A SUBSTITUTED TRIAZOLO-PYRIDAZINE DERIVATIVE, PHARMACEUTICAL COMPOSITIONS MADE THEREFROM

The present invention relates to a substituted triazolo-pyridazine derivative and to its use in therapy. More particularly, this invention is concerned with a particular substituted 1,2,4-triazolo[4,3-*b*]pyridazine derivative which is a $GABA_A$ receptor ligand and is 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 α1βγ2, α2βγ2 or α3βγ2 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 α1-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 α1 subunit. Accordingly, it is considered that $GABA_A$ receptor agonists which interact more favourably with the α2 and/or α3 subunit than with α1 will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Also, agents which are antagonists or inverse agonists at α1 might be employed to reverse sedation or hypnosis caused by α1 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.

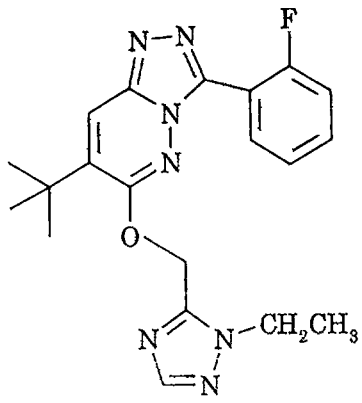
Further disorders for which selective ligands for $GABA_A$ receptors may be of benefit include pain and nociception; emesis, including acute, delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as post-operative nausea and vomiting; eating disorders including 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.

WO 98/04559 describes a class of substituted and 7,8-ring fused 1,2,4-triazolo[4,3-*b*]pyridazine derivatives which are stated to be selective ligands for $GABA_A$ receptors beneficial in the treatment and/or prevention of neurological disorders including anxiety and convulsions.

The present invention provides a particular triazolo-pyridazine derivative, and pharmaceutically acceptable salts thereof, 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 α2 and/or α3 subunit of the human $GABA_A$ receptor. The compounds of this invention interact more favourably with the α2 and/or α3 subunit than with the α1 subunit. Indeed, the compounds of the invention 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 less than 1 nM. Furthermore, the compounds in accordance with this invention exhibit functional selectivity in terms of a selective efficacy for the α2 and/or α3 subunit relative to the α1 subunit. Moreover, the compounds according to the present invention possess interesting pharmacokinetic properties, notably in terms of improved oral bioavailability.

The present invention provides 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine of formula I:



(I)

or a pharmaceutically acceptable salt thereof.

The compounds in accordance with the present invention are encompassed within the generic scope of WO 98/04559. There is, however, no specific disclosure therein of the compound of formula I as depicted above, or pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compound of formula I above will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compound of formula I or of its pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compound of formula I include acid addition salts which may, for example, be formed by mixing a solution of the compound of formula I 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.

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 the compound of formula I as depicted above or a pharmaceutically acceptable salt 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 the compound of formula I as depicted above or a pharmaceutically acceptable salt 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 less than 1 nM.

The compounds according to the present invention elicit a selective potentiation of the GABA EC_{20} response in stably transfected recombinant cell lines expressing the α3 subunit of the human $GABA_A$ receptor relative to the potentiation of the GABA EC_{20} response elicited 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 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 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.

Since they elicit behavioural effects, the compounds of the invention plainly are brain-penetrant; in other words, these compounds are capable of crossing the so-called "blood-brain barrier". Advantageously, the compounds of the invention are capable of exerting their beneficial therapeutic action following administration by the oral route.

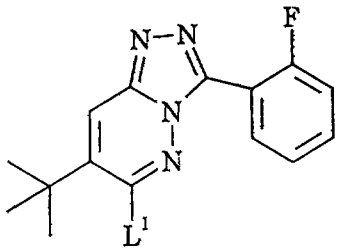
The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions 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.

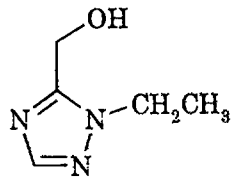
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut 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 compound of formula I as depicted above may be prepared by a process which comprises reacting a compound of formula III with the compound of formula IV:



(III)



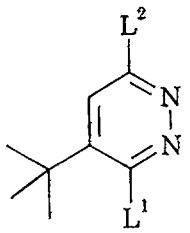
(IV)

wherein L^1 represents a suitable leaving group.

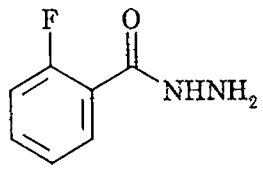
The leaving group L^1 is typically a halogen atom, especially chloro.

The reaction between compounds III and IV is conveniently effected by stirring the reactants in a suitable solvent, in the presence of a base. Typically, the solvent is *N,N*-dimethylformamide, and the base is a strong base such a sodium hydride. Preferably, the solvent is dimethyl sulfoxide, and the base is cesium carbonate. More preferably, the solvent is 1-methyl-2-pyrrolidinone, and the base is sodium hydroxide, in which case the reaction is advantageously performed at a temperature in the region of 0°C.

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



(V)



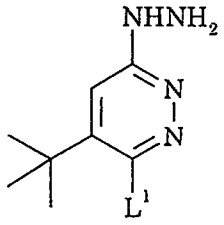
(VI)

wherein L^1 is 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.

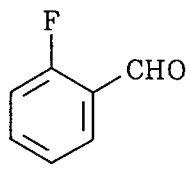
The leaving group L^2 is typically a halogen atom, especially chloro. In the intermediates of formula V, the leaving groups L^1 and L^2 may be the same or different, but are suitably the same, preferably both chloro.

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.

Alternatively, the intermediates of formula III above may be prepared by reacting a hydrazine derivative of formula VII with the aldehyde derivative of formula VIII:



(VII)



(VIII)

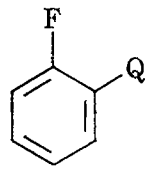
wherein L^1 is as defined above; followed by cyclization of the intermediate Schiff's base thereby obtained.

The reaction between compounds VII and VIII is conveniently effected under acidic conditions, for example in the presence of a mineral acid such as hydrochloric acid. Cyclization of the resulting Schiff's base intermediate may then conveniently be carried out by treatment with iron(III) chloride in a suitable solvent, e.g. an alcoholic solvent such as ethanol, at an elevated temperature, typically at a temperature in the region of 60-70°C.

The intermediates of formula VII above may be prepared by reacting the appropriate compound of formula V as defined above with hydrazine hydrate, typically in isobutyl alcohol at an elevated temperature, e.g. a temperature in the region of 90°C, or in 1,4-dioxane at

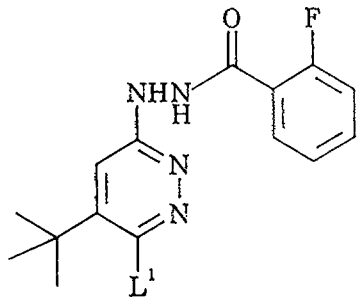
the reflux temperature of the solvent; followed, if necessary, by separation of the resulting mixture of isomers by conventional means.

In an alternative approach, the intermediates of formula III above may be prepared by reacting the hydrazine derivative of formula VII as defined above with a compound of formula IX:



(IX)

wherein Q represents a reactive carboxylate moiety; followed by cyclization of the hydrazide derivative of formula X thereby obtained:



(X)

wherein L^1 is as defined above.

Suitable values for the reactive carboxylate moiety Q include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles. Suitably, Q represents an acid chloride moiety.

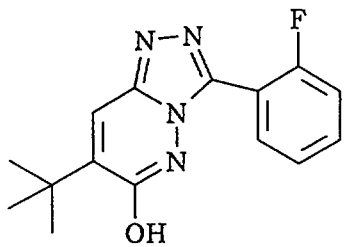
The reaction between compounds VII and IX is conveniently effected under basic conditions, e.g. in the presence of triethylamine, suitably in an

inert solvent such as diethyl ether, and typically at a temperature in the region of 0°C. Cyclization of the resulting compound of formula X may then conveniently be carried out by treatment with 1,2-dibromo-1,1,2,2-tetrachloroethane and triphenylphosphine, in the presence of a base such as triethylamine, suitably in an inert solvent such as acetonitrile, and typically at a temperature in the region of 0°C.

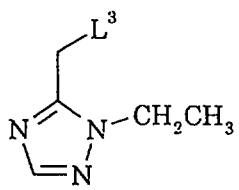
In a preferred method, the reaction between compounds VII and IX may be effected by mixing the reactants in a solvent such as 1-methyl-2-pyrrolidinone at a temperature in the region of 0°C; cyclization of the compound of formula X thereby obtained may then be accomplished *in situ* by heating the reaction mixture at a temperature in the region of 130°C.

The reaction between compound V and hydrazine hydrate or compound VI will, as indicated above, possibly give rise to a mixture of isomeric products depending upon whether the hydrazine nitrogen atom displaces the leaving group L^1 or L^2. Thus, in addition to the required product of formula III or VII, the alternative isomer will possibly be obtained to some extent. For this reason it might be necessary to separate the resulting mixture of isomers by conventional methods such as chromatography.

In another procedure, the compound of formula I as depicted above may be prepared by a process which comprises reacting the compound of formula XI (or its 1,2,4-triazolo[4,3-*b*]pyridazin-6-one tautomer) with a compound of formula XII:



(XI)



(XII)

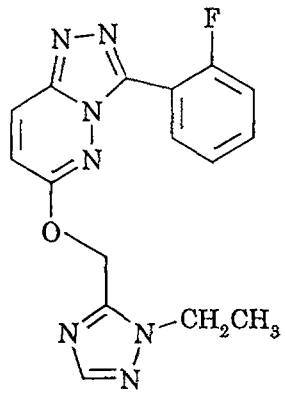
wherein L^3 represents a suitable leaving group.

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

The reaction between compounds XI and XII 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 intermediate of formula XI 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 compound of formula I as depicted above may be prepared by a process which comprises reacting trimethylacetic acid with the compound of formula XIII:



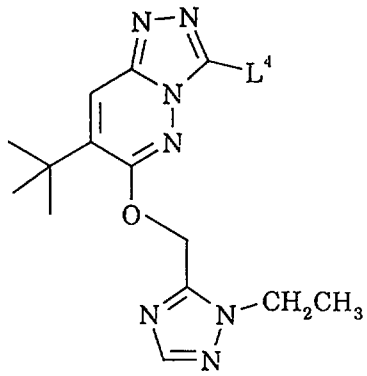
(XIII)

in the presence of silver nitrate and ammonium persulphate.

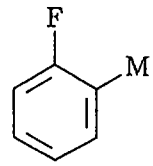
The reaction is conveniently carried out in a suitable solvent, for example in water or aqueous acetonitrile, optionally under acidic conditions, e.g. using trifluoroacetic acid or sulphuric acid, typically at an elevated temperature.

The intermediate of formula XIII corresponds to the compound of formula I as depicted above wherein the *tert*-butyl substituent at the 7-position is absent, and the intermediate XIII may therefore be prepared by methods analogous to those described above for preparing the compound of formula I.

In a still further procedure, the compound of formula I as depicted above may be prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

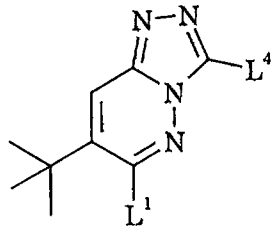
wherein M represents $-B(OH)_2$ or $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, typically *n*-butyl, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

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 XIV and XV comprises dichlorobis(triphenylphosphine)-palladium(II) or tetrakis(triphenylphosphine)palladium(0).

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

The intermediates of formula XIV may be prepared by reacting the compound of formula IV as defined above with a compound of formula XVI:

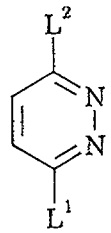


(XVI)

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

The intermediate of formula IV above may be prepared by the procedures described in EP-A-0421210, or by methods analogous thereto. Suitable methods are described in the accompanying Examples.

The intermediates of formula V above may be prepared by reacting trimethylacetic acid with a compound of formula XVII:



(XVII)

wherein 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 trimethylacetic acid and compound XIII. Where L^1 and L^2 are both chloro in compound XVII, the reaction is advantageously effected in the presence of trifluoroacetic acid.

Where they are not commercially available, the starting materials of formula VI, VIII, IX, XII, XV, XVI and XVII may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

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.

Four anhydrous polymorphs, two solvates and a dihydrate of 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine have been synthesised and characterised. All the polymorphs and solvates revert to the most thermodynamically stable form, polymorph A (for formation and characterisation see Example 3), after stirring as a suspension in water. A dihydrate of polymorph A is stable, but only at elevated humidities.

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 compound of the accompanying Examples was tested in the above assay, and was 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 less than 1 nM.

EXAMPLE 1

7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

a) 3,6-Dichloro-4-(1,1-dimethylethyl)pyridazine

Concentrated sulphuric acid (53.6 ml, 1.0 mol) was added carefully to a stirred suspension of 3,6-dichloropyridazine (50.0 g, 0.34 mol) in water (1.25 l). This mixture was then heated to 70°C (internal temperature) before the addition of trimethylacetic acid (47.5 ml, 0.41 mol). A solution of silver nitrate (11.4 g, 0.07 mol) in water (20 ml) was then added over approximately one minute. This caused the reaction mixture to become milky in appearance. A solution of ammonium persulphate (230 g, 1.0 mol) in water (0.63 l) was then added over 20-30 minutes. The internal temperature rose to approximately 85°C. During the addition the product formed as a sticky precipitate. Upon complete addition the reaction was stirred for an additional 10 minutes, then allowed to cool to room temperature. The mixture was then poured onto ice and basified with concentrated aqueous ammonia, with the addition of more ice as required to keep the temperature below 10°C. The aqueous was extracted with dichloromethane (3 x 300 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated to give 55.8 g of crude product as an oil. This was purified by silica gel chromatography using 0-15% ethyl acetate in hexane as eluent to give 37.31 g (53%) of the desired compound. Data for the title compound: ^1H NMR (360 MHz, d_6-DMSO) δ 1.50 (9H, s), 7.48 (1H, s); MS (ES^+) m/e 205 $[MH]^+$, 207 $[MH]^+$.

b) 6-Chloro-7-(1,1-dimethylethyl)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

A mixture of 3,6-dichloro-4-(1,1-dimethylethyl)pyridazine (20 g, 0.097 mol), 2-fluorobenzhydrazide (22.6 g, 0.145 mol) and triethylamine hydrochloride (20 g, 0.0145 mol) in dioxan (1.2 l) was stirred and heated at reflux under a stream of nitrogen for 4 days. Upon cooling the volatiles were removed *in vacuo* and the residue was triturated with dichloromethane (200 ml), filtered and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting with 0%→25% ethyl acetate/dichloromethane to give the title compound (12.95 g, 44%) as a white solid. Data for the title compound: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.57 (9H, s), 7.26-7.35 (2H, m), 7.53-7.60 (1H, m), 7.89-7.93 (1H, m), 8.17 (1H, s); MS (ES^+) m/e 305 $[MH]^+$, 307 $[MH]^+$.

c) (2-Ethyl-2*H*-1,2,4-triazol-3-yl)methanol

To a solution of 1,2,4-triazole (10 g, 0.145 mol) in DMF (150 ml) at room temperature was added sodium hydride (6.4 g of a 60% disp. in oil, 0.16 mol) in portions over 15 min. When the addition was complete, the reaction mixture was allowed to cool to room temperature, then cooled in an ice-bath and iodoethane (14 ml, 0.174 mol) added dropwise over 10 min. The reaction mixture was allowed to warm to room temperaure and after stirring for 3 h the solvents were removed under high vacuum to leave a residue which was partitioned between water (300 ml) and ethyl acetate (3 x 300 ml). The combined organic layers were washed with saturated brine and dried ($MgSO_4$), filtered and concentrated under vacuum to leave an oily residue which was purified by distillation (120°C @ ~20 mmHg) to give 1-ethyl-1,2,4-triazole contaminated with ~15% DMF (2.4 g). The crude product (2.4 g, 0.025 mol) was dissolved in dry THF (35 ml), cooled to -40°C and *n*-butyllithium (16.2 ml of a 1.6 M solution in hexane, 0.026 mol) was added slowly over 20 min keeping the temperature constant. DMF (2.03 ml, 0.026 mol) was then added and after 15 min the reaction

mixture was allowed to warm slowly to room temperature over 2 h. To the reaction mixture was added methanol (20 ml) followed by sodium borohydride (1 g, 0.026 mol) and the solution was allowed to stir for 14 h. The solvents were removed under vacuum and the residue was partitioned between brine (50 ml) and dichloromethane (6 x 50 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to leave a residue which was purified by silica gel chromatography using 0-5% methanol in dichlorometane as eluent to give the title compound as an off-white solid (0.5 g, 3%). Data for the title compound: ^1H NMR (250 MHz, $CDCl_3$) δ 1.48 (3H, t, J = 7.3 Hz), 4.25 (2H, q, J = 7.3 Hz), 4.75 (2H, s), 5.14 (1H, br s), 7.78 (1H, s).

d) 7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

To a solution of (2-ethyl-2*H*-1,2,4-triazol-3-yl)methanol (0.094 g, 0.74 mmol) and 6-chloro-7-(1,1-dimethylethyl)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (0.15 g, 0.49 mmol) in DMF (10 ml) was added sodium hydride (0.024 g of a 60% dispersion in oil, 1.1 mol eq.) and the reaction mixture was stirred at room temperature for 30 minutes. After this time, the reaction mixture was diluted with water (80 ml) and the solid that precipitated was collected by filtration and washed several times with water in the sinter funnel. The solid was recrystallised from ethyl acetate/hexane to give pure title compound (0.085 g, 44%). Data for the title compound: ^1H NMR (250 MHz, $CDCl_3$) δ 1.40-1.47 (12H, m), 4.14 (2H, t, J = 7.3 Hz), 5.26 (2H, s), 7.26-7.38 (2H, m), 7.53-7.58 (1H, m), 7.86-7.90 (1H, m), 7.93 (1H, s), 7.99 (1H, s); MS (ES^+) m/e 396 $[MH]^+$. Anal. Found C, 61.02; H, 5.45; N, 24.75%. $C_{20}H_{22}FN_7O$ requires C, 60.75; H, 5.61; N, 24.79%.

EXAMPLE 2

7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine: Alternative Synthetic Route

a) 3,6-Dichloro-4-(1,1-dimethylethyl)pyridazine

A mixture of dichloropyridazine (100 g, 0.67 mol), trimethylacetic acid (96 g, 0.94 mol) and water (800 ml) in a 10 l flask with overhead stirring was warmed to 55°C resulting in a two-phase solution. A solution of $AgNO_3$ (11.4 g, 0.134 mol) in water (125 ml) was added in one portion resulting in an opaque solution. Trifluoroacetic acid (10.3 ml, 0.134 mol) was added in one portion. Ammonium persulfate (245 g, 1.07 mol) was dissolved in water (500 ml) and added dropwise to the suspension over 45-60 min resulting in an exotherm (typically temperature increases to between 75-80°C and can be controlled by rate of persulfate addition). The temperature was maintained at 75°C for a further 1 h and then cooled to room temperature. The reaction mixture was extracted with isobutyl alcohol (1 l) and the aqueous layer discarded. The organic layer was washed with water (250 ml) and the aqueous cut discarded. HPLC assay yield is 134 g (97%). The isobutyl alcohol solution was used *as is* in the next step.

b) 6-Chloro-5-(1,1-dimethylethyl)pyridazin-3-ylhydrazine

Hydrazine hydrate (95 ml, 1.95 mol) was added to the isobutyl alcohol solution from step a in a 3 l flask and heated at 90°C for 20 h. The reaction mixture was cooled to room temperature and the lower aqueous layer discarded. The reaction mixture was washed with water (450 ml) and the aqueous cut discarded. The reaction mixture was distilled under reduced pressure until the product started to crystallise and then 1-methyl-2-pyrrolidinone (NMP) (550 ml) was added. Distillation was

continued to remove the last of the isobutyl alcohol. The solution was used *as is* in the next step.

c) 6-Chloro-7-(1,1-dimethylethyl)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

2-Fluorobenzoyl chloride (103 g, 0.65 mol) was added dropwise to the cooled (0°C) NMP solution from step b maintaining the internal temperature <5°C. After the addition the reaction mixture was heated at 130°C for 2 h. The reaction mixture was cooled to room temperature which resulted in the crystallisation of the product. Water (1.3 l) was added dropwise over 30 min. The slurry was cooled to 10°C and the solid isolated by filtration, then dried under reduced pressure to afford product (145 g, 71% yield from 3,6-dichloropyridazine).

d) 1-Ethyl-1,2,4-triazole

1,2,4-Triazole (100.0 g, 1.45 mol) in anhydrous THF (950 ml) was cooled to 0°C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (220 g, 1.45 mol) was added in one portion. The reaction mixture was stirred for 30 min until complete dissolution was observed. Whilst maintaining the ice/water cooling bath, iodoethane (317 g, 2.03 mol) was added dropwise over a 15 min period resulting in an internal temperature rise to 30°C. The reaction was stirred at room temperature for 16 h, after which the DBU hydroiodide was removed by filtration. The filtrate solution was used *as is* in the next step.

e) (2-Ethyl-2*H*-1,2,4-triazol-3-yl)methanol

The stirred solution from the preceding step was cooled to -75°C internal temperature in a solid CO_2/acetone slurry bath. Hexyllithium (458 ml of 33% solution in hexanes) was added dropwise over 25 min keeping the internal temperature below -55°C. The reaction mixture was

aged for 30 min (back to -75°C) and then neat DMF (108 ml, 1.39 mol) was added dropwise over 10 min maintaining internal temperature below -60°C. The reaction mixture was aged at -70°C for 90 min before the cooling bath was removed and the reaction mixture allowed to warm to 0°C over 30 min. Industrial methylated spirits (340 ml) was added over 10 min. Sodium borohydride (26.3 g, 0.695 mol) was then added portionwise maintaining internal temperature below 6°C. After the addition the reaction mixture was allowed to warm to room temperature and stirred for 1 h at that temperature. The reaction was quenched by the careful addition of 2M H_2SO_4 (200 ml) and then stirred at room temperature for 20 h. The reaction mixture was concentrated to 675 ml and sodium sulfate (135 g) was added in one portion. The reaction mixture was warmed to 35°C and stirred for 15 min. The solution was extracted with warm (45°C) isobutyl alcohol (2 x 675 ml). The combined organic fractions were concentrated under reduced pressure 450 ml at which point the product crystallised. Heptane (1.125 l) was added and the slurry concentrated under reduced pressure to remove most of the isobutyl alcohol. Heptane was added to give a final slurry volume of 680 ml. After cooling to 0°C, filtration gave the title compound (137 g, 74% from 1,2,4-triazole).

f) 7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

Method A

6-Chloro-7-(1,1-dimethylethyl)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (255 g, 0.819 mol), (2-ethyl-2*H*-1,2,4-triazol-3-yl)methanol (125 g, 0.983 mol) and cesium carbonate (640 g, 1.966 mol) were charged to a 10 l flask equipped with an overhead stirrer. Dimethyl sulfoxide (2.5 l) was added in one portion and the reaction mixture stirred at room temperature for 20 h. The product had crystallised. The reaction mixture was maintained at <25°C whilst water (5 l) was added dropwise over 45

min to the stirred suspension. After cooling to 10°C, the product was isolated by filtration and the cake washed with water (1.75 l). Drying at 50°C *in vacuo* gave the title compound (317 g, 98%) as a white solid.

Method B

6-Chloro-7-(1,1-dimethylethyl)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (10 g, 32.12 mmol) and (2-ethyl-2*H*-1,2,4-triazol-3-yl)methanol (5.01 g, 38.55 mmol) were charged to a 500 ml flask equipped with an overhead stirrer. NMP (100 ml) was added in one portion and the reaction mixture stirred until complete dissolution was achieved. The reaction mixture was cooled to 0°C and 48% w/w sodium hydroxide solution (4.02 g, 46 mmol) was added in one portion. After stirring for 1 h at 0°C, the product had crystallised. Water (100 ml) was added dropwise over 15 min and the slurry aged for 30 min. The product was isolated by filtration and the cake washed with water (100 ml). Drying at 50°C *in vacuo* gave the title compound (12.50 g, 98%) as a white solid.

EXAMPLE 3

Formation and Characterisation of Polymorphs and Solvates of 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine

7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine (hereinafter referred to as Compound I) was recrystallised from a selection of organic solvents and the resultant solids were dried *in vacuo* overnight at 60°C unless otherwise stated. Each batch was then characterised by optical microscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and X-ray powder diffraction (XRPD). Four distinct

anhydrous polymorphs, a hydrate and two solvates have been characterised, as summarised in Table 1.

Table 1: Polymorphs of Compound I

Polymorph	Recrystallisation Solvent	Crystal Habit	M.P. °C
A	Methanol Ethyl acetate Acetonitrile Acetone Acetic acid/H_2O	Elongated rectangular or irregular	*ca.* 186
B	Isobutanol	Elongated rectangular or irregular	*ca.* 181
C	Dimethylformamide Tetrahydrofuran	Acicular	*ca.* 170
D	Isopropanol Isobutanol	Acicular	*ca.* 170
Methanol Solvate	Methanol (air-dried)	Irregular	*ca.* 186
Ethanol Solvate	Ethanol	Irregular	*ca.* 186

Polymorph A

Polymorph A consists of irregular or elongated rectangular birefringent crystals. It shows one major endotherm by DSC at *ca.* 186°C due to melting. In the case of some of the samples prepared this melt displays several events happening within it, typified by shoulders on the melting endotherm. Polymorph A is anhydrous and displays no losses by

TGA. It has a unique XRPD diffractogram, typified by two peaks at $2\theta \approx 7.3°$.

Polymorph B

Polymorph B consists of irregular or elongated rectangular birefringent crystals. Polymorph B displays one major endotherm by DSC at *ca.* 181°C due to melting. It is anhydrous and displays no weight loss by TGA. It has a unique XRPD diffractogram.

Polymorph C

Polymorph C consists of acicular, birefringent crystals. The DSC thermograms of polymorph C show an endotherm at *ca.* 170°C, an exotherm at *ca.* 173°C, a small endotherm at *ca.* 181°C, and an endotherm due to melting at *ca.* 186°C. No losses are observed by thermogravimetric analysis.

Polymorph D

Polymorph D consists of acicular birefringent crystals. The XRPD diffractogram of polymorph D is similar in pattern to that of polymorph C. However, significant differences are observed, notably additional peaks at $2\theta = 9.861$, 15.113, 18.015 and 22.224. The DSC trace of polymorph D displays a very broad exotherm at *ca.* 108°C, followed by an endotherm and exotherm at 170°C and 173°C, as for polymorph C. The major melting is observed at *ca.* 181°C, and several events are seen to occur within the melting endotherm, with minor melting at 186°C. No losses are observed by TGA.

Methanol Solvate

The DSC thermogram of the methanol solvate shows one endotherm at *ca.* 157°C due to loss of methanol, and one endotherm at 186°C due to

melting. A gradual loss is observed by TGA up to *ca.* 150°C, at which point a step loss is observed, coincident with the endotherm observed by DSC. This step loss is in some instances composed of more than one event, and the amount varies among recrystallised samples and does not appear to correspond to a stoichiometric solvate. However, methanol vapour sorption studies on polymorph A show the presence of a distinct hemisolvate. The XRPD diffractogram of the solvate is unique.

Ethanol Solvate

The ethanol solvate is typified by its DSC thermogram which shows one endotherm at *ca.* 111°C due to loss of ethanol, and an endotherm at *ca.* 186°C due to melting. TGA shows the loss to be variable in different recrystallised samples, between *ca.* 4 and 6.5%, and does not correspond to a stoichiometric solvate. The XRPD diffractogram is unique.

Hydrate of Polymorph A

Figure 1 shows the adsorption/desorption isotherm of Compound I polymorph A at 25°C. These moisture vapour sorption studies show formation of a dihydrate above 80% relative humidity (RH) at 25°C. Hysteresis indicative of hydrate formation is seen to occur, with desorption occurring below *ca.* 60% RH.

Figure 2 shows side-by-side XRPD diffractograms of anhydrous Compound I polymorph A and of the dihydrate of polymorph A. The XRPD diffractogram of the dihydrate, obtained on a wetted sample of polymorph A, demonstrates the distinct differences observed between the two forms. The major changes in diffraction can be seen to be loss of the peak at 2θ = 11.2°, and the appearance of two major peaks at 2θ = 11.9° and 12.3°.

Conversion of Compound I Polymorphs to Polymorph A

On slurrying in water all of the polymorphs and solvates decribed above convert to polymorph A over a period of 1-4 days, indicating that

this is the most stable form at room temperature. This conversion is slow due to the low aqueous solubility of Compound I in relation to the large excess of solid compound slurried.

X-Ray Powder Diffraction Data

Figure 3 shows side-by-side XRPD diffractograms of anhydrous Compound I polymorphs A, B, C and D, of the methanol and ethanol solvates, and of the dihydrate of polymorph A. Numerical data associated therewith are presented below.

Compound I Polymorph A: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.243	12.19523	2214	88.5	22.885	3.88289	195	7.8
7.559	11.68660	613	24.5	23.621	3.76351	307	12.3
8.601	10.27227	50	2	23.67	3.75587	256	10.2
9.694	9.11647	211	8.4	23.767	3.74068	253	10.1
10.703	8.25928	270	10.8	24.12	3.68684	102	4.1
11.027	8.01719	213	8.5	24.518	3.62778	281	11.2
11.239	7.86640	1464	58.5	25.223	3.52803	162	6.5
12.943	6.83420	2501	100	25.275	3.52082	185	7.4
13.441	6.58218	41	1.6	25.478	3.49324	808	32.3
14.497	6.10492	740	29.6	26.088	3.41292	2178	87.1
15.178	5.83251	1211	48.4	26.686	3.33787	86	3.4
15.376	5.75802	187	7.5	27.093	3.28857	138	5.5
15.42	5.74169	144	5.8	27.74	3.21330	186	7.4
15.854	5.58536	391	15.6	28.056	3.17789	87	3.5
16.081	5.50706	236	9.4	28.607	3.11788	248	9.9
16.134	5.48931	250	10	28.703	3.10770	155	6.2
16.419	5.39437	135	5.4	29.135	3.06255	131	5.2
16.76	5.28552	36	1.4	29.267	3.04911	284	11.4
17.165	5.16167	304	12.1	29.353	3.04034	193	7.7
17.199	5.15149	235	9.4	29.787	2.99703	71	2.8
17.24	5.13933	329	13.2	30.357	2.94205	106	4.2
17.355	5.10550	281	11.2	30.954	2.88666	38	1.5
18.556	4.77774	213	8.5	31.436	2.84343	52	2.1
18.829	4.70917	85	3.4	32.618	2.74309	163	6.5
19.27	4.60224	372	14.9	32.773	2.73047	161	6.5
19.499	4.54892	233	9.3	33.254	2.69202	64	2.6
20.203	4.39192	118	4.7	33.897	2.64245	66.4	2.7
20.635	4.30098	238	9.5	34.14	2.62417	162	6.5
21.584	4.11385	250	10	36.522	2.45827	53	2.1
21.689	4.09416	704	28.2	38.532	2.33459	40	1.6
21.867	4.06119	1621	64.8	38.859	2.31564	78	3.1
22.28	3.98692	154	6.2	39.594	2.27434	47	1.9

Compound I Polymorph B: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.379	11.97023	651	49.2	20.179	4.39705	119	9
10.096	8.75424	481	36.4	20.9	4.24699	54	4.1
10.821	8.16974	1323	100	21.718	4.08884	1300	98.3
12.482	7.08575	61	4.6	22.285	3.98602	446	33.7
12.739	6.94328	149	11.3	22.96	3.87033	87	6.6
13.036	6.78588	194	14.7	23.304	3.81394	111	8.4
13.475	6.56586	123	9.3	24.018	3.70224	73	5.5
13.828	6.39890	69	5.2	24.459	3.63648	75	5.7
14.815	5.97480	322	24.3	25.081	3.54765	141	10.7
15.078	5.87109	307	23.2	25.837	3.44555	47	3.6
15.584	5.68147	86	6.5	26.204	3.39810	193	14.6
16.082	5.50675	391	29.6	27.078	3.29031	176	13.3
16.979	5.21789	147	11.1	28.449	3.13490	91	6.9
17.02	5.20548	163	12.3	28.889	3.08812	51	3.9
17.287	5.12570	257	19.4	29.84	2.99177	166	12.6
17.616	5.03052	72	5.4	29.922	2.98380	121	9.1
18.125	4.89033	83.1	6.3	30.227	2.95440	58	4.4

18.161	4.88081	129	9.7	31.94	2.79975	70.5	5.3
18.192	4.87269	143	10.8	32.837	2.72528	117	8.8
19.022	4.66174	69	5.2	33.295	2.68885	40	3
19.542	4.53891	119	9	34.407	2.60440	52	3.9
19.68	4.50748	70.5	5.3	38.876	2.31472	27	2

Compound I Polymorph C: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.254	12.17653	25	0.6	24.647	3.60908	75	1.8
8.023	11.01169	798	19.3	24.961	3.56448	398	9.6
9.686	9.12421	4130	100	25.341	3.51181	182	4.4
10.489	8.42726	64	1.5	25.549	3.48378	617	14.9
10.813	8.17559	107	2.6	25.981	3.42671	832	20.1
11.277	7.83989	31	0.8	26.794	3.32466	328	7.9
12.193	7.25327	48	1.2	27.782	3.20863	166	4
12.961	6.82506	40	1	27.985	3.18576	158	3.8
14.357	6.16430	146	3.5	28.257	3.15573	241	5.8
14.497	6.10512	213	5.2	28.788	3.09868	257	6.2
15.225	5.81495	35	0.8	29.242	3.05164	322	7.8
16.007	5.53248	917	22.2	29.301	3.04560	322	7.8
16.545	5.35385	681	16.5	29.56	3.01950	111	2.7
16.951	5.22646	61	1.5	30.544	2.92444	158	3.8
17.672	5.01479	402	9.7	30.942	2.88768	70	1.7
18.337	4.83428	536	13	31.839	2.80834	156	3.8
18.578	4.77228	533	12.9	32.457	2.75628	157	3.8
19.396	4.57272	3486	84.4	32.745	2.73271	369	8.9
20.034	4.42851	57	1.4	34.246	2.61626	150	3.6
20.913	4.24430	193	4.7	34.979	2.56310	76	1.8
21.189	4.18959	1917	46.4	35.42	2.53225	74	1.8
21.523	4.12543	476	11.5	35.753	2.50941	92	2.2
21.876	4.05969	329	8	36.71	2.44615	91	2.2
22.654	3.92185	151	3.7	37.036	2.42537	145	3.5
23.207	3.82968	463	11.2	37.549	2.39339	137	3.3
23.238	3.82472	462	11.2	38.915	2.31247	74	1.8
24.316	3.65757	87	2.1	39.41	2.28456	166	4

Compound I Polymorph D: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
8.024	11.00971	501	33.4	22.224	3.99690	414	27.6
9.664	9.14458	1501	100	22.654	3.92192	112	7.5
9.861	8.96259	502	33.5	23.22	3.82757	322	21.5
10.497	8.42115	38	2.5	24.052	3.69702	89	5.9
10.8	8.18489	229	15.3	24.313	3.65791	295	19.7
11.462	7.71362	40	2.7	24.948	3.56619	272	18.1
12.105	7.30563	216	14.4	25.3	3.51744	120	8
12.951	6.83035	573	38.2	25.543	3.48455	304	20.3
13.312	6.64558	107	7.1	25.977	3.42728	362	24.1
13.817	6.40392	39	2.6	26.036	3.41965	416	27.7
14.478	6.11305	282	18.8	26.789	3.32518	539	35.9
14.823	5.97145	76	5.1	27.479	3.24329	173	11.5
15.113	5.85746	162	10.8	27.754	3.21176	198	13.2
16	5.53485	396	26.4	28.019	3.18199	170	11.3
16.533	5.35742	774	51.6	28.261	3.15525	314	20.9
16.952	5.22613	72	4.8	28.478	3.13170	144	9.6

17.661	5.01784	509	33.9	28.809	3.09646	205	13.7
18.015	4.92003	479	31.9	29.257	3.05012	176	11.7
18.316	4.83994	545	36.3	29.83	2.99276	178	11.9
18.46	4.80255	512	34.1	30.533	2.92545	157	10.5
18.543	4.78110	498	33.2	30.904	2.89114	96	6.4
19.239	4.60966	196	13.1	31.818	2.81015	131	8.7
19.41	4.56957	775	51.6	32.454	2.75655	119	7.9
20.005	4.43493	158	10.5	32.744	2.73282	182	12.1
20.525	4.32367	82	5.5	33.654	2.66094	94	6.3
20.798	4.26748	386	25.7	34.22	2.61823	95	6.3
20.882	4.25060	416	27.7	34.526	2.59568	80	5.3
21.188	4.18982	1344	89.5	34.934	2.56632	99	6.6
21.509	4.12810	1313	87.5	36.998	2.42775	122	8.1
21.853	4.06378	296	19.7	37.545	2.39366	97	6.5

Compound I Methanol Solvate: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.357	12.00677	9531	90.4	21.153	4.19677	224	2.1
7.608	11.61023	260	2.5	22.081	4.02236	10545	100
9.616	9.19052	260	2.5	22.588	3.93327	526	5
9.755	9.05958	433	4.1	22.825	3.89290	1150	10.9
10.943	8.07881	1145	10.9	23.14	3.84065	362	3.4
11.274	7.84189	406	3.9	23.742	3.74460	291	2.8
12.36	7.15546	3517	33.4	24.295	3.66064	440	4.2
12.942	6.83511	472	4.5	24.818	3.58463	3357	31.8
12.981	6.81447	530	5	25.434	3.49921	933	8.8
14.42	6.13754	440	4.2	25.967	3.42863	2020	19.2
14.69	6.02552	3179	30.1	26	3.42428	2000	19
15.196	5.82583	371	3.5	26.761	3.32860	402	3.8
15.651	5.65758	767	7.3	27.151	3.28169	230	2.2
15.913	5.56476	954	9	28.642	3.11415	273	2.6
16.507	5.36597	379	3.6	28.951	3.08162	298	2.8
16.539	5.35556	426	4	29.56	3.01950	1793	17
16.871	5.25102	1070	10.1	30.365	2.94130	455	4.3
17.226	5.14355	237	2.2	31.319	2.85382	313	3
18.226	4.86354	372	3.5	32.074	2.78834	173	1.6
18.613	4.76331	112	1.1	32.739	2.73323	134	1.3
19.283	4.59933	291	2.8	33.77	2.65210	344	3.3
19.545	4.53827	195	1.8	35.185	2.54858	129	1.2
19.961	4.44452	1703	16.2	37.166	2.41715	145	1.4
20.675	4.29264	161	1.5	37.694	2.38454	218	2.1

Compound I Ethanol Solvate: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.357	12.00679	943	52.5	25.061	3.55045	462	25.7
9.541	9.26191	201	11.2	25.341	3.51184	1795	100
9.809	9.00980	208	11.6	25.712	3.46196	290	16.2
10.951	8.07238	1365	76.1	26.055	3.41713	463	25.8
12.031	7.35019	1500	83.6	26.235	3.39415	401	22.4
12.499	7.07637	115	6.4	26.599	3.34857	178	9.9
14.158	6.25067	245	13.7	27.054	3.29329	159	8.9
14.707	6.01841	236	13.2	28.355	3.14498	311	17.3
15.719	5.63302	428	23.8	28.491	3.13034	190	10.6
15.899	5.56980	657	36.6	28.667	3.11154	150	8.4

16.304	5.43218	869	48.4	29.029	3.07353	142	7.9
16.895	5.24359	1076	60	29.658	3.00975	207	11.5
18.227	4.86334	500	27.9	29.819	2.99388	604	33.7
19.109	4.64073	148	8.2	30.421	2.93596	132	7.4
19.49	4.55085	1045	58.2	30.609	2.91837	133	7.4
20.998	4.22731	211	11.8	31.383	2.84817	131	7.3
21.177	4.19195	168	9.3	32.048	2.79050	154	8.6
21.982	4.04035	1230	68.6	32.116	2.78480	146	8.1
22.124	4.01471	1146	63.9	33.78	2.65134	233	13
22.82	3.89385	904	50.4	35.079	2.55608	119	6.6
23.017	3.86082	475	26.5	35.267	2.54289	123	6.9
23.321	3.81127	295	16.5	36.866	2.43614	89	5
23.459	3.78909	282	15.7	37.84	2.37564	88	4.9
23.961	3.71094	701	39.1	39.182	2.29730	102	5.7
24.159	3.68094	1504	83.8	39.406	2.28477	104	5.8

Compound I Hydrate of Polymorph A: X-Ray Powder Diffraction Data

Angle 2θ	d value Å	Intensity Count	Intensity %	Angle 2θ	d value Å	Intensity Count	Intensity %
7.261	12.16414	447	100	18.657	4.75222	48.4	10.8
9.1	9.70988	25.6	5.7	18.779	4.72155	35.7	8
9.626	9.18058	31	6.9	18.859	4.70171	43.7	9.8
10.796	8.18860	283	63.2	19.276	4.60089	82	18.3
11.858	7.45707	170	38	19.504	4.54766	46	10.3
12.218	7.23806	51.8	11.6	20.22	4.38821	28	6.3
12.261	7.21317	79.4	17.7	20.655	4.29677	133	29.7
12.302	7.18922	78	17.4	21.68	4.09588	163	36.4
12.97	6.82039	173	38.7	21.86	4.06263	223	49.8
14.462	6.11993	132	29.5	22.316	3.98062	88.8	19.8
14.518	6.09637	138	30.8	22.537	3.94207	254	56.7
15.19	5.82798	229	51.2	22.579	3.93478	281	62.7
15.402	5.74824	114	25.6	22.901	3.88013	78	17.4
15.866	5.58141	222	49.6	23.673	3.75541	84	18.8
15.906	5.56750	196	43.9	24.507	3.62946	46	10.3
16.08	5.50763	102	22.7	25.469	3.49445	203	45.4
16.127	5.49137	117	26.1	26.087	3.41311	128	28.6
16.178	5.47423	112	25.1	27.754	3.21175	56	12.5
16.221	5.46004	78	17.4	28.613	3.11725	65	14.5
16.357	5.41482	65.9	14.7	29.291	3.04663	57	12.7
16.418	5.39480	71.3	15.9	29.935	2.98248	43	9.6
17.189	5.15467	146	32.6	32.747	2.73253	63	14.1
17.345	5.10866	105	23.5	34.176	2.62146	32	7.2
18.57	4.77428	71	15.9	38.848	2.31630	31	6.9

CLAIMS:

1. 7-(1,1-Dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine.

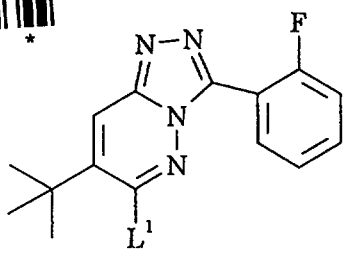
2. Polymorph A of 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine as characterised herein.

3. A pharmaceutical composition comprising 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine in association with a pharmaceutically acceptable carrier.

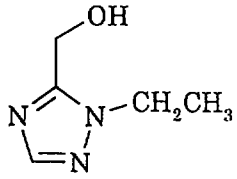
4. The use of 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine for the manufacture of a medicament for the treatment and/or prevention of anxiety.

5. A process for the preparation of 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine, which comprises:

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



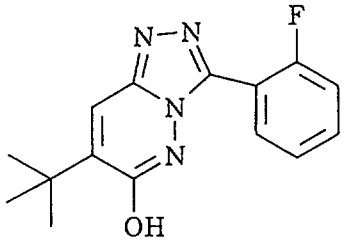
(III)



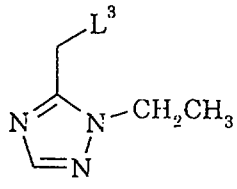
(IV)

wherein L^1 represents a suitable leaving group; or

(B) reacting the compound of formula XI (or its 1,2,4-triazolo[4,3-*b*]pyridazin-6-one tautomer) with a compound of formula XII:



(XI)

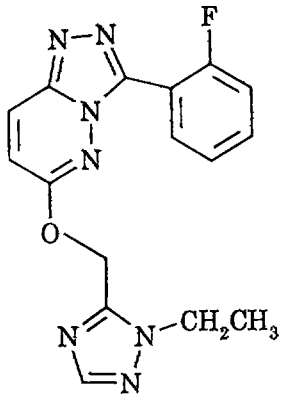


(XII)

wherein L^3 represents a suitable leaving group; or

(C) reacting trimethylacetic acid with the compound of formula XIII:

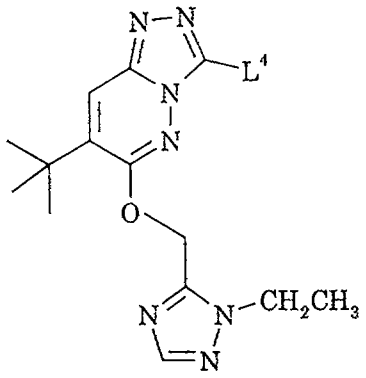


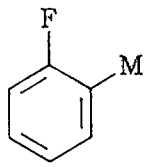


(XIII)

in the presence of silver nitrate and ammonium persulphate; or

(D) reacting a compound of formula XIV with a compound of formula XV:





(XIV) (XV)

wherein M represents $-B(OH)_2$ or $-Sn(Alk)_3$ in which Alk represents a C_{1-6} alkyl group, and L^4 represents a suitable leaving group; in the presence of a transition metal catalyst.

6. A process as claimed in claim 5 wherein reaction (A) is carried out in 1-methyl-2-pyrrolidinone, in the presence of sodium hydroxide, at a temperature in the region of 0°C.

7. 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 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-*b*]pyridazine.



This Sheet Has Been Replaced

