, (6H); 4.7, t, (1H); 6.0, q, (2H); 6.55—6.65, q+s, (4H); 7.65—8.0, m, (6H); 8.5, m, (6H). 15

Example 10

3-(3-Pyridylmethyl)-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine

20 A solution of N-amino-N'-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]guanidine hydroiodide hemitartrate (5 g) in water (50 ml) was basified with sodium hydroxide and extracted with ethyl acetate. The extract was evaporated to give a gum (2.33 g) which was heated at 150° for 12h with 3-pyridylacetic acid hydrochloride (1.46 g). The mixture was dissolved in water (50 ml), basified with sodium hydroxide, washed with cyclohexane and extracted with ether. The ethereal extracts were dried and evaporated to leave a brown residue which was recrystallised from ethyl acetate to give the *title compound* as a cream crystalline solid (0.12 g), m.p. 126—129°.

25 Nmr (CDCl₃): -2.0, br s, (1H); 1.4—1.6, m, (2H); 2.4, dd, (1H); 2.65—2.9, m+t, (2H); 3.0—3.3, m, (3H); 4.77, t, (1H); 6.1—6.13, t+s, (4H); 6.6—6.65, s+q, (4H); 7.6, m, (4H); 8.1, m, (2H); 8.5, m, (6H). 25

Example 11

30 1-Methyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-3-trifluoromethyl-1H-1,2,4-triazole-5-amine 30

N-[1-Methyl-3-trifluoromethyl-1H-1,2,4-triazol-5-yl]-4-[3-(1-piperidinylmethyl)phenoxy]butanamide

35 A solution of 4-[3-(1-piperidinylmethyl)phenoxy]butanoic acid (8.3 g), thionyl chloride (9 ml) and dimethylformamide (1 ml) in methylene chloride (250 ml) was stirred at 25° for 2h. After evaporation the residue was dissolved in methylene chloride and 1-methyl-3-trifluoromethyl-1H-1,2,4-triazole-5-amine (5 g) was added and the mixture was stirred for 18 h at room temperature. The solution was evaporated, diluted with water, basified with sodium bicarbonate and extracted with ethyl acetate. The extract was dried and evaporated to give a brown oil which was extracted with hot diethyl ether. On standing the *title compound* (5.2 g) crystallised from the ether solution, m.p. 96—97°.

Found: C, 56.8; H, 6.2; N, 16.1; F, 13.7;

C₂₀H₂₆F₃N₅O₂ requires: C, 56.4; H, 6.2; N, 16.5; F, 13.4%

1-Methyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-3-trifluoromethyl-1H-1,2,4-triazole-5-amine

45 A suspension of the above butanamide (5 g) and lithium aluminium hydride (5 g) in dry tetrahydrofuran was stirred at room temperature for 18h and then heated at reflux for 1h. The suspension was treated with water and sodium hydroxide, filtered and evaporated to give white crystals which were recrystallised from hot ethyl acetate to give the *title compound* (1.1 g), m.p. 70°.

Found: C, 58.1; H, 6.9; N, 16.7;

C₂₀H₂₆F₃N₅O requires: C, 58.4; H, 6.9; N, 17.0%

Example 12

3-Methylsulphonyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-1H-1,2,4-triazole-5-amine

55 Peracetic acid (1.8 ml) in acetic acid (13 ml) was added at 0° to a solution of 3-methylthio-N-[4-[3-(1-piperidinyl-methyl)phenoxy]butyl]-1H-1,2,4-triazole-5-amine (1.6 g) and sodium acetate (0.69 g) in acetic acid (22 ml) and the mixture was stirred at room temperature, for 18h. Excess peracetic acid was decomposed with sodium sulphite (3.0 g) in water and the resulting suspension evaporated. The residue was neutralised with sodium bicarbonate solution and extracted with chloroform. The extract

was evaporated to give an oil which was crystallised from methyl acetate-petroleum ether (5:1) to give the *title compound* as a beige powder (0.75 g), m.p. 79—81°.

Found: C, 55.8; H, 7.1; N, 16.9;
 $C_{19}H_{28}N_6O_3S$ Requires: C, 56.0; H, 7.2; N, 17.2%

5 Example 13

(a) 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde Oxime Hemi-fumarate

A solution of hydroxylamine hydrochloride (0.36 g) in ethanol (20 ml) was treated with potassium hydroxide (0.28 g). A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde (A) (1.5 g) in ethanol (20 ml) was added. The mixture was stirred for 15 minutes and then filtered. The filtrate was evaporated and the residue was dissolved in chloroform and washed with water. The organic solution was dried, filtered and evaporated and the solid residue was dissolved in ethyl acetate/ethanol and treated with a solution of fumaric acid in ethyl acetate/ethanol, to give the *title compound* (0.05 g) m.p. 173—4°.

Assay Found: C, 58.2; H, 7.0; N, 19.1;
 $C_{19}H_{28}N_6O_2 \cdot \frac{1}{2}C_4H_4O_4$ requires: C, 58.6; H, 7.0; N, 19.5%

(b) Similarly prepared from A (0.5 g) and methoxyamine (0.14 g) was 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde O-methyloxime (0.4 g). T.l.c. System B, Rf 0.7.

Nmr ($CDCl_3$): 2.03, s, (1H); 2.78, t, (1H); 3.0—3.3, m, (3H); 5.18, t, (1H); 5.90—6.02, t+s, (5H); 6.32—6.42, q+s, (5H); 6.58, s, (2H); 7.6—7.88, m, (6H); 8.5, m, (6H).

Example 14

1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carbonitrile

A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde oxime (0.75 g) in acetic anhydride (4 ml) was heated at 100° for 10 hours. The mixture was poured onto aqueous sodium bicarbonate and extracted with toluene. The extract was dried (Na_2SO_4), filtered, and evaporated to give a solid, which was crystallized from diethyl ether and petroleum ether (b.p. 60—80°) to give the *title compound* (0.3 g) as a white powder, m.p. 66—7°.

Found: C, 64.2; H, 7.4; N, 23.3;
 $C_{19}H_{28}N_6O$ requires: C, 64.4; H, 7.4; N, 23.7%

Example 15

1-Methyl-3-methylsulphonylmethyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine

Peracetic acid (1.05 ml of a 6.1 M solution) in acetic acid (7 ml) was added to an ice-cooled solution of 1-methyl-3-methylthiomethyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine (0.82 g) in acetic acid (10 ml) with sodium acetate (0.52 g). The mixture was stirred at room temperature for 18h, sodium sulphite (1.25 g) added and the mixture evaporated to dryness. The residue was basified to pH 8 with sodium bicarbonate solution, washed with ethyl acetate, basified to pH 10 with sodium carbonate and extracted with ethyl acetate to give a foam (0.46 g). This was crystallised from methyl acetate-petroleum ether (b.p. 60—80°) to give the *title compound* as a white solid (0.22 g), m.p. 121—122°.

Found: C, 57.0; H, 7.4; N, 16.5;
 $C_{20}H_{31}N_6O_3S$ requires: C, 57.0; H, 7.4; N, 16.6%

Example 16

N-[3-[3-[(Dimethylamino)methyl]phenoxy]propyl]-1-methyl-3-[(methylsulphonyl)methyl]-1H-1,2,4-triazol-5-amine

Methyl 1-methyl-N-[(methylsulphonyl)acetyl]-2-(phenylmethylene)hydrazinecarboximidothioate (1.3 g) and 3-[3-[(dimethylamino)methyl]phenoxy]propanamine (0.81 g) were heated at 70° under water vacuum for 1h. After cooling, the reaction mixture was dissolved in toluene (10 ml) and 5N hydrochloric acid (6 ml), and stirred at 20° during 18h. The acidic layer was washed with toluene and basified (pH 10) with potassium carbonate. The mixture was then extracted with ethyl acetate to give the *title compound* (1.2 g) as an oil. T.l.c. System A Rf 0.39.

Nmr ($CDCl_3$): 2.71, t, (1H); 3.0—3.3, m, (3H); 5.4, t, (1H); 5.7—6.0, m, (4H); 6.35, t, (2H); 6.45, s, (3H); 6.63, s, (2H); 6.93, s, (3H); 7.74, s, (6H); 7.8, m, (2H).

Example 17

(a) N-Methyl-N'-[[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]-2-nitro-1,1-ethenediamine

1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-

methanamine (0.2 g) and methyl-N-methyl-2-nitroimidothioate (0.08 g) in water (2.5 ml) was stirred for 48h at 22° under water vacuum. The reaction mixture was acidified with glacial acetic acid and washed with ethyl acetate. The aqueous layer was basified to pH9 with solid potassium carbonate and extracted with ethyl acetate to give an oil (0.13g), which was chromatographed using methanol to give

the *title compound* as a solidified lemon-yellow foam (0.065 g).

Nmr (CDCl₃): -0.5, m, (1H); 2.1, m, (1H); 2.80, t, (1H); 3.0—3.3, m, (3H); 3.48, brs, (1H); ca 4.5, m, (1H); 5.78, brd, (2H); 5.98, t, (2H); 6.48, s+m, (5H); 6.63, s, (2H); 7.20, br, (2H); 7.67, m, (4H); 7.93, m, (2H); 8.6, m, (6H). Ir (CHBr₃): 2805 cm⁻¹, 2760, 2725, 1385, 760.

(b) Similarly prepared from 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-propanamine (0.46 g) and methyl N-methyl-2-nitroimidothioate (0.27 g) was N-methyl-N'-[3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]propyl]-2-nitro-1,1-ethenediamine as a gum (0.47 g). T.l.c. System C, Rf 0.34.

Nmr (CDCl₃): -0.4, m, (1H); 1.9, m, (1H); 2.75—3.3, m, (4H); 3.38, s, (1H); 4.9, m, (1H); 5.87, t, (2H); 6.3—6.6, m, (9H); 7.1—8.2, m, (13H); 8.3—8.6, m, (6H).

15 Example 18

3-[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-2-propenoic Acid Hydrate (1:2.5)

A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxaldehyde (0.8 g), malonic acid (0.23 g), piperidine (0.05 ml) and pyridine (5 ml) was heated at 90° for 4h. The resulting solution was azeotroped with toluene to give a brown foam (0.9 g) which was partitioned between aqueous sodium hydroxide and diethyl ether. The aqueous layer was acidified (pH 5.5.) to precipitate the *title compound* (0.4 g) as a white solid, m.p. 95—100° [decomp].

Found: C, 56.7; H, 8.0; N, 15.5;
C₂₁H₂₀N₅O₃·2.5H₂O requires: C, 56.7; H, 7.7; N, 15.8%

25 Example 19

3-[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-3-propenol

Ethyl 3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-2-propenoate

A solution of 3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-2-propenoic acid (0.8 g) and concentrated hydrochloric acid (1 ml) in ethanol was stirred 60° for 18h, followed by 6h at reflux. Sodium carbonate (5 g) was added and the reaction mixture was evaporated *in vacuo* to give an off-white solid which was partitioned between sodium carbonate solution and chloroform. The organic phase was evaporated to give the *title compound* as a brown gum (0.85 g). T.l.c. System C, Rf 0.66.

Nmr (CDCl₃): 2.46, d, (1H); 2.69, t, (1H); 2.93—3.28, 3.23, m+d, (4H); 5.43, t, (1H); 5.58—5.9, m, (4H); 6.32—6.38, q+s (5H); 6.52, s, (2H); 7.55, m, (2H); 7.80, m, (2H); 8.44—8.68, m+t, (9H).

3-[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]-2-propenol

A stirred solution of the above 2-propenoate (0.8 g) in tetrahydrofuran at 0°C under nitrogen was treated with aluminium hydride solution (0.3M; 6.2 ml) for 4h. The reaction mixture was quenched with water and filtered through hyflo. The residue was washed with tetrahydrofuran and the combined filtrate evaporated to leave a brown oil which was chromatographed using dichloroethane:ethanol:0.88 ammonia (60:8:1) to give the *title compound* (0.1 g) contaminated with the corresponding 3-hydroxypropyl triazole as a brown gum. T.l.c. System C, Rf 0.12.

Nmr (CDCl₃): 2.7, t; 3.0—3.2, m; 3.22, dt; 3.55, d; 5.15, t; 5.72, d; 5.9, m; 6.3, q; 6.5, s; 6.52, s; 7.55, m; 7.85, m; 8.45, m; contaminant peaks: 6.4, t; 7.3, t; 8.0, m.

Example 20

1-[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]ethanone α,1-Dimethyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol

A mixture of 3-[3-[1-(piperidinylmethyl)]phenoxy]propanamine (1.8 g) and methyl N-[2-(acetyloxy-1-oxypropyl)-1-methyl-2-(phenylmethylene)hydrazinecarboximidothioate (2.3 g) was heated at 60—70° for 1 hour. The mixture was dissolved in toluene (50 ml) and 2N hydrochloric acid (15 ml) was added. The mixture was stirred for 18h and heated at 80° for 40 minutes. The mixture was neutralized with sodium bicarbonate and washed with toluene. The aqueous solution was basified with aqueous sodium hydroxide and extracted with ethyl acetate. The extract was dried, filtered and evaporated to give a solid residue, which was crystallized from diethyl ether and petroleum ether (b.p. 60—80°) to give the *title compound* (1.2 g) as a white solid. m.p. 67—68°.

1-[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]ethanone

Activated manganese dioxide (9 g) was added to a stirred solution of the above α -methylmethanol (0.5 g) in dichloromethane (10 ml). After 48 hours the mixture was filtered through hyflo and the filtrate evaporated to give the *title compound* (0.073 g) as a colourless oil. T.l.c. System A, Rf 0.7.

Nmr (CDCl_3): 2.77, t, (1H); 3.0—3.3, m, (3H); 5.02, t, (1H), 5.90, t, (2H); 6.37, s+m, (5H); 6.58, s, (2H); 7.45, s, (3H); 7.6, m, (4H); 7.88, m, (2H); 8.3—8.7, m, (6H).

Example 21

N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl-N'-phenyl urea

A mixture of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanamine (0.75 g) and phenyl isocyanate (0.25 ml) in dry acetonitrile was stirred at 30° for 3h. The solvent was removed *in vacuo* and the solid residue was crystallized from methyl acetate and petroleum ether (b.p. 60—80°) to give the *title compound* (0.94 g) as a white solid, m.p. 120—1°.

T.l.c. System A, Rf 0.6.

Example 22

N-Cyano-N'-methyl-N'-[[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]guanidine

A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanamine (1.0 g) in diethylether (20 ml) was added to a refluxing solution of N-cyanocarbimidothioic acid dimethyl ester (0.45 g) in ether (50 ml) and the mixture heated at reflux for 8h. After cooling, a colourless solid (0.65 g) precipitated and was collected by filtration, m.p. 121—122°. This material was added to a solution of methylamine (33% in ethanol, 10 ml) in ethanol (50 ml) and the solution heated at reflux for 16h. The mixture was evaporated to give a solid which was recrystallized from ethyl acetate to give the *title compound* as a colourless solid (0.34 g), m.p. 138—139°.

Nmr (CDCl_3): 2.73, t, (1H); 2.8—3.3, m(4H); 3.93, t, (1H); 5.0, t, (1H); 5.8, d, (2H); 5.9, t, (2H); 6.45, q, (2H); 6.48, s, (3H); 6.58, s, (2H); 7.16, d, (3H); 7.65, m, (4H); 7.9, m, (2H); 8.5, m, (6H).

Example 23

N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]benzamide

50% Benzoic anhydride (0.57 g) was added to a solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanamine (0.4 g) in pyridine (10 ml) and stirred for 0.5h at 80°. Excess pyridine was evaporated and the residue was diluted with water (50 ml), basified with solid potassium carbonate and extracted with ethyl acetate. The extract was evaporated to give a gum which was chromatographed using methanol. The resulting oil was crystallized from ethyl acetate-petroleum ether (b.p. 60—80°) (1:2) to give the *title compound* (0.26 g) as white crystals, m.p. 70°.

Found: C, 65.6; H, 7.3; N, 17.6;
 $\text{C}_{26}\text{H}_{34}\text{N}_6\text{O}_2$ requires: C, 65.6; H, 7.5; N, 17.7%

Example 24

(a) N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]methane-sulphonamide

A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanamine (0.5 g) and methane sulphonyl chloride (0.16 g) in pyridine (25 ml) was stirred at room temperature for 18h. The solution was evaporated to give a brown oil which was crystallised from a mixture of ethyl acetate and petroleum ether (b.p. 60—80°) to give the *title compound* (0.14 g) as a white powder, m.p. 117—118°.

Found: C, 55.1; H, 7.4; N, 18.8;
 $\text{C}_{20}\text{H}_{32}\text{N}_6\text{O}_3\text{S}$ requires: C, 55.0; H, 7.4; N, 19.2%

The following compounds were similarly prepared from the appropriate 3-aminoalkyl-triazole:

(b) 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-propanamine (0.46 g) and methane sulphonyl chloride (0.11 ml) gave N-[[3-[1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]propyl]methanesulphonamide as a gum (0.26 g). T.l.c. System C, Rf 0.35.

Nmr (CDCl_3): 2.7—3.3, m, (4H); 3.45, t, (1H); 5.40, t, (1H); 5.88, t, (2H); 6.2—6.7, m, (9H); 6.79, q, (2H); 7.10, s, (3H); 7.32, t, (2H); 7.6—8.5, m, (10H).

(c) 1-methyl-5-[2-[[2-[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]-1H-1,2,4-triazole-3-methanamine (0.8 g) and methane sulphonyl chloride (0.25 g) gave N-[[1-methyl-5-[2-[[2-[3-(1-piperidinylmethyl)phenoxy]ethoxy]ethyl]amino]-1H-1,2,4-triazol-3-yl]methyl]methanesulphonamide (0.6 g) as a pale brown oil. T.l.c. System B, Rf 0.4.

Nmr (CDCl₃): 2.77, t, (1H); 3.0—3.3, m, (3H); 4.55, br.t, (1H); 5.45, t, (1H); 5.8, s, (2H); 5.9—6.2, m, (4H); 6.33, t, (2H); 6.45, q, (2H); 6.58, 2xs, (5H); 7.06, s, (3H); 7.65, m, (4H); 8.5, m, (6H).

Example 25

(a) 5-[[3-[3-[(Dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazole-3-carboxaldehyde Fumarate

5-[[3-[3-[(Dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanol (2.12 g) and activated manganese dioxide (6.32 g) were stirred together in chloroform (40 ml) for 4h at 24°. The mixture was filtered, and the filtrate evaporated to give a gum which was chromatographed on "Florisil" (registered Trade Mark) using ethanol:ethyl acetate (1:9). The resulting oil was dissolved in ethyl acetate/ethanol and added to a solution of fumaric acid in ethyl acetate/ethanol to give the *title compound* (0.71 g) as a white solid, m.p. 133—135°.

Nmr (D₂O): 0.50, s, (1H); 2.63, t, (1H); 2.75—3.05, m, (3H); 3.3, s, (2H); 5.76, m, (4H); 6.31—6.33, s+q, (5H); 7.18, s, (6H); 7.90, t, (2H).

(b) Similarly prepared from 5-[[2-[[[5-(dimethylamino)methyl]-4-methyl-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanol (0.8 g) and activated manganese dioxide (6.0 g) in chloroform (40 ml after 6 h at 24° was 5-[[2-[[[5-(dimethylamino)methyl]-4-methyl-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazole-3-carboxaldehyde fumarate (0.4 g) m.p. 149—151°.

Nmr (D₂O): 0.3, s, (1H); 3.29, s, (2H); 4.05, s, (1H); 5.7, s, (2H); 6.20, s, (2H); 6.3, s, (2H); 6.45, m, (3H); 7.10—7.25, t+s, (8H); 7.95, s, (3H).

Example 26

1-Methyl-3-(methylsulphonyl)methyl-N-[3-[4-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine

1-Methyl-3-(methylthio)methyl-N-[3-[4-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine

Methyl N-[2-(methylthio)acetyl]-1-methyl-2-(phenylmethylene)hydrazine carboximidothioate (1.2 g) and 3-[4-(1-piperidinylmethyl)phenoxy]propanamine (0.9 g) were heated at 55° under water vacuum for 2h. Additional carboximidothioate (0.09 g) was then added and the mixture heated for a further 1h. The reaction mixture was dissolved in toluene (5 ml) and 5N hydrochloric acid (4 ml), stirred at room temperature for 18h and the phases separated. The aqueous phase was basified to pH 10 with sodium carbonate and extracted with ethyl acetate to give an oil, which was chromatographed using ethyl acetate-methanol (3:1) to give the *title compound* (1.04 g) as an orange brown oil.

Nmr (CDCl₃): 2.72, m, (2H); 3.13, m, (2H); 5.56, t, (1H); 5.87, t, (2H); 6.36, q, (2H); 6.42, s, (2H); 6.48, s, (3H); 6.56, s, (2H); 7.60, m, (4H); 7.82, s, (3H); 7.84, m, (2H); 8.2—8.8, m, (6H).

Ir (CHBr₃): 3400cm⁻¹, 2790, 2745, 2710, 1583, 1523.

1-Methyl-3-(methylsulphonyl)methyl-N-[3-[4-(1-piperidinyl-methyl)phenoxy]-propyl]-1H-1,2,4-triazole-5-amine

Peracetic acid (0.9 ml, 6.1M) in acetic acid (5 ml) was added at 0° to a solution of the above 3-(methylthio) methyl-triazole (0.69g) and the mixture was stirred at room temperature for 18h. Excess peracetic acid was decomposed with sodium sulphite (1 g) in water and the mixture was evaporated.

The residue was basified with sodium bicarbonate solution and extracted with chloroform. The extract was evaporated to give a white solid which was recrystallised from methyl acetate-petroleum ether to give the *title compound* (230 mg) as a white solid, m.p. 131—4°.

Nmr (CDCl₃): 2.70, d, (2H); 3.13, d, (2H); 5.40, t, (1H); 5.80, s, (2H); 5.90, t, (2H); 6.35, dt, (2H); 6.45, s, (3H); 6.55, s, (2H); 6.90, s, (3H); 7.60, m, (4H); 7.81, m, (2H); 8.2—8.8, m, (6H).

Example 27

N-[[5-[2-[[5-[(Dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]methanesulphonamide

A solution of 5-[[2-[[5-[(Dimethylamino)methyl]-2-furanylmethyl]thio]ethyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (0.65 g) and methane sulphonyl chloride (0.17 ml) in pyridine (5 ml) was stirred at room temperature for 18h. The pyridine solution was decanted off to leave a dark red oil which was treated with saturated sodium carbonate solution (25 ml) and extracted with ethyl acetate to give the *title compound* (0.07 g) as a pale brown oil. T.l.c. System A, Rf 0.5.

Nmr (CDCl₃): 3.90, s, (2H); 5.22, brt, (1H); 5.80, s, (2H); 6.30, s, (2H); 6.48, s, (3H); 6.55, q, (2H); 6.60, s, (2H); 7.03, s, (3H); 7.76, s, (6H).

Example 28

N-[[5-[[3-[3-[(Dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazol-3-yl]methyl]methanesulphonamide

- A mixture of 5-[[3-[3-[(Dimethylamino)methyl]phenoxy]propyl]amino]-1-methyl-1H-1,2,4-triazole-3-methanamine (0.75 g) and methane sulphonyl chloride (0.18 ml) in dry pyridine (15 ml) was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue was dissolved in aqueous sodium carbonate and extracted with ethyl acetate. The organic solution was evaporated leaving the *title compound* (0.5 g). T.l.c. System B, Rf 0.6
- Nmr (CDCl₃): 2.8—2.9, t, (1H); 3.1—3.25, m, (3H); 3.9, brs., (1H); 4.55, t, (1H); 5.7—6.00, s+t, (4H); 6.3—6.7, m+s+s, (7H); 7.10, s, (3H); 7.75—8.0, s+m, (8H).

Example 29

(a) N-[3-[3-[(2-Furanylmethyl)amino]methyl]phenoxy]propyl]-1-methyl-3-[(phenylsulphonyl)methyl]-1H-1,2,4-triazol-5-amine

- A solution of 3-[3-[[1-Methyl-3-[(phenylsulphonyl)methyl]-1H-1,2,4-triazol-5-yl]amino]propoxy]benzaldehyde (A), (1.5 g) in ethanol (50 ml) was treated with furfurylamine (7.5 ml) at room temperature for 1.5h. The solution was treated with sodium borohydride (2.0 g) and the suspension stirred for 18h at room temperature. The mixture was quenched with water, partially evaporated and extracted with ethyl acetate to give a red oil which was purified by column chromatography using methanol:ethyl acetate (1:4) to give the *title compound* as a yellow oil (1.2 g). T.l.c. methanol:ethyl acetate (1:4), Rf 0.4.
- Nmr (CDCl₃): 2.10, m, (2H); 2.3—2.8, m, (5H); 3.0—3.3, m, (3H); 3.7—3.9, m, (2H); 5.48, t, (1H); 5.65, s, (2H); 5.93, t, (2H); 6.22, s, (4H); 6.50, s+q, (5H); 7.95, m, (2H); 8.10, s, (1H).

- (b) Similarly prepared from A (1.5 g) and hexylamine (7.5 ml) was N-[3-[3-[(hexylamino)methyl]phenoxy]propyl]-1-methyl-3-[(phenylsulphonyl)methyl]-1H-1,2,4-triazol-5-amine (1.3 g) as a red oil. T.l.c. methanol:ethyl acetate (1:1), Rf 0.8.
- Nmr (CDCl₃): 2.10, m, (2H); 2.2—2.9, m, (4H); 3.0—3.3, m, (3H); 5.43, t, (1H); 5.69, s, (2H); 5.95, t, (2H); 6.25, s, (2H); 6.43, s+q, (5H); 7.3—7.5, t+s, (4H); 7.98, m, (2H); 8.3—9.0, m, (8H); 9.13, t, (3H).

Example 30

- (a) Ethyl 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-acetate salt with Tartaric Acid (1:1)**

Ethyl 3-[[[1-methyl-2-(phenylmethylene)hydrazino][3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]methylene]amino]3-oxopropanoate

- A mixture of 3-[3-(1-piperidinylmethyl)phenoxy]propanamine (A) (3.61 g) and ethyl 3-[[[1-methyl-2-(phenylmethylene)hydrazino](methylthio)methylene]amino]-3-oxopropanoate (4.7 g) was heated at 50° under water pump vacuum during 4h. to give the *title compound* as an orange gum (7.3 g). T.l.c. System D, R_f 0.65.

Ethyl 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-acetate salt with tartaric acid (1:1)

- A solution of the above 3-oxopropanoate (1.84 g) in ethanol (50 ml) and 2N hydrochloric acid (7 ml), was heated under reflux during 4h. The cool solution was washed with ethyl acetate (50 ml). The aqueous layer was basified to pH 9 with potassium carbonate and extracted with ethyl acetate (3x50 ml). The solvent was evaporated to leave a pale yellow oil (0.6 g) which was purified by column chromatography using methanol to give a pale yellow oil (0.47 g). This oil was dissolved in ethyl acetate (10 ml) and treated with a solution of d-tartaric acid (30 mg) in ethyl acetate (100 ml) to give the *title compound* (60 mg) as a white powder, m.p. 65° (softens).

- Nmr (CDCl₃), free base: 2.77, t, (1H); 3—3.3, m, (3H); 5.4, t, (1H); 5.8, q, (2H); 5.9, t, (2H); 6.3—6.6, 3x s+q, (9H); 7.6, m, (4H); 7.85, m, (2H); 8.5, m, (6H); 8.72, t, (3H).

- (b) Similarly prepared from ethyl-4-[[[1-methyl-2-(phenylmethylene)hydrazino](methylthio)methylene]amino]-4-oxobutanoate (9.0 g) and A (6.5 g) was 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]1H-1,2,4-triazole-3-propanoic acid (A) (3.7 g). T.l.c. methanol: Rf 0.3.

- Nmr (CDCl₃): 2.75—3.0, m, (2H); 3.05—3.3, m, (2H); 4.95, m, (1H); 5.97, t, (2H); 6.3, s, (2H); 6.2—6.7, q, (2H); 6.55, s, (3H); 7.0—7.65 m, (8H); 7.92, m, (2H); 8.15—8.7, m, (6H).

Example 31

- 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-acetic Acid Hydrate**

- Ethyl 3-[[[1-methyl-2-(phenylmethylene)hydrazino][3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]methylene]amino]-3-oxo-propanoate (5.77 g) was dissolved in toluene (10 ml) and 5N hydrochloric acid (12 ml) and stirred at 25° for 18h. The phases were separated and the aqueous layer basified to pH 10 with sodium carbonate solution, washed with ethyl acetate and evaporated to dryness. The solid residue was extracted with chloroform (4x50 ml) to give

an oil (1.8 g) which was chromatographed using 2:3 ethyl acetate:methanol to give a foam which was triturated with ether to give the *title compound* (0.4 g) as a white solid.

Found: C, 59.5; H, 7.6; N, 16.8;
 $C_{20}H_{29}N_5O_3 \cdot H_2O$ requires: C, 59.2; H, 7.7; N, 17.3%

5 Nmr (D_2O): 2.55, dd, (1H); 2.8—3.0, m, (3H); 5.80, t, (2H); 5.92, s, (2H); 6.46, s, (3H); 6.46, m, (2H); 6.57, s, (2H); 6.8—7.05, m, (4H); 7.87, m, (2H); 8.0—8.5, m, (6H). 5

Example 32

3-(Chloromethyl)-1-methyl-N-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]-1H-1,2,4-triazole-5-amine

10 A mixture of 1-methyl-5-[4-[3-(1-piperidinylmethyl)phenoxy]butyl]amino-1H-1,2,4-triazole-3-methanol (0.75 g) and thionyl chloride (4 ml) was stirred at room temperature for 2h. The mixture was evaporated *in vacuo* and the residue was dissolved in chloroform and washed with sodium bicarbonate. The organic extract was dried and evaporated to give the *title compound* as an oil (0.75 g) T.l.c. System E R_f 0.65. 10

15 NMR ($CDCl_3$): 2.76, t, (1H); 3.0—3.3, m, (3H); 5.53, s, (2H); 5.7—6.0, t+m, (3H); 6.5—6.6, s+s+m, (7H); 7.65, m, (4H); 8.0—8.3, m, (4H); 8.3—8.6, m, (6H). 15

Example 33

N-[2-[[[5-(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-1-methyl-3-[(methylsulphonyl)methyl]-1H-1,2,4-triazol-5-amine

20 Methyl 1-methyl-N-[(methylsulphonyl)acetyl]-2-(phenylmethylene)hydrazinecarboximidothioate (1.05 g) and 5-[[2-aminoethyl]thio]methyl-N,N-dimethylfuranmethanamine (0.85 g) in acetonitrile (3 ml) were heated on a steam bath at atmospheric pressure for 5 minutes then under water vacuum for 10 minutes. The oily residue was dissolved in acetonitrile (3 ml) and the solution re-evaporated under water vacuum. The oily residue was dissolved in 2N hydrochloric acid (3 ml) and 5N hydrochloric acid (4 ml) added to the solution. The solution was heated on a steam bath for 15 minutes and after cooling 25 to room temperature, water (10 ml) was added and the oily suspension extracted with ethyl acetate. The aqueous phase was basified with sodium carbonate and the oily suspension extracted with ethyl acetate to yield an oil (0.84 g). This was chromatographed (using solvent system D) to give the *title compound* (0.78 g) as an oil. T.l.c. System D, R_f 0.5. 25

30 Nmr. ($CDCl_3$) 3.85, s, (2H); 5.20, brt, (1H); 5.78, s, (2H); 6.28, s, (2H); 6.45, s, 6.52, q, 6.58, s, (7H); 6.90, s, (3H), 7.21, t, (2H), 7.73, s, (6H). 30

Example 34

1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-acetonitrile

35 A solution of 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol (3.6 g) in dry dichloromethane was treated with methane sulphonyl chloride (0.85 ml) at 0° for 3h, poured into sodium carbonate solution (2M; 50 ml), and extracted with dichloromethane. The extract was washed with sodium hydroxide, water and brine and evaporated to give a white foam (4 g). This foam was dissolved in dimethylformamide (80 ml) and potassium cyanide (0.65 g) was added. The mixture was stirred at room temperature for 2h and then at 65° for 24h, cooled, concentrated, poured into sodium carbonate solution (2M; 100 ml) and extracted with ethyl acetate. The extract was washed with water and brine and evaporated to leave a brown oil (1.5 g) which was chromatographed 40 using dichloromethane: ethanol:0.88 ammonia (60:8:0.5) to give the *title compound* as a brown gum (0.5 g). T.l.c. System C R_f 0.6. 40

Nmr ($CDCl_3$): 2.57, 3.0—3.3, m, (3H); 5.48, brt, (1H); 5.90, t, (2H); 6.2—6.6, 3xs+q, (9H); 7.6—7.9, m, (6H); 8.5, m, (6H).

45 Examples of Pharmaceutical compositions according to the invention are as follows: 45

	(a) Tablets		
	mg/tablet	mg/tablet	
50	Active ingredient	20.0	40.0
	Microcrystalline cellulose	99.5	199.0
	BPC		
	Magnesium stearate B.P.	0.5	1.0
	Compression weight	120.0	240.0

The drug is sieved through a 250 μ m sieve, blended with the excipients and compressed using 6.5 mm and 8.0 mm diameter punches for the 20 and 40 mg strengths respectively. Tablets of other strengths may be prepared by increasing the compression weight and using punches to suit.

55 The tablets may be film coated with suitable film forming materials, e.g. methyl cellulose, ethyl 55

cellulose or hydroxypropylmethyl cellulose, using standard techniques. Alternatively the tablets may be sugar coated.

<i>(b) Capsules</i>		<i>mg/capsule</i>	
5	Active ingredient	20.0	5
	**Sta-Rx 1500 Starch	79.5	
	Magnesium Stearate B.P.	0.5	
	Fill weight	100.0	

**A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The active ingredient is sieved through a 250 μ m sieve and blended with other materials. The mix is filled into No. 3 hard gelatin capsules using a suitable filling machine. Other doses may be prepared by increasing the fill weight and if necessary changing the capsule size to accommodate the increase.

<i>(c) Sustained Release Tablets</i>		<i>mg/tablet</i>	
15	Active ingredient	80	15
	**"Cutina" (registered Trade Mark) HR	25	
	Lactose B.P.	142.5	
	Magnesium stearate B.P.	2.5	
Compression weight		250.0	

**"Cutina" HR is a grade of microfine hydrogenated castor oil supplied by Sipon Products Ltd., London.

The drug is sieved through a 250 μ m sieve and blended with the "Cutina" HR and lactose. The mixed powders are moistened with Industrial Methylated Spirits 74 O.P., granules are made, dried, screened and blended with the magnesium stearate. The lubricated granules are compressed using 8.5 mm punches to produce tablets with a hardness of not less than 10Kp (Schleuniger tester).

<i>(d) Injection for Intravenous Administration</i>		<i>% w/v</i>	
25	Active ingredient	0.25	25
	Water for Injections BP to	100.00	

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability using either dilute acid or alkali.

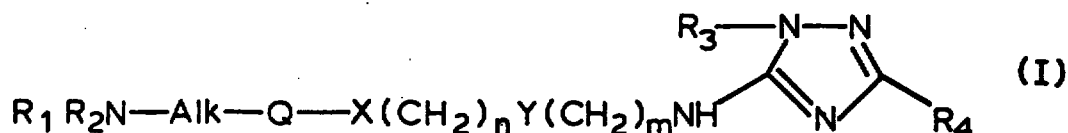
The solution is prepared, clarified and filled under nitrogen into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions.

<i>(e) Syrup</i>		<i>mg/5ml dose</i>	
35	Active ingredient	20.0 mg	35
	Sucrose	2750.0 mg	
	Glycerine	500.0 mg	
	Buffer		
40	Flavour	as necessary	40
	Colour		
	Preservative		
	Distilled water		
		to 5.0 ml	

The active ingredient, buffer, flavour, preservative and colour are dissolved in some of the water. The remainder of the water is heated to approximately 80°C and the sucrose is dissolved in this and cooled. The two solutions are mixed, adjusted to volume and clarified by filtration.

45 Claims

1. Compounds of the general formula (1)





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cellulose or hydroxypropylmethyl cellulose, using standard techniques. Alternatively the tablets may be sugar coated.

(b) Capsules		mg/capsule	
5	Active ingredient	20.0	
	**Sta-Rx 1500 Starch	79.5	
	Magnesium Stearate B.P.	0.5	5
	Fill weight	100.0	

**A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.
The active ingredient is sieved through a 250 μ m sieve and blended with other materials. The mix is filled into No. 3 hard gelatin capsules using a suitable filling machine. Other doses may be prepared by increasing the fill weight and if necessary changing the capsule size to accommodate the increase.

(c) Sustained Release Tablets		mg/tablet	
15	Active ingredient	80	
	**"Cutina" (registered Trade Mark) HR	25	
	Lactose B.P.	142.5	
	Magnesium stearate B.P.	2.5	15
Compression weight		250.0	

**"Cutina" HR is a grade of microfine hydrogenated castor oil supplied by Sipon Products Ltd., London.

The drug is sieved through a 250 μ m sieve and blended with the "Cutina" HR and lactose. The mixed powders are moistened with Industrial Methylated Spirits 74 O.P., granules are made, dried, screened and blended with the magnesium stearate. The lubricated granules are compressed using 8.5 mm punches to produce tablets with a hardness of not less than 10Kp (Schleuniger tester).

(d) Injection for Intravenous Administration		% w/v	
25	Active ingredient	0.25	
	Water for Injections BP to	100.00	25

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability using either dilute acid or alkali.

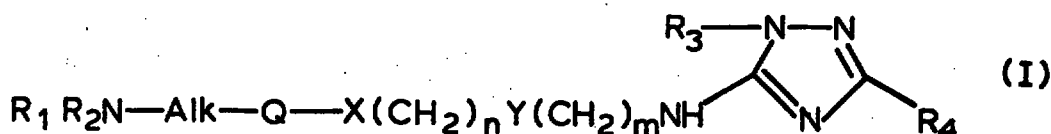
The solution is prepared, clarified and filled under nitrogen into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions.

(e) Syrup		mg/5ml dose	
35	Active ingredient	20.0 mg	
	Sucrose	2750.0 mg	
	Glycerine	500.0 mg	
	Buffer		35
40	Flavour	as necessary	
	Colour		
	Preservative		
	Distilled water	to 5.0 ml	40

The active ingredient, buffer, flavour, preservative and colour are dissolved in some of the water. The remainder of the water is heated to approximately 80°C and the sucrose is dissolved in this and cooled. The two solutions are mixed, adjusted to volume and clarified by filtration.

45 Claims

1. Compounds of the general formula (1)



and physiologically acceptable salts, hydrates and bioprecursors thereof, in which

R_1 represents hydrogen, C_{1-14} alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, trifluoroalkyl or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or C_{1-4} alkyl; or R_1 and R_2 may together with the nitrogen atom to which they are attached form a 5 to 10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl groups or a hydroxy group and/or may contain another heteroatom selected from oxygen or sulphur;

Alk represents a straight or branched alkylene chain of 1 to 6 carbon atoms,

Q represents a furan or thiophen ring in which incorporation into the rest of the molecule is

through bonds at the 2- and 5- positions, the furan or thiophen ring optionally bearing a further substituent R_5 adjacent to the group $R_1R_2N-Alk-$; or Q represents a thiophen ring in which incorporation into the rest of the molecule is through bonds at the 2- and 4- positions, the thiophen ring optionally bearing a further substituent R_5 adjacent to the group R_1R_2NAlk with the proviso that when the group R_1R_2NAlk is in the 4- position then the group R_5 is in the 5- position; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4- positions;

R_5 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

X represents oxygen, sulphur, $-NH-$, methylene or a bond;

Y represents oxygen, sulphur, methylene or a bond;

n represents zero, 1, 2 or 3, and m is an integer from 2 to 5, with the provisos that (a) the total number of atoms in the chain $X(CH_2)_nY(CH_2)_m$ is an integer from 3 to 8, (b) when X and Y represent oxygen or sulphur then n is 2 or 3, and (c) when X represents $-NH-$ then Q is a benzene ring and Y represents methylene or a bond;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, or C_{2-6} alkyl substituted by hydroxy or alkoxy;

R_4 represents the group $(CH_2)_pCH=CHR_6$ or $(CH_2)_qR_7$ where p is zero, 1, or 2 and q is zero, 1, 2, 3, 4, 5 or 6 and the alkylene chain $(CH_2)_q$ may be straight or branched, and

R_6 is hydroxymethyl, 1H-tetrazol-5-yl, cyano, or the group CH_2NHCOR_{17} or $CH_2NHSO_2R_{17}$ where R_{17} is alkyl; or the group COR_{19} where R_{19} is hydrogen, hydroxyl, alkyl, alkoxy, amino, alkylamino or dialkylamino; or the group $CR_{19}^a=NR_{20}$ where R_{19}^a is hydrogen or alkyl and R_{20} is hydroxy, alkoxy, aralkyloxy or $-NHC(=A)NH_2$ where A is oxygen or sulphur;

R_7 is nitro, cyano, halomethyl, heteroaryl, arylaminomethyl, aralkylaminomethyl, alkylthioalkyl, arylthioalkyl, 1H-tetrazol-5-yl, aryl $CH=NCH_2-$ or $CH_2NHC(=B)NHR_{17}$ where B is NCN, NSO_2 Methyl, NSO_2 Phenyl or $CHNO_2$;

or R_7 is the group SO_2R_8 in which R_8 is hydroxy, alkyl, aryl or the group NR_9R_{10} where R_9 and R_{10} are the same or different and represent hydrogen, alkyl, aryl or aralkyl;

or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy, alkoxy, aryloxy, aralkyloxy, alkyl, aryl, aralkyl or the group $NR_{12}R_{13}$ where R_{12} is hydrogen or alkyl optionally substituted by a hydroxy or alkoxy group, and R_{13} is hydrogen, alkyl (optionally substituted by a hydroxy or alkoxy group), alkenyl, aryl, aralkyl or cycloalkyl, or $NR_{12}R_{13}$ forms a 5 to 8 membered ring which may contain another heteroatom or a double bond and/or may be substituted by hydroxy or one or two C_{1-3} alkyl groups; or R_7 is the group $CR_{11}^a=NR_{20}$ where R_{11}^a is hydrogen, alkyl, aryl or aralkyl and R_{20} is as defined above;

or R_7 is the group $CH_2NR_{18}SO_2R_{14}$ where R_{14} is alkyl or aryl and R_{18} is hydrogen or alkyl;

or R_7 is the group $CH_2NR_{18}COR_{15}$ where R_{15} is hydrogen, alkyl, aryl, aralkyl, alkoxy, halomethyl, or the group NHR_{16} where R_{16} is hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

with the proviso that when the group R_7 contains a carbon atom through which it is linked to the alkylene group $(CH_2)_q$ then the total number of carbon atoms in the resulting chain is not greater than 6 (i.e. q is not greater than 5).

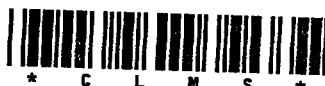
2. Compounds as claimed in Claim 1 in which R_1 represents C_{1-12} alkyl, C_{5-7} cycloalkyl, C_{3-5} alkenyl, phenyl C_{1-3} alkyl, C_{1-4} alkyl substituted by a trifluoromethyl, hydroxy, C_{1-3} alkoxy or di- C_{1-3} alkylamino group or a heteroaryl C_{1-3} alkyl group where the heteroaryl ring contains one heteroatom; and R_2 represents hydrogen, methyl or ethyl; or R_1R_2N represents a 5 to 8 membered ring optionally containing one double bond and/or substituted by one or two C_{1-3} alkyl groups or a hydroxy group.

3. Compounds as claimed in Claim 1 or 2 wherein R_4 represents nitro, alkylthiomethyl, heteroarylthiomethyl, $CH=NR_{20}$ where R_{20} is hydroxy; or the group $(CH_2)_qR_7$ where q is zero, 1 or 2, and R_7 is the group $CH_2NHC(=B)NHR_{17}$ where B is NCN or $CHNO_2$ and R_{17} is alkyl; or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy or $NR_{12}R_{13}$ where R_{12} and/or R_{13} are hydrogen or alkyl or $NR_{12}R_{13}$ forms a 5- or 6-membered ring; or R_7 is the group SO_2R_8 where R_8 is alkyl or aryl; or R_7 is the group $CH_2NHSO_2R_{14}$ or CH_2NHCOR_{15} where R_{14} is alkyl, and R_{15} is alkyl, aryl or NHR_{16} where R_{16} is aryl.

4. Compounds as claimed in any of Claims 1 to 3 in which R_3 represents hydrogen or C_{1-3} alkyl.

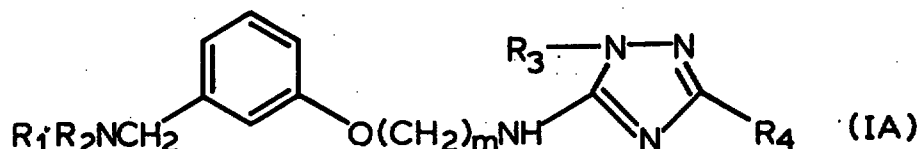
5. Compounds as claimed in any of Claims 1 to 4 in which the group Alk is methylene.

6. Compounds as claimed in any of Claims 1 to 5 in which Q is a benzene ring incorporated through bonds at the 1- and 3 position and the group $X(CH_2)_nY(CH_2)_m$ represents $-O(CH_2)_{3-5}-$ or $-O(CH_2)_2O(CH_2)_{0082}-$.



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7. Compounds as claimed in Claim 1 of the formula (IA)



where R_1R_2N is pyrrolidino, piperidino or hexamethylenimino; m is 3 or 4; R_3 is hydrogen or methyl; and R_4 is the group $(CH_2)_qR_7$, where q is zero, 1 or 2, and R_7 is methylthio-methyl, $CH_2NHC(=B)NHCH_3$ (where B is NCN or $CHNO_2$), SO_2Me , $CH=NOH$; or the group COR_{11} , where R_{11} is hydroxy, amino, dimethylamino or pyrrolidino; or the group CH_2NHSO_2Me ; or the group CH_2NHCOR_{15} where R_{15} is methyl or phenyl.

8. N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]methanesulphonamide and physiologically acceptable salts thereof.

9. 1-Methyl-3-methylsulphonylmethyl-N-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1H-1,2,4-triazole-5-amine and physiologically acceptable salts thereof.

10. N-[[1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazol-3-yl]methyl]acetamide and physiologically acceptable salts thereof.

11. 1-Methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-carboxamide and physiologically acceptable salts thereof.

12. Compounds as claimed in Claim 1 in which

R_1 represents hydrogen, C_{1-10} alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, trifluoroalkyl, or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl; and R_2 represents hydrogen or C_{1-4} alkyl; or R_1 and R_2 may together with the nitrogen atom to which they are attached form a 5 to 10 membered ring which may be saturated or may contain at least one double bond, may be unsubstituted or may be substituted by one or more C_{1-3} alkyl groups or a hydroxy group and/or may contain another heteroatom;

Alk represents a straight or branched alkylene chain of 1 to 6 carbon atoms;

Q represents a furan or thiophene ring in which incorporation into the rest of the molecule is through bonds at the 2- and 5- positions, the furan ring optionally bearing a further substituent R_5 adjacent to the group R_1R_2N-Alk ; or Q represents a benzene ring in which incorporation into the rest of the molecule is through bonds at the 1- and 3- or 1- and 4- positions;

R_5 represents halogen or C_{1-4} alkyl which may be substituted by hydroxy or C_{1-4} alkoxy;

X represents a bond; or when Q is a benzene ring and Y is methylene or a bond, $-NH-$;

Y represents oxygen, sulphur or methylene;

n represents zero, 1 or 2;

m represents 2, 3 or 4;

R_3 represents hydrogen, alkyl, alkenyl, aralkyl, or C_{2-6} alkyl substituted by hydroxy or alkoxy; and

R_4 represents the group $(CH_2)_qR_7$, where q is zero, 1, 2, 3, 4, 5 or 6 and the alkylene chain $(CH_2)_q$ may be straight or branched, and

R_7 is nitro, cyano, halomethyl, heteroaryl, arylaminomethyl, aralkylaminomethyl or Aryl $CH=NCH_2-$;

or R_7 is the group SO_2R_8 in which R_8 is alkyl, aryl or the group NR_9R_{10} where R_9 and R_{10} are the same or different and represent hydrogen, alkyl, aryl or aralkyl;

or R_7 is the group COR_{11} where R_{11} is hydrogen, hydroxy, alkoxy, aryloxy, aralkyloxy, alkyl, aryl, aralkyl or the group $NR_{12}R_{13}$ where R_{12} is hydrogen or alkyl optionally substituted by a hydroxy or alkoxy group, and R_{13} is hydrogen, alkyl optionally substituted by a hydroxy or alkoxy group, alkenyl, aryl, aralkyl or cycloalkyl, or $NR_{12}R_{13}$ forms a 5 to 8 membered ring which may contain another heteroatom, or a double bond and/or may be substituted by hydroxy one or two C_{1-3} alkyl groups;

or R_7 is the group $CR^{a_{11}}=NR_{20}$ where $R^{a_{11}}$ is hydrogen, alkyl, aryl or aralkyl, and R_{20} is hydroxy, alkoxy or $-NHC(=A)NH_2$ where A is oxygen or sulphur;

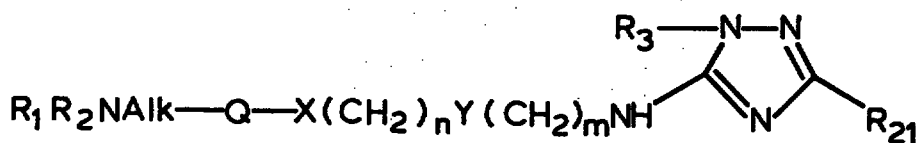
or R_7 is the group $CH_2NR_{18}SO_2R_{14}$ where R_{14} is alkyl or aryl and R_{18} is hydrogen or alkyl;

or R_7 is the group $CH_2NR_{18}COR_{15}$ where R_{15} is hydrogen, alkyl, aryl, aralkyl, alkoxy or the group NHR_{16} where R_{16} is hydrogen, alkyl, cycloalkyl, aryl or aralkyl;

with the proviso that when the group R_7 contains a carbon atom through which it is linked to the alkylene group $(CH_2)_q$ then the total number of carbon atoms in the resulting chain is not greater than 6 (i.e. is not greater than 5).

13. A process for the preparation of compounds as claimed in Claim 1 which comprises:

a) for the preparation of compounds of formula (I) in which R_7 is the group $CH_2NR_{18}COR_{15}$, $CH_2NR_{18}SO_2R_{14}$, $CH_2NHC(=B)NHR_{17}$ or $-CH_2N=CH$ Aryl or R_8 is the group CH_2NHCOR_{17} or $CH_2NHSO_2R_{17}$, treating an aminoalkyltriazole of formula (II)

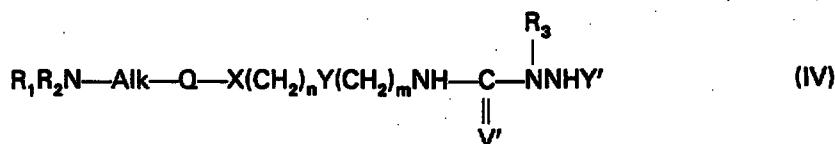


(II)

in which R_1 , R_2 and R_3 are as defined in formula (I) or are groups readily convertible thereto, and R_{21} is the group $(CH_2)_{q+1}NHR_{18}$ or the group $(CH_2)_pCH=CHCH_2NH_2$, with a compound capable of replacing the hydrogen atom in the group NHR_{18} by the group COR_{19} , SO_2R_{14} or $C(=B)NHR_{17}$, or the hydrogen atom in the group NH_2 by the group COR_{17} or SO_2R_{17} , or both hydrogen atoms in the group NHR_{18} where R_{18} is hydrogen by $=CH$ Aryl; or

b) for the preparation of compounds of formula (I) in which R_7 is the group $CH_2NHC(=B)NHR_{17}$, treating a diamine of formula (II) in which R_{21} is the group $(CH_2)_{q+1}NH_2$ with a compound of formula $LC(=B)L$ in which L is a leaving group, followed by reaction with an appropriate amine $R_{17}NH_2$; or

c) for the preparation of compounds of formula (I) in which R_4 is other than nitro, cyano, mono- or dihaloalkyl, 1H-tetrazol-5-yl, the group SO_2R_8 , the group COR_{11} where R_{11} is hydrogen, alkyl, aryl or aralkyl or the group $CR_{11}^a=NR_{20}$ cyclising a compound of formula (IV)



in which V' is



and Y' is hydrogen where V is oxygen or sulphur and R'_4 is a group as defined for R_4 or a group convertible thereto under the conditions of the cyclisation reaction or V' is NH and Y' is

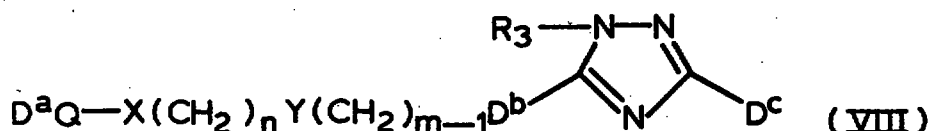


where Y'' is sulphur, oxygen or NH ; or V' is sulphur or oxygen and Y' is



or

d) reducing a compound of formula (VIII)



in which at least one of D^a , D^b and D^c represents a reducible group and the other(s) take the appropriate meaning corresponding to formula (I), where

D^a represents $R_1 R_2 NAlk$ or a group convertible thereto under reducing conditions;

D^b represents $-CH_2NH-$, $-CONH-$ or $-CH=N-$; and

D^c represents R_4 or a group convertible thereto under reducing conditions; or

e) for the preparation of compounds in which q is zero and R_7 is an activating group, heating a diamine of formula (III) with a triazole of formula (X)

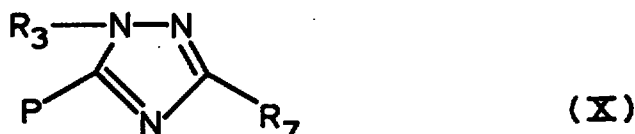
e) for the preparation of compounds in which q is zero and R_7 is an activating group, heating a diamine of formula (III)



with a triazole of formula (X)



A1



- in which P is a leaving group and R_7 is an activating group; or
- f) introducing the group $R_1R_2NCH_2-$ into the group Q present in a suitable intermediate; or
- g) for the preparation of compounds of formula (I) in which R_4 is the group $(CH_2)_qR_7$ in which R_7 is
- 5 COR_{11} (where R_{11} is hydrogen, hydroxy, alkyl, aryl or aralkyl), or SO_2R_9 oxidising the corresponding compound in which R_4 is the group $(CH_2)_qCHR_{11}OH$, $(CH_2)_qCHO$, $(CH_2)_qSR_8$ (where R_8 is other than hydroxy) or $(CH_2)_qSH$; or
- h) for the preparation of compounds of formula (I) in which R_6 is $CR^{a_{19}}=NR_{20}$ or R_7 is $CR^{a_{11}}=NR_{20}$, reacting the corresponding carbonyl compound with an appropriate reagent H_2NR_{20} ; or
- 10 i) for the preparation of compounds of formula (I) in which R_4 is the group $CH=CHCOR_{19}$ where R_{19} is alkyl or alkoxy, treating the corresponding aldehyde in which R_4 is CHO with an appropriate compound containing an activated methylene group, followed by hydrolysis and decarboxylation or for the preparations of compounds of formula (I) in which R_4 is the group $CH=CHCOR_{19}$ where R_{19} is hydroxy, heating a compound of formula (I) in which R_4 is CHO with malonic acid; or
- 15 j) for the preparation of compounds of formula (I) in which R_4 is the group $(CH_2)_qCH=CHCOR_{19}$ where R_{19} is amino, alkylamino or dialkylamino or R_4 is the group $(CH_2)_qR_7$ where R_7 is $SO_2NR_9R_{10}$ or $CONR_{12}R_{13}$, reacting an activated derivative of the corresponding carboxylic acid or sulphonic acid with ammonia or an appropriate amino HNR_9R_{10} or $HNR_{12}R_{13}$; or
- k) for the preparation of compounds of formula (I) in which R_7 is $-CO_2H$ or R_7 is $CONH_2$,
- 20 hydrolysing the corresponding ester or nitrile; or
- l) for the preparation of compounds of formula (I) in which R_7 is cyano and q is other than zero, treating a corresponding compound in which R_7 is a leaving group with an alkali metal cyanide; or
- m) for the preparation of compounds of formula (I) in which R_7 is cyano, heating an oxime of formula (I) in which R_7 is the group $-CH=NOH$ with a dehydrating agent; or
- 25 n) for the preparation of compounds of formula (I) in which R_6 or R_7 is a 1H-tetrazol-5-yl group, treating the corresponding compound of formula (I) in which R_6 or R_7 is a cyano group with an alcohol in a concentrated mineral acid to give an intermediate imidate which is treated with sodium azide; or
- o) for the production of compounds of formula (I) in which R_7 is a monohalomethyl group, treating the corresponding hydroxyalkyl compound with an appropriate acid halide;
- 30 and where the compound of formula (I) is produced in the form of a free base, optionally converting the free base into a salt.
14. A pharmaceutical composition comprising a compound as claimed in Claim 1 and at least one inert pharmaceutically acceptable carrier or diluent, optionally together with at least one other active ingredient.

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ERRATUM

SPECIFICATION No. 2 075 007 B.

Page 28, line 63, for
 $-O(CH_2)_2O(CH_2)OO82-$
 read $-O(CH_2)_2O(CH_2)_2-$

THE PATENT OFFICE
 15th September, 1983