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(54) Title: TRIAZOLO–PYRIDAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

(57) Abstract

A class of substituted 1,2,4–triazolo[4,3–*b*]pyridazine derivatives, possessing an optionally substituted cycloalkyl, phenyl or heteroaryl substituent at the 3–position, a substituted alkoxy moiety at the 6–position, and an optionally substituted bicycloalkyl ring system at the 7–position, are selective ligands for $GABA_A$ receptors, in particular having high affinity for the $\alpha 2$ and/or $\alpha 3$ subunit thereof, and are accordingly of benefit in the treatment and/or prevention of disorders of the central nervous system, including anxiety and convulsions.

TRIAZOLO-PYRIDAZINE DERIVATIVES AS LIGANDS FOR GABA RECEPTORS

The present invention relates to a class of substituted triazolo-pyridazine derivatives and to their use in therapy. More particularly, this invention is concerned with substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are ligands for $GABA_A$ receptors and are therefore useful in the therapy of deleterious mental states.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) $GABA_A$ receptors, which are members of the ligand-gated ion channel superfamily; and (2) $GABA_B$ receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual $GABA_A$ receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ε subunit and two ρ subunits.

Although knowledge of the diversity of the $GABA_A$ receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional $GABA_A$ receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ, ε and ρ subunits also exist, but are present only to a minor extent in $GABA_A$ receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native $GABA_A$ receptor exists in pentameric form. The selection of at least one α, one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional

permutations that would be possible if the arrangement of subunits around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha1\beta2\gamma2$, $\alpha2\beta2/3\gamma2$, $\alpha3\beta\gamma2/3$, $\alpha2\beta\gamma1$, $\alpha5\beta3\gamma2/3$, $\alpha6\beta\gamma2$, $\alpha6\beta\delta$ and $\alpha4\beta\delta$. Subtype assemblies containing an $\alpha1$ subunit are present in most areas of the brain and are thought to account for over 40% of $GABA_A$ receptors in the rat. Subtype assemblies containing $\alpha2$ and $\alpha3$ subunits respectively are thought to account for about 25% and 17% of $GABA_A$ receptors in the rat. Subtype assemblies containing an $\alpha5$ subunit are expressed predominantly in the hippocampus and cortex and are thought to represent about 4% of $GABA_A$ receptors in the rat.

A characteristic property of all known $GABA_A$ receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored of the $GABA_A$ receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the $GABA_A$ receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been shown to be pharmacologically equivalent to a $GABA_A$ receptor comprising the $\alpha1$ subunit in combination with a β subunit and $\gamma2$. This is the most abundant $GABA_A$ receptor subtype, and is believed to represent almost half of all $GABA_A$ receptors in the brain.

Two other major populations are the $\alpha2\beta\gamma2$ and $\alpha3\beta\gamma2/3$ subtypes. Together these constitute approximately a further 35% of the total $GABA_A$ receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha5$-containing subtype assemblies. The physiological role of these subtypes has hitherto

been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha1\beta\gamma2$, $\alpha2\beta\gamma2$ or $\alpha3\beta\gamma2$ subunits will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the $GABA_A$ receptor by acting as BZ agonists are referred to hereinafter as "$GABA_A$ receptor agonists". The $\alpha1$-selective $GABA_A$ receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through $GABA_A$ receptors containing the $\alpha1$ subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the $\alpha2$ and/or $\alpha3$ subunit than with $\alpha1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at $\alpha1$ might be employed to reverse sedation or hypnosis caused by $\alpha1$ agonists.

The compounds of the present invention, being selective ligands for $GABA_A$ receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; and hearing loss. Selective ligands for $GABA_A$ receptors may also be effective as pre-medication prior to anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

In DE-A-2741763, and in US Patents 4,260,755, 4,260,756 and 4,654,343, are described various classes of 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are alleged to be useful as anxiolytic agents. The compounds described in DE-A-2741763 and in US Patents 4,260,755 and 4,654,343 possess a phenyl substituent at the 6-position of the triazolo-pyridazine ring system. The compounds described in US Patent 4,260,756, meanwhile, possess a heteroaryl moiety at the 6- or 8-position. In none of these publications, however, is there any disclosure or suggestion of 1,2,4-triazolo[4,3-*b*]pyridazine derivatives wherein the substituent at the 6-position is attached through a directly linked oxygen atom.

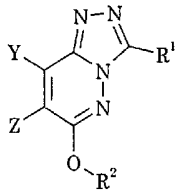
EP-A-0085840 and EP-A-0134946 describe related series of 1,2,4-triazolo[3,4-*a*]phthalazine derivatives which are stated to possess antianxiety activity. However, there is no disclosure nor any suggestion in either of these publications of replacing the benzo moiety of the triazolo-phthalazine ring system with any other functionality.

The present invention provides a class of triazolo-pyridazine derivatives which possess desirable binding properties at various $GABA_A$ receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the $\alpha 2$ and/or $\alpha 3$ subunit of the human $GABA_A$ receptor. The compounds of this invention may interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with the $\alpha 1$ subunit. Desirably, the compounds of the invention will exhibit functional

selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

The compounds of the present invention are $GABA_A$ receptor subtype ligands having a binding affinity (K_i) for the α2 and/or α3 subunit, as measured in the assay described hereinbelow, of 100 nM or less, typically of 50 nM or less, and ideally of 10 nM or less. The compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the α2 and/or α3 subunit relative to the α1 subunit. However, compounds which are not selective in terms of their binding affinity for the α2 and/or α3 subunit relative to the α1 subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit.

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



(I)

wherein

Y represents hydrogen or C_{1-6} alkyl;

Z represents an optionally substituted C_{6-8} bicycloalkyl moiety;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted; and

R^2 represents cyano(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, propargyl, C_{3-7} heterocycloalkylcarbonyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

The groups Z, R^1 and R^2 may be unsubstituted, or substituted by one or more, suitably by one or two, substituents. In general, the groups Z, R^1 and R^2 will be unsubstituted or monosubstituted. Examples of optional substituents on the groups Z, R^1 and R^2 include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxy, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, C_{3-7} cycloalkoxy, amino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl, di(C_{1-6})alkylmorpholinyl(C_{1-6})alkyl and imidazolyl(C_{1-6})alkyl. Representative substituents include C_{1-6} alkyl, aryl(C_{1-6})alkyl, halogen, cyano, hydroxy, hydroxymethyl, C_{1-6} alkoxy and C_{3-7} cycloalkyl(C_{1-6})alkoxy, especially C_{1-6} alkyl or halogen.

As used herein, the expression "C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 1,1-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy" are to be construed accordingly.

Typical C_{3-7} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The expression "C_{3-7} cycloalkyl(C_{1-6})alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

Typical aryl groups include phenyl and naphthyl, preferably phenyl.

The expression "aryl(C_{1-6})alkyl" as used herein includes benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl,

indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

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

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

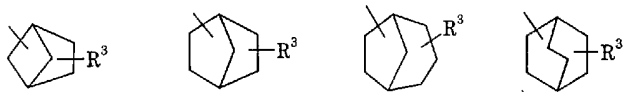
The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily

convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

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

Suitably, Y represents hydrogen or methyl, especially hydrogen.

Examples of suitable bicycloalkyl moieties for the group Z include the ring systems of formula Za, Zb, Zc and Zd:



(Za) (Zb) (Zc) (Zd)

wherein R^3 represents hydrogen, halogen or C_{1-6} alkyl.

Particular values of R^3 include hydrogen, fluoro and methyl, especially hydrogen.

Typical bicycloalkyl moieties for the group Z include the ring systems of formula Za and Zb as depicted above. One particular bicycloalkyl moiety Z is represented by the ring system of formula Zb as depicted above. Another particular bicycloalkyl moiety Z is represented by the ring system of formula Za as depicted above.

Specific examples of the bicycloalkyl moiety Z include bicyclo[2.1.1]hex-1-yl and bicyclo[2.2.1]hept-1-yl. In one typical embodiment, the group Z represents bicyclo[2.2.1]hept-1-yl. In another typical embodiment, the group Z represents bicyclo[2.1.1]hex-1-yl.

Examples of typical optional substituents on the group R^1 include methyl, fluoro and methoxy.

Representative values of R^1 include cyclopropyl, phenyl, methylphenyl, fluorophenyl, difluorophenyl, methoxyphenyl, furyl, thienyl, methyl-thienyl and pyridinyl. Suitably, R^1 may represent unsubstituted or monosubstituted phenyl. Specific values of R^1 include phenyl and fluorophenyl. More particularly, R^1 represents phenyl.

Suitable values for the substituent R^2 in the compounds according to the invention include cyanomethyl, hydroxybutyl, cyclohexylmethyl, propargyl, pyrrolidinylcarbonylmethyl, benzyl, pyrazolylmethyl, isoxazolylmethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, benzimidazolylmethyl, oxadiazolylmethyl, triazolylmethyl, tetrazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl, any of which groups may be optionally substituted by one or more substituents. Typical values of R^2 include triazolylmethyl and pyridinylmethyl, either of which groups may be optionally substituted.

Examples of suitable optional substituents on the group R^2 include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, amino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, (C_{1-6})alkyl, morpholinyl(C_{1-6})alkyl and di(C_{1-6})alkylmorpholinyl(C_{1-6})alkyl.

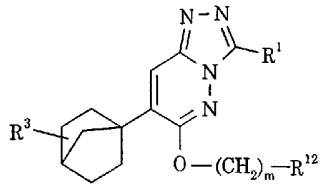
Specific illustrations of particular substituents on the group R^2 include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, chloromethyl, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, aminoethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl, *N*-methylpiperidinyl, pyrrolidinylethyl, piperazinylethyl, morpholinylmethyl and dimethylmorpholinylmethyl, especially methyl.

Representative values of R^2 include cyanomethyl, hydroxybutyl, hydroxymethyl-cyclohexylmethyl, propargyl, dimethylaminomethyl-propargyl, dimethylmorpholinylmethyl-propargyl, pyrrolidinylcarbonylmethyl, cyanobenzyl, hydroxymethyl-benzyl, pyrazolylmethyl, dimethyl-pyrazolylmethyl, methyl-isoxazolylmethyl, thiazolylmethyl, methyl-thiazolylmethyl, ethyl-thiazolylmethyl, methyl-thiazolylethyl, imidazolylmethyl, methyl-imidazolylmethyl, ethyl-imidazolylmethyl, benzyl-imidazolylmethyl, benzimidazolylmethyl, methyl-oxadiazolylmethyl, triazolylmethyl, methyl-triazolylmethyl, propyl-triazolylmethyl, benzyl-triazolylmethyl, pyridinylmethyl-triazolylmethyl, cyanomethyl-triazolylmethyl, dimethylaminomethyl-triazolylmethyl, aminoethyl-triazolylmethyl, dimethylaminoethyl-triazolylmethyl, dimethylaminocarbonylmethyl-triazolylmethyl, *N*-methylpiperidinyl-triazolylmethyl, pyrrolidinylethyl-triazolylmethyl, piperazinylethyl-triazolylmethyl, morpholinylethyl-triazolylmethyl, methyl-tetrazolylmethyl, pyridinylmethyl, methyl-pyridinylmethyl, dimethyl-pyridinylmethyl, ethoxy-pyridinylmethyl, cyclopropylmethoxy-pyridinylmethyl, pyridazinylmethyl, chloro-pyridazinylmethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl, isoquinolinylmethyl and quinoxalinylmethyl.

Specific values of R^2 include methyl-triazolylmethyl, pyridinylmethyl and methyl-pyridinylmethyl.

A favoured value of R^2 is methyl-triazolylmethyl.

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



(IIA)

wherein

R^1 and R^3 are as defined above;

m is 1 or 2, preferably 1; and

R^{12} represents aryl or heteroaryl, either of which groups may be optionally substituted.

Suitable values for R^{12} include phenyl, pyrazolyl, isoxazolyl, thiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl, any of which groups may be optionally substituted.

Particular values for R^{12} include triazolyl and pyridinyl, either of which groups may be optionally substituted.

Examples of typical substituents on the group R^{12} include C_{1-6} alkyl, aryl(C_{1-6})alkyl, pyridyl(C_{1-6})alkyl, halogen, cyano, cyano(C_{1-6})alkyl, hydroxymethyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl(C_{1-6})alkoxy, di(C_{1-6})alkylamino(C_{1-6})alkyl, amino(C_{1-6})alkyl, di(C_{1-6})alkylaminocarbonyl(C_{1-6})alkyl, *N*-(C_{1-6})alkylpiperidinyl, pyrrolidinyl(C_{1-6})alkyl, piperazinyl(C_{1-6})alkyl and morpholinyl(C_{1-6})alkyl.

Illustrative values of specific substituents on the group R^{12} include methyl, ethyl, *n*-propyl, benzyl, pyridinylmethyl, chloro, cyano, cyanomethyl, hydroxymethyl, ethoxy, cyclopropylmethoxy, dimethylaminomethyl, aminoethyl, dimethylaminoethyl, dimethylaminocarbonylmethyl, *N*-methylpiperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylmethyl, especially methyl.

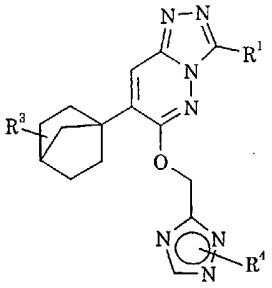
Particular values of R^{12} include cyanophenyl, hydroxymethyl-phenyl, pyrazolyl, dimethyl-pyrazolyl, methyl-isoxazolyl, thiazolyl, methyl-

thiazolyl, ethyl-thiazolyl, imidazolyl, methyl-imidazolyl, ethyl-imidazolyl, benzyl-imidazolyl, benzimidazolyl, methyl-oxadiazolyl, triazolyl, methyl-triazolyl, propyl-triazolyl, benzyl-triazolyl, pyridinylmethyl-triazolyl, cyanomethyl-triazolyl, dimethylaminomethyl-triazolyl, aminoethyl-triazolyl, dimethylaminoethyl-triazolyl, dimethylaminocarbonylmethyl-triazolyl, *N*-methylpiperidinyl-triazolyl, pyrrolidinylethyl-triazolyl, piperazinylethyl-triazolyl, morpholinylethyl-triazolyl, methyl-tetrazolyl, pyridinyl, methyl-pyridinyl, dimethyl-pyridinyl, ethoxy-pyridinyl, cyclopropylmethoxy-pyridinyl, pyridazinyl, chloro-pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and quinoxalinyl.

Specific values of R^{12} include methyl-triazolyl, pyridinyl and methyl-pyridinyl.

A favoured value of R^{12} is methyl-triazolyl.

A particular subset of the compounds of formula IIA above is represented by the compounds of formula IIB, and pharmaceutically acceptable salts thereof:



(IIB)

wherein

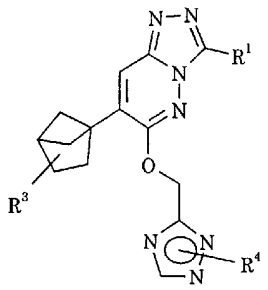
R^1 and R^3 are as defined above; and

R^4 represents hydrogen or methyl.

In relation to formula IIB above, R^1 suitably represents phenyl.

Suitably, R^4 represents methyl.

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



(IIC)

wherein R^1, R^3 and R^4 are as defined above.

In relation to formula IIC above, R^1 suitably represents fluorophenyl.

Specific compounds within the scope of the present invention include:

7-(bicyclo[2.2.1]hept-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(6-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.1.1]hex-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.1.1]hex-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;
and salts and prodrugs thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof or a prodrug thereof.

The binding affinity (K_i) of the compounds according to the present invention for the α3 subunit of the human $GABA_A$ receptor is conveniently as measured in the assay described hereinbelow. The α3 subunit binding affinity (K_i) of the compounds of the invention is ideally 10 nM or less, preferably 2 nM or less, and more preferably 1 nM or less.

The compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at most a 10%, potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α1 subunit of the human $GABA_A$ receptor.

The potentiation of the GABA EC_{20} response in stably transfected cell lines expressing the α3 and α1 subunits of the human $GABA_A$ receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, **50**, 670-678. The

procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk- fibroblast cells.

The compounds according to the present invention exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, **121**, 109-117). Moreover, the compounds of the invention are substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al., J. Psychopharmacol.*, 1996, **10**, 206-213).

The compounds according to the present invention may also exhibit anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, **279**, 492-501.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

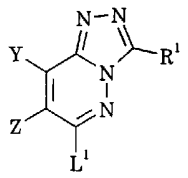
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium

stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

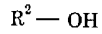
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut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

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

The compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



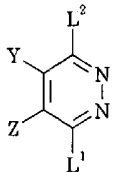
(IV)

wherein Y, Z, R^1 and R^2 are as defined above; and L^1 represents a suitable leaving group.

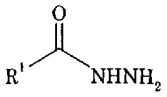
The leaving group L^1 is typically a halogen atom, especially chloro.

The reaction between compounds III and IV is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride or lithium bis(trimethylsilyl)amide.

The intermediates of formula III above may be prepared by reacting a compound of formula V with a substantially equimolar amount of a hydrazine derivative of formula VI:



(V)



(VI)

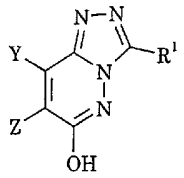
wherein Y, Z, R^1 and L^1 are as defined above, and L^2 represents a suitable leaving group; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

The leaving group L^2 is typically a halogen atom, especially chloro. In the intermediates of formula V, the leaving groups L^1 and L^2 may be the same or different, but are suitably the same, preferably both chloro.

The reaction between compounds V and VI is conveniently effected by heating the reactants in the presence of a proton source such as triethylamine hydrochloride, typically at reflux in an inert solvent such as xylene or 1,4-dioxane.

The reaction between compounds V and VI will, as indicated above, usually give rise to a mixture of isomeric products depending upon whether the hydrazine derivative VI displaces the leaving group L^1 or L^2. Thus, in addition to the required product of formula III, the isomeric compound wherein the Y and Z moieties are reversed will usually be obtained to some extent. For this reason it will generally be necessary to separate the resulting mixture of isomers by conventional methods such as chromatography.

In another procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula VII with a compound of formula VIII:



(VII)

(VIII)

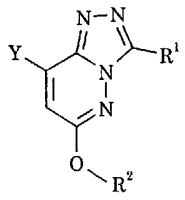
wherein Y, Z, R^1 and R^2 are as defined above; and L^3 represents a suitable leaving group.

The leaving group L^3 is suitably a halogen atom, typically chloro or bromo.

The reaction between compounds VII and VIII is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride.

The intermediates of formula VII above may conveniently be prepared by reacting a compound of formula III as defined above with an alkali metal hydroxide, e.g. sodium hydroxide. The reaction is conveniently effected in an inert solvent such as aqueous 1,4-dioxane, ideally at the reflux temperature of the solvent.

In a further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula Z-CO_2H with a compound of formula IX:

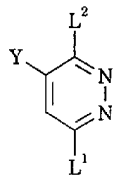


(IX)

wherein Y, Z, R^1 and R^2 are as defined above; in the presence of silver nitrate and ammonium persulphate.

The reaction is conveniently carried out under acidic conditions in a suitable solvent, for example using sulphuric acid in water or aqueous acetonitrile, typically at an elevated temperature.

Similarly, the intermediates of formula V above may be prepared by reacting a compound of formula $Z\text{-}CO_2H$ with a compound of formula X:

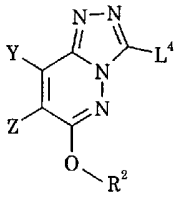


(X)

wherein Y, Z, L^1 and L^2 are as defined above; in the presence of silver nitrate and ammonium persulphate; under conditions analogous to those described above for the reaction between $Z\text{-}CO_2H$ and compound IX; followed, if necessary, by separation of any resulting mixture of isomers by conventional means such as chromatography.

The intermediates of formula IX correspond to the compounds of formula I as defined above wherein Z is hydrogen, and they may therefore be prepared by methods analogous to those described above for preparing the corresponding compounds of formula I.

In a still further procedure, the compounds of formula I as defined above may be prepared by a process which comprises reacting a compound of formula XI with a compound of formula XII:



(XI)

R^1 — $Sn(Alk)_3$

(XII)

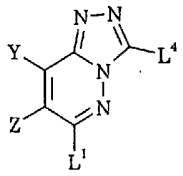
wherein Y, Z, R^1 and R^2 are as defined above, Alk represents a C_{1-6} alkyl group, typically *n*-butyl, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

The leaving group L^4 is suitably a halogen atom, e.g. bromo.

A suitable transition metal catalyst of use in the reaction between compounds XI and XII comprises dichlorobis(triphenylphosphine)-palladium(II).

The reaction between compounds XI and XII is conveniently effected in an inert solvent such as *N,N*-dimethylformamide, typically at an elevated temperature.

The intermediates of formula XI may be prepared by reacting a compound of formula IV as defined above with a compound of formula XIII:



(XIII)

wherein Y, Z, L^1 and L^4 are as defined above; under conditions analogous to those described above for the reaction between compounds III and IV.

Where they are not commercially available, the starting materials of formula IV, VI, VIII, X, XII and XIII may be prepared by methods

analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I initially obtained wherein R^2 is unsubstituted may be converted into a corresponding compound wherein R^2 is substituted, typically by standard alkylation procedures, for example by treatment with a haloalkyl derivative in the presence of sodium hydride and *N,N*-dimethylformamide, or with a hydroxyalkyl derivative in the presence of triphenylphosphine and diethyl azodicarboxylate. Furthermore, a compound of formula I initially obtained wherein R^2 represents cyano(C_{1-6})alkyl may be converted into the corresponding 3-substituted 1,2,4-triazol-5-yl(C_{1-6})alkyl analogue by treatment with the appropriate acyl hydrazine derivative in the presence of a base such as sodium methoxide. Similarly, a compound of formula I initially obtained wherein R^2 represents an optionally substituted propargyl moiety may be converted into the corresponding 1,2,3-triazolylmethyl analogue by treatment with azide anion. A compound of formula I initially obtained wherein the R^2 substituent is substituted by a halogen atom, e.g. chloro, may be converted into the corresponding compound wherein the R^2 substituent is substituted by a di(C_{1-6})alkylamino moiety by treatment with the appropriate di(C_{1-6})alkylamine, typically with heating in a solvent such as 1,4-dioxane in a sealed tube.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds

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

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

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

The compounds in accordance with this invention potently inhibit the binding of [^{3}H]-flumazenil to the benzodiazepine binding site of human $GABA_A$ receptors containing the α2 or α3 subunit stably expressed in Ltk$^-$ cells.

Reagents

- Phosphate buffered saline (PBS).
- Assay buffer: 10 mM KH_2PO_4, 100 mM KCl, pH 7.4 at room temperature.
- [^{3}H]-Flumazenil (18 nM for α1β3γ2 cells; 18 nM for α2β3γ2 cells; 10 nM for α3β3γ2 cells) in assay buffer.
- Flunitrazepam 100 μM in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 µl of assay buffer.
- 50 µl of [^{3}H]-flumazenil (final concentration for $\alpha1\beta3\gamma2$: 1.8 nM; for $\alpha2\beta3\gamma2$: 1.8 nM; for $\alpha3\beta3\gamma2$: 1.0 nM).
- 50 µl of buffer or solvent carrier (e.g. 10% DMSO) if compounds are dissolved in 10% DMSO (total); test compound or flunitrazepam (to determine non-specific binding), 10 µM final concentration.
- 100 µl of cells.

Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of

[^{3}H]-flumazenil from the α2 and/or α3 subunit of the human $GABA_A$ receptor of 100 nM or less.

EXAMPLE 1

7-(Bicyclo[2.2.1]hept-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

a) 4-(Bicyclo[2.2.1]hept-1-yl)-3,6-dichloropyridazine

Concentrated sulphuric acid (2.17ml, 40mM) was added carefully to a suspension of 3,6-dichloropyridazine (2.11g, 14.3mM) in water (50ml). This mixture was then heated to 70°C and bicyclo[2.2.1]heptane-1-carboxylic acid (*Org. Synth.*, ***59***, *85*; 2.0g, 14.3mM) was added. After ten minutes a solution of silver nitrate (0.48g, 2.8mM) in water (5ml) was added dropwise over two minutes. A solution of ammonium persulphate (9.8g, 43mM) in water (20ml) was added over 20 minutes. The reaction was heated at 70°C for a further 40 minutes and then allowed to cool to room temperature. The mixture was poured onto ice and basified with concentrated aqueous ammonia; the temperature was kept below 10°C by addition of more ice. The aqueous phase was extracted with dichloromethane (3 x 200ml) and the combined extracts were dried ($MgSO_4$), filtered and evaporated to give the crude product, which was purified by column chromatography using ethyl acetate/hexane mixtures as the eluent to give the title compound (3.4g). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.49-2.00 (8H, m), 2.17 (2H, m), 2.43 (1H, m), 7.45 (1H, s); MS (ES^+) m/e 244 $[MH]^+$.

b) 7-(Bicyclo[2.2.1]hept-1-yl)-6-chloro-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

A mixture of 4-(bicyclo[2.2.1]hept-1-yl)-3,6-dichloropyridazine (1g, 4.1mM), benzoic hydrazide (0.84g, 6.2mM) and triethylamine

hydrochloride (0.85g, 6.2mM) in *p*-xylene (80ml) was heated at reflux for 18 hours, after which time more benzoic hydrazide (0.28g, 2mM) and triethylamine hydrochloride (0.28g, 2mM) were added and the reaction heated at reflux for a further 3 hours. The mixture was allowed to cool, then placed directly onto silica gel for purification by column chromatography using ethyl acetate/hexane mixtures as the eluent. This yielded the title compound (0.38g, lower R_f of the two isomeric products). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.55-2.06 (8H, m), 2.22 (2H, m), 2.44 (1H, m), 7.25 (3H, m), 8.13 (1H, s), 8.45 (2H, m); MS (ES^+) m/e 244 $[MH]^+$.

c) 7-(Bicyclo[2.2.1]hept-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

To a solution of 7-(bicyclo[2.2.1]hept-1-yl)-6-chloro-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine (0.125g, 0.39mM) and (2-methyl-2*H*-1,2,4-triazol-3-yl)methanol (0.08g, 0.47mM; prepared using the conditions described in EP-A-421210) in *N,N*-dimethylformamide (20ml) was added sodium hydride (0.015g of a 60% dispersion in oil, 0.47 mM eq) and the reaction mixture was stirred at room temperature for 3 hours. Water was added until the solution became cloudy and after stirring for a further 15 minutes a solid was collected by filtration. This solid was recrystallised from ethyl acetate-dichloromethane to give the required product (0.048g, m.p. = 244-246°C). ^{1}H NMR (360 MHz, DMSO) δ 1.39 (2H, m), 1.67-1.84 (8H, m), 2.30 (1H, m), 3.93 (3H, s), 5.70 (2H, s), 7.52-7.62 (3H, m), 8.00 (1H, s), 8.35 (1H, s), 8.38 (2H, m); (Regiochemistry was established using nOe data). MS (ES^+) m/e 402 $[MH]^+$. Anal. Found C, 65.71; H, 5.65; N, 24.07. $C_{22}H_{23}N_7O$ requires C, 65.82; H, 5.77; N, 24.42%.

EXAMPLE 2

7-(Bicyclo[2.2.1]hept-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

This compound was prepared using the procedure described in Example 1 step c with (1-methyl-1*H*-1,2,4-triazol-3-yl)methanol (prepared using the conditions described in EP-A-421210) used instead of (2-methyl-2*H*-1,2,4-triazol-3-yl)methanol. Data for the title compound: m.p. = 218-220°C; ^{1}H NMR (360 MHz, DMSO) δ 1.39 (2H, m), 1.68-1.90 (8H, m), 2.31 (1H, m), 3.88 (3H, s), 5.51 (2H, s), 7.52-7.63 (3H, m), 8.09 (1H, s), 8.44 (2H, m), 8.56 (1H, s); MS (ES$^+$) m/e 402 [MH]$^+$. Anal. Found C, 65.65; H, 5.58; N, 24.22. $C_{22}H_{23}N_7O$ requires C, 65.82; H, 5.77; N, 24.42%.

EXAMPLE 3

7-(Bicyclo[2.2.1]hept-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine

To a solution of 7-(bicyclo[2.2.1]hept-1-yl)-6-chloro-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine (0.08g, 0.25mM, Example 1, step b) and 2-pyridylcarbinol (0.06ml, 0.5mM) in *N,N*-dimethylformamide (2ml) under nitrogen was added lithium bis(trimethylsilyl)amide as a 1 mol solution in hexanes (0.375ml). The reaction was stirred for 3 hours. Water was added until the solution became cloudy and after stirring for a further 15 minutes a solid was collected by filtration. This solid was recrystallised from ethyl acetate-hexane to give the required product (0.050g, m.p. = 166-168°C). ^{1}H NMR (360 MHz, DMSO) δ 1.55 (2H, m), 1.91 (4H, m), 1.97 (2H, m), 2.13 (2H, m), 2.49 (1H, m), 5.77 (2H, s), 7.54 (1H, m), 7.69 (4H, s), 8.00 (1H, t, *J* = 7.6 Hz), 8.28 (1H, s), 8.34 (2H, dd, *J* = 7.6 and 1.5 Hz), 8.80 (1H, m); MS (ES$^+$) m/e 398 [MH]$^+$. Anal. Found C, 72.16; H, 5.59; N, 17.41. $C_{24}H_{23}N_5O$. $0.1H_2O$ requires C, 72.20; H, 5.86; N, 17.54%.

EXAMPLE 4

7-(Bicyclo[2.2.1]hept-1-yl)-6-(6-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

This compound was prepared using the procedure described in Example 3 with 6-methyl-2-pyridylcarbinol used instead of 2-pyridylcarbinol. Data for the title compound: m.p. = 162-164°C; ^{1}H NMR (360 MHz, DMSO) δ 1.66 (2H, m), 1.99-2.13 (8H, m), 2.59 (1H, m), 2.22 (3H, s), 5.93 (2H, s), 7.62 (1H, m), 7.89 (3H, s), 8.00 (1H, d, J = 7.4 Hz), 8.40 (1H, s), 8.61 (2H, dd, J = 7.4 and 1.5 Hz), 8.71 (1H, m); MS (ES$^+$) m/e 412 [MH]$^+$. Anal. Found C, 73.15; H, 5.97; N, 16.95. $C_{25}H_{25}N_5O$ requires C, 72.97; H, 6.12; N, 17.02%.

EXAMPLE 5

7-(Bicyclo[2.2.1]hept-1-yl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine

This compound was prepared using the procedure described in Example 3 with 3-methyl-2-pyridylcarbinol used instead of 2-pyridylcarbinol. Data for the title compound: m.p. = 214-216°C; ^{1}H NMR (360 MHz, DMSO) δ 1.39 (2H, m), 1.73-1.97 (8H, m), 2.32 (1H, m), 2.49 (3H, s), 5.55 (2H, s), 7.20 (2H, m), 7.53 (3H, s), 7.73 (1H, m), 8.09 (1H, s), 8.28 (2H, dd, J = 7.4 and 1.5 Hz); MS (ES$^+$) m/e 412 [MH]$^+$. Anal. Found C, 73.10; H, 6.01; N, 17.02. $C_{25}H_{25}N_5O$ requires C, 72.97; H, 6.12; N, 17.02%.

EXAMPLE 6

7-(Bicyclo[2.1.1]hex-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

This compound was prepared using the procedure described in Example 1a-c with bicyclo[2.1.1]hexane-1-carboxylic acid used instead of bicyclo[2.2.1]heptane-1-carboxylic acid (*Org. Prep. & Procedures Int.*, 1980, **12**, 357-360), and 2-fluorobenzhydrazide instead of benzoic hydrazide. Data for the title compound: m.p. = 198-200°C; ^{1}H NMR (360 MHz,

DMSO) δ 1.55 (2H, m), 1.78-1.85 (6H, m), 2.57 (1H, m), 3.18 (3H, s), 5.47 (2H, s), 7.24-7.37 (2H, m), 7.57 (1H, m), 7.77 (1H, s), 7.82-7.88 (2H, m); MS (ES^+) m/e 406 $[MH]^+$. Anal. Found C, 62.24; H, 4.91; N, 24.08. $C_{21}H_{20}FN_7O$ requires C, 62.21; H, 4.97; N, 24.18%.

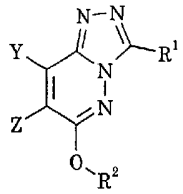
EXAMPLE 7

7-(Bicyclo[2.1.1]hex-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

This compound was prepared using the procedure described in Example 6 with (1-methyl-1*H*-1,2,4-triazol-3-yl)methanol (prepared using the conditions described in EP-A-421210) used instead of (2-methyl-2*H*-1,2,4-triazol-3-yl)methanol. Data for the title compound: m.p. = 170-172°C; ^1H NMR (360 MHz, DMSO) δ 1.58 (2H, m), 1.79-1.92 (6H, m), 2.54 (1H, m), 3.92 (3H, s), 5.39 (2H, s), 7.23-7.34 (2H, m), 7.53 (1H, m), 7.73 (1H, s), 7.92-7.97 (2H, m), 8.02 (1H, s); MS (ES^+) m/e 406 $[MH]^+$. Anal. Found C, 61.89; H, 4.70; N, 23.68. $C_{21}H_{20}FN_7O.0.2\ H_2O$ requires C, 61.66; H, 5.03; N, 23.97%.

CLAIMS:

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



(I)

wherein

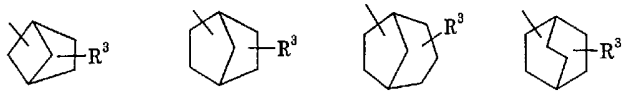
Y represents hydrogen or C_{1-6} alkyl;

Z represents an optionally substituted C_{6-8} bicycloalkyl moiety;

R^1 represents C_{3-7} cycloalkyl, phenyl, furyl, thienyl or pyridinyl, any of which groups may be optionally substituted; and

R^2 represents cyano(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, propargyl, C_{3-7} heterocycloalkylcarbonyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

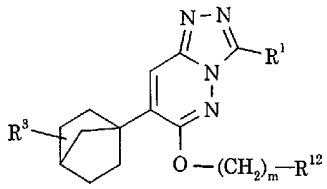
2. A compound as claimed in claim 1 wherein Z represents a ring system of formula Za, Zb, Zc or Zd:



(Za) (Zb) (Zc) (Zd)

wherein R^3 represents hydrogen, halogen or C_{1-6} alkyl.

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



(IIA)

wherein

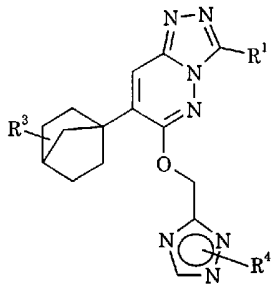
R^1 is as defined in claim 1;

R^3 is as defined in claim 2;

m is 1 or 2; and

R^{12} represents aryl or heteroaryl, either of which groups may be optionally substituted.

4. A compound as claimed in claim 3 represented by formula IIB, and pharmaceutically acceptable salts thereof:



(IIB)

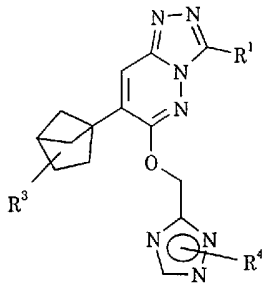
wherein

R^1 is as defined in claim 1;

R^3 is as defined in claim 2; and

R^4 represents hydrogen or methyl.

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



(IIC)

wherein R^1 is as defined in claim 1;

R^3 is as defined in claim 2; and

R^4 is as defined in claim 4.

6. A compound selected from:

7-(bicyclo[2.2.1]hept-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-3-phenyl-6-(pyridin-2-ylmethoxy)-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(6-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.2.1]hept-1-yl)-6-(3-methylpyridin-2-ylmethoxy)-3-phenyl-1,2,4-triazolo[4,3-*b*]pyridazine;

7-(bicyclo[2.1.1]hex-1-yl)-6-(2-methyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;

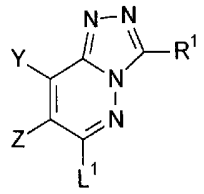
7-(bicyclo[2.1.1]hex-1-yl)-6-(1-methyl-1*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine;

and salts and prodrugs thereof.

7. A triazolopyridazine derivative, substantially as hereinbefore described with reference to any one of the examples.

8. A process for the preparation of a compound as claimed in claim 1, which comprises:

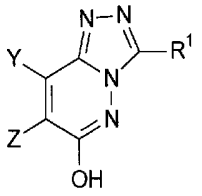
(A) reacting a compound of formula III with a compound of formula IV:



(III) R^2-OH (IV)

wherein Y, Z, R^1 and R^2 are as defined in claim 1, and L^1 represents a suitable leaving group; or

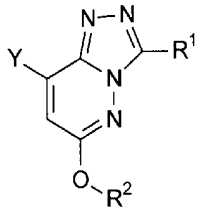
(B) reacting a compound of formula VII with a compound of formula VIII:



(VII) R^2-L^3 (VIII)

wherein Y, Z, R^1 and R^2 are as defined in claim 1, and L^3 represents a suitable leaving group; or

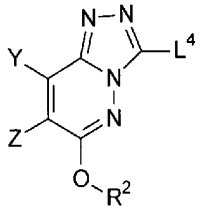
(C) reacting a compound of formula Z-CO_2H with a compound of formula IX:



(IX)

wherein Y, Z, R^1 and R^2 are as defined in claim 1, in the presence of silver nitrate and ammonium persulphate; or

(D) reacting a compound of formula XI with a compound of formula XII:



(XI) $R^1-Sn(Alk)_3$ (XII)

wherein Y, Z, R^1 and R^2 are as defined in claim 1, Alk represents a C_{1-6} alkyl group, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst; and

(E) subsequently, if desired, converting a compound of formula I initially obtained into a further compound of formula I by standard methods.

9. A process for the preparation of a triazolopyridazine derivative, substantially as hereinbefore described with reference to any one of the examples.

10. The product of the process of claim 8 or claim 9.

11. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof or a prodrug thereof in association with a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising a compound according to one of claims 2-7 or 10 or a prodrug thereof in association with a pharmaceutically acceptable carrier.

13. The use of a compound as claimed in any one of claims 1 to 7 or 10 for the manufacture of a medicament for the treatment and/or prevention of anxiety.

14. The use of a compound as claimed in any one of claims 1 to 7 or 10 for the manufacture of a medicament for the treatment and/or prevention of convulsions.

15. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

16. A method for the treatment and/or prevention of convulsions which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

17. A compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof, when used for the treatment and/or prevention of anxiety in a patient in need thereof.

18. A compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof, when used for the treatment and/or prevention of convulsions in a patient in need thereof.

19. A method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment a compound according to any one of claims 2-7 or 10.

20. A method for the treatment and/or prevention of convulsions which comprises administering to a patient in need of such treatment a compound according to any one of claims 2-7 or 10.

21. A compound according to any one of claims 2-7 or 10, when used for the treatment and/or prevention of anxiety in a patient in need thereof.

22. A compound according to any one of claims 2-7 or 10, when used for the treatment and/or prevention of convulsions in a patient in need thereof.

Dated 25 February, 2002

Merck Sharpe & Dohme Limited

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON