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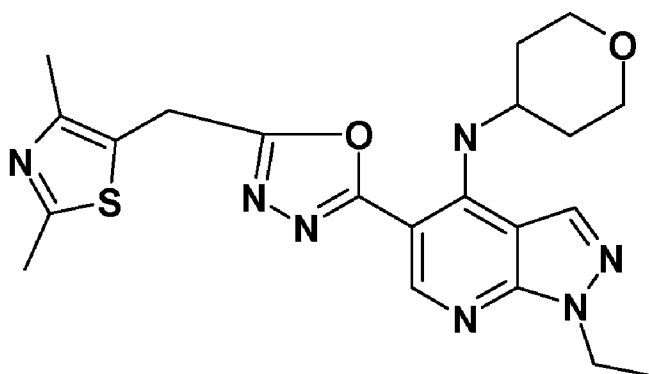
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(54) Title: TREATMENT OF ANXIETY DISORDERS



(I)

(57) Abstract: Use of a compound of formula (I): 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine, Formula (I), or a pharmaceutically acceptable salt thereof for the treatment of anxiety disorders and a process for its preparation.



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Treatment of Anxiety Disorders

This invention relates to the use of pyrazolopyridine derivatives for the treatment or prophylaxis of anxiety disorders and a new process for the preparation of such compounds.

The family of phosphodiesterase (PDE) enzymes hydrolyse the cyclic nucleotide intracellular second messengers, cAMP and cGMP leading to their inactivation. Inhibition of these enzymes leads to elevated levels of cAMP and cGMP in the cell and prolongs their action on downstream signalling pathways. Signalling through these second messengers, has been implicated in the pathophysiology of diseases and disorders such as depression, and have been shown to be involved in the therapeutic action of existing antidepressant drugs (Tardito, D. et al (2006) Pharmacol. Rev. 58(1) pp115-134; Dlaboga, D. et al (2006) Brain Res. 1096(1) pp104-112).

The PDE family consists of eleven subtypes (PDE1 to PDE11). These eleven subtypes differ in their ability to hydrolyse cAMP and/or cGMP, their tissue and intracellular distribution, their sensitivity to intracellular modulators and their inhibitor pharmacology. Each subtype exists as multiple forms generated by different genes and by alternative splicing of the N-terminus.

The PDE4 subtype consists of four isoforms (PDE4A to PDE4D), which can be further divided on the basis of splicing differences (O'Donnell, J.M. and Zhang, H.T. (2004) Trends Pharmacol. Sci. 25(3) pp158-163). The PDE4A, PDE4B and PDE4D isoforms are predominantly found in the brain, where they are expressed widely, but differentially. PDE4A, PDE4B and PDE4D knockout mice show differences with respect to wild type animals in growth and survival, fertility, airway hyperactivity, inflammatory response, myocyte contraction and neurological function, consistent with the wide distribution and role of PDE4 enzymes (Houslay, M.D. et al (2005) Drug Discovery Today 10(22) pp1503-1519).

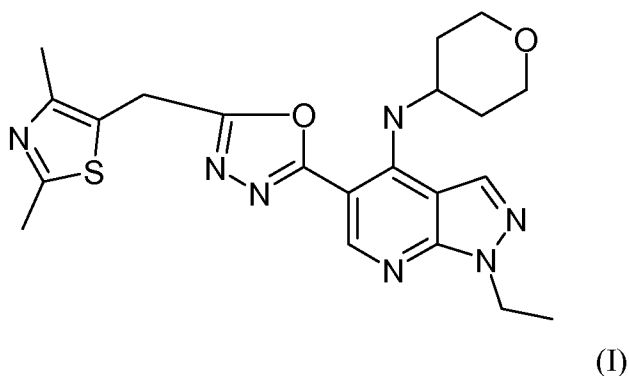
PDE4 inhibitors, such as the prototypical brain-penetrant inhibitor rolipram, influence central function in animals in a dose-dependent manner, consistent with their potential use in the treatment of depression and cognitive disorders in humans. However higher doses of these compounds can give rise to mechanism-related side effects such as emesis, sedation and vascular inflammation.

The pyrazolopyridine compounds disclosed in WO04/056823 are phosphodiesterase 4 (PDE4) inhibitors. The compounds are disclosed as being useful for the treatment or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis or allergic rhinitis.

The present invention concerns the unexpected finding that in an animal model of anxiety a potent and selective brain-penetrant pan-PDE4 inhibitor exhibits an apparent anxiolytic effect. In addition this compound, 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-*b*]pyridin-4-amine, may provide a greater therapeutic window between

said anxiolytic effects and nausea or other mechanism-related side effects. This compound is disclosed in WO2004/056823 as Example 98.

Therefore the present invention provides the use of a compound of formula (I):
5 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine



10 or a pharmaceutically acceptable salt thereof for the treatment or prophylaxis of an anxiety disorder.

If the compound of formula (I) is used in the salt form, the salt of the compound of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art.

15 Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse J.Pharm.Sci (1977) 66, pp 1-19. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or
20 naphthalenesulfonic acid. Other salts e.g. oxalates or formates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention.

The compound of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope the use of the
25 compound of formula (I) in all possible stoichiometric and non-stoichiometric forms.

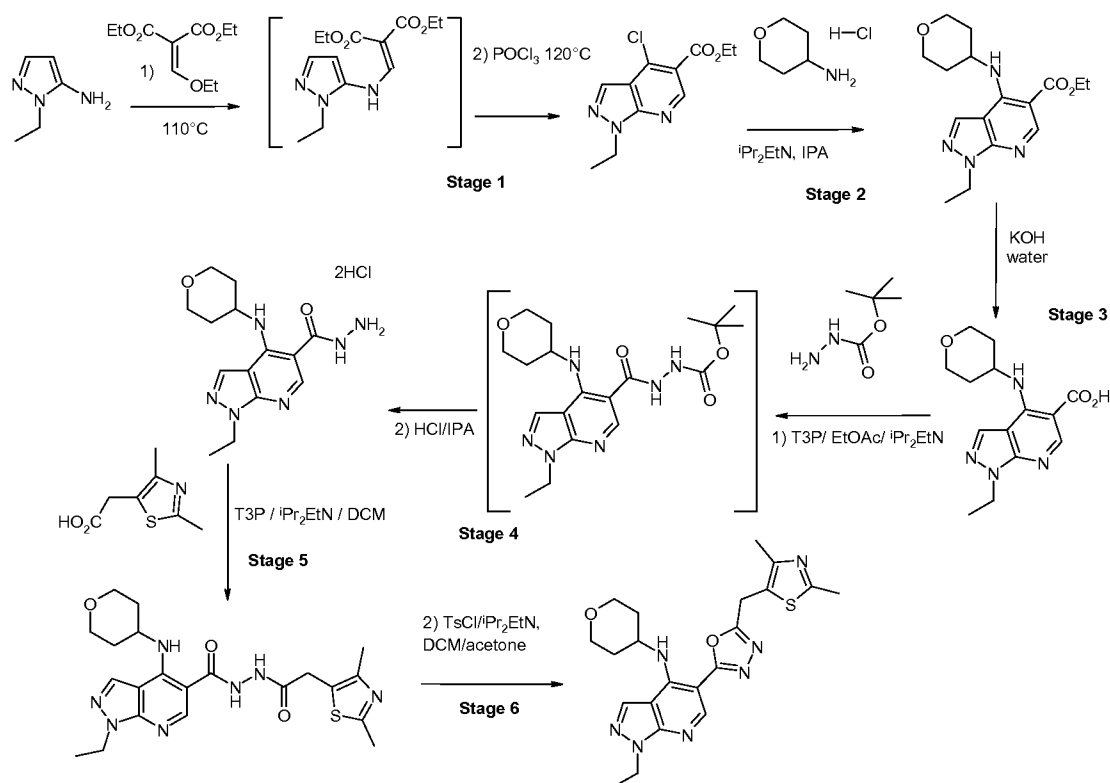
The compound of formula (I) may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water). In addition, different
30 crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. The present invention includes within its scope the use of the compound of formula (I) in any polymorphic form.

Since the invention relates to the use of the compound of formula (I) in pharmaceutical compositions it will readily be understood that the compound is
35 preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (%)

are on a weight for weight basis). Impure preparations of the compound may be used for preparing the more pure forms used in the pharmaceutical compositions.

The compound of formula (I) may be prepared using methods disclosed in WO04/056823.

- 5 An alternative route for the synthesis of the compound of formula (I) is as follows. The starting material used in each step may not necessarily be the material from an earlier step referred to.



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Abbreviations used here are:

IPA- isopropanol

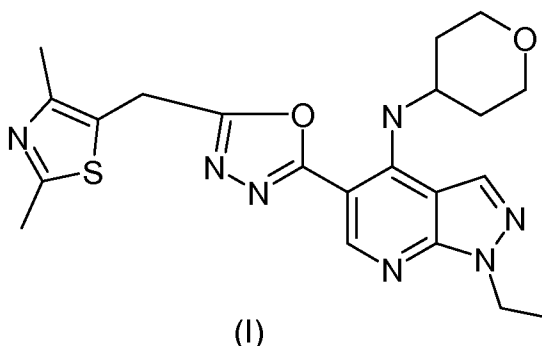
T3P – propylphosphonic anhydride (CAS number [68957-94-8])

DCM- dichloromethane

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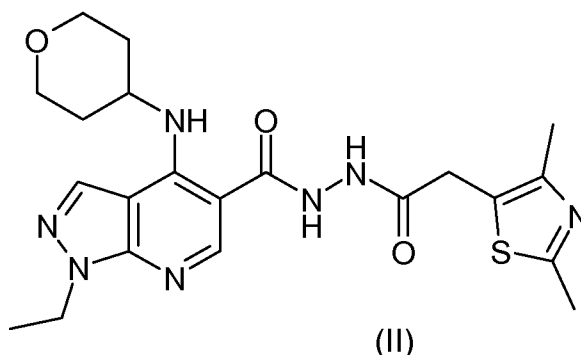
TsCl- tosyl chloride

A further aspect of the invention is a process for the preparation of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; comprising cyclising a compound of formula (II);



(II)

using tosyl chloride, a soluble organic base for example diisopropylethylamine ($i\text{Pr}_2\text{EtN}$) or analine, in a non protonic solvent for example dichloromethane or acetone or a mixture thereof;

and optionally preparing a pharmaceutically acceptable salt of a compound of formula (I).

In one embodiment a mixture of DCM/acetone is used.

In one embodiment the organic base used is $i\text{Pr}_2\text{EtN}$.

Suitable solvents in which both the compound of formula (I) and the compound of formula (II) are soluble will be readily identifiable by the skilled person.

The present process avoids the use of the Burgess reagent described in WO04/056823. The use of the Burgess reagent in the prior process can lead to undesirable levels of the reagent in the resulting material. It can be difficult to purify the final material to remove the reagent.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General

Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00).

The present invention also includes the use in the treatment or prophylaxis of anxiety as comorbid anxiety and depression also referred to as mixed anxiety and depression. In addition, depression (and, thus, comorbid depression and anxiety) is associated with other psychiatric and nonpsychiatric medical conditions (eg, cardiovascular disease, diabetes, HIV/AIDS, maternal and reproductive-related syndromes, and psychosomatic illnesses).

The numbers in brackets after the listed disorders refer to the classification code in DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association. The various subtypes of the disorders mentioned herein are contemplated as part of the present invention.

The invention also provides a method for the treatment or prophylaxis of an anxiety disorder, for example those anxiety disorders mentioned hereinabove, in a subject in need thereof, comprising administering to said subject an effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of an anxiety disorder, for example those anxiety disorders mentioned hereinabove.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of an anxiety disorder, for example those anxiety disorders mentioned hereinabove.

For use in therapy the compound of formula (I) is usually administered as a pharmaceutical composition.

The compound of formula (I), or its pharmaceutically acceptable salts, may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compound of formula (I) or its pharmaceutically acceptable salts which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared

using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

5 Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

10 Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for
15 use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can
20 also take the form of pump-atomisers.

 Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

 Compositions for rectal administration are conveniently in the form of
25 suppositories containing a conventional suppository base such as cocoa butter.

 Compositions suitable for transdermal administration include ointments, gels and patches.

 In one embodiment the composition is in unit dose form such as a tablet, capsule or ampoule.

30 The composition may contain from 0.1% to 100% by weight, for example from 10 to 60% by weight, of the active material, depending on the method of administration. The composition may contain from 0% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The composition may contain from 0.05mg to 1000mg, for example
35 from 1.0mg to 500mg, of the active material, depending on the method of administration. The composition may contain from 50 mg to 1000 mg, for example from 100mg to 400mg of the carrier, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and
40 other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 500 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

It is to be understood that as used herein any reference to treatment includes both treatment of established symptoms and prophylactic treatment.

In another aspect of the present invention the compound of formula (I) its salts and/or pharmaceutical compositions may be used in combination with another therapeutically active agent. In particular the compound of formula (I) its salts and/or pharmaceutical compositions may be used in combination with compounds that affect monoamine transmission, for example serotonin reuptake inhibitors (SERT) for example paroxetine, fluoxetine, clomipramine and citalopram; dopamine transporter inhibitors (DAT) for example bupropion; norepinephrine transporter inhibitors (NET) for example, reboxetine or atomoxetine.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus a pharmaceutical composition comprising a combination as defined above together with one or more pharmaceutically acceptable carriers and/or excipients represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical composition(s).

The invention also provides a method of preparing a combination as defined herein,

the method comprising either

(a) preparing a separate pharmaceutical composition for administration of the individual compounds of the combination either sequentially or simultaneously, or

(b) preparing a combined pharmaceutical composition for administration of the individual compounds of the combination simultaneously,

wherein the pharmaceutical composition comprises the combination together with one or more pharmaceutically acceptable carriers and/or excipients.

The following Examples illustrate the invention.

Example 1: Marmoset Human Threat Test (HTT)

The study used was based on the method described in Costall, B. et al (1988) Br. J. Pharmac. 95 p475P. The method utilised in house laboratory-bred male and female common marmosets over 2 years of age, weighing 300-500g. The animals were caged in couples, in a housing room maintained at $25 \pm 1^\circ\text{C}$, 60% humidity and a 12 hour light/dark cycle (lights on at 0600, with 30 min simulated dawn and twilight). Both animals in each pair were involved in the test, which was carried out with the animals situated in the home cage.

As there can be variability in the behavioural response between different marmosets, the "responder" animals were pre-selected to meet the baseline criteria of at least 10 postures exhibited in the 2 minutes test period.

The postures recorded in the test were those described by Costall et al *supra*;

- *Genital presenting* ("Tail Posture"): the animal's back is turned to the observer with elevation of the tail to expose the genital region;
- *Scent-marking*: the animal scent-marks the cage surfaces using circum-anal and circum-genital scent glands;
- *Slit-stare*: the animal stares at the observer with flattened ear tufts and eyes reduced to "slits"
- *Arch-piloerection*: the animal moves around the cage with arched back and full-body piloerection, failing to make eye contact with the observer

The number of jumps from the back of the cage to the cage front provided an index of locomotor activity to assess potential for sedation or locomotor stimulation.

A selective reduction in postures in the absence of sedation as assessed by the number of jumps is interpreted as an anxiolytic profile in this assay.

Example 2: The effects of 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine in the marmoset human threat test

Central anxiolytic effects of the test compound can be assessed from their ability to reduce the characteristic defensive postures of marmosets in response to a threatening approach by a human in the HTT test described in Example 1. The ability of a drug to reduce the number of postures made by marmosets can be compared with effects of the drug on jumps, a measure of locomotor activity. Reduced jumps would indicate a sedative effect of the drug, which would confound the measure of postures. In a HTT, the effect of single doses of 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (0.03, 0.1, 0.3, 1 or 3 mg/kg) or vehicle (HPMC 0.5%, Tween80 0.1% in citrate buffer) administered orally 1 hour prior to testing on the number of postures and jumps was measured in male/female marmosets (n=5 or 6 per group). 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine significantly reduced the number of postures at 0.1, 0.3 and 1 mg/kg without any effects on jumps (see table) indicative of an anxiolytic response without sedation. Within this anxiolytic dose range 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine was well tolerated.

Table 1 Effect of 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine in the Marmoset HTT

Dose (mg/kg)	Postures (number)	Jumps (number)	Blood Concentration (ng/mL)
0	12.0	12.7	NQ
0.03	10.7	10.0	1.3 ^a
0	11.7	13.0	NQ
0.1	7.2**	10.8	4.2 ^a
0.3	5.3**	8.5	12.7 ^a
1	5.5**	8.5	42.5 ^a

Key:

5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine was administered orally 60 minutes before the test (data represent means from two separate experiments with matching vehicle control groups; n=5 to 6/group).

** = Statistical significance (p<0.01) versus control group.

a = Extrapolated value from a separate pharmacokinetic study.

NQ =Not quantifiable.

5

The lowest anxiolytic dose (0.1 mg/kg) was associated with a blood exposure of 4.2 ng/mL (see table 1). As it was not possible to obtain blood samples from marmosets used in the HTT, blood concentrations were extrapolated from an independent pharmacokinetic study with marmosets (n=4) in which a 1 mg/kg oral dose of 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine produced a blood exposure of 42 ng/mL (range 12.8 to 60.9 ng/mL).

10

These data demonstrate that 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine is able to induce a central effect on behaviour at doses that do not cause side effects in the marmoset, providing evidence that 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine may be efficacious in the treatment of anxiety disorders in the absence of PDE4-related side effects such as nausea and vomiting.

15

20

Example 3. Preparation of 5-{5-[(2,4-Dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

5 **Stage 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**
1-Ethyl-1H-pyrazol-5-amine (1000 g) and diethyl [(ethyloxy)methylidene] propanedioate (1900 mL) were heated to reflux (internal temperature ~100°C) for 1.5 hours then ethanol was removed via vacuum distillation.

POCl₃ (2500 mL) was added and the mixture heated to reflux (internal temperature
10 ~115°C) for 3.5 hours. The mixture was cooled to 20°C, acetonitrile (1000 mL) was added and then the solution further cooled down to 10°C.
The mixture was added dropwise to cold (about 10°C) water (16000 mL), keeping the internal temperature below 20°C. Acetonitrile (1000 mL) was used to wash the line.
The obtained suspension was stirred for about 20 hours then the solid was collected
15 by filtration, washed with water (4 x 3000 mL) and dried under vacuum at 50°C overnight to obtain ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate as a pale brown solid (1610 g), overall yield of 70% theoretical.

20 **Stage 2: Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (1610g), tetrahydro-2H-pyran-4-amine hydrochloride (918 g) and ⁱPr₂EtN (3220 mL) were combined in isopropanol (4830 mL) and heated to reflux for 22 hours.
The solution was cooled down to 50°C and seeded with ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (1.61 g).
25 After 1 hour at 50°C the slurry was cooled down to 0°C in 2 hours and stirred for about 4 hours. The solid was collected by filtration, washed with cold isopropanol (0°C, 2 x 3220 mL) and dried under vacuum at 50°C to obtain ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate as a
30 white solid (1735 g), overall yield about 86% theoretical.

Stage 3: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

Solid ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (1735 g) was suspended in water (8670 mL); solid KOH (451 g) was then added and the suspension heated to 75°C for about 1 hour.
The mixture was cooled down to 20°C and HCl 3N (2600 mL) was added then the mixture was aged for about 19 hours, and then the solid was collected by filtration, washes with water (2 x 5200 mL) and dried under vacuum at 50°C for 24 hours to
40 obtain 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid as a white solid (1523 g), overall yield 96% theoretical.

Stage 4: 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride

1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (1523g), 1,1-dimethylethyl hydrazinecarboxylate (838 g), ⁱPr₂EtN (4110 mL) and EtOAc (3050 mL) were charged in the vessel and cooled to 5-10°C. Commercial T3P 50% w/w in EtOAc (6850 mL) was slowly added in about 1.5 hours. The solution was then heated to 25°C and stirred for 1 hour. Potassium carbonate 10% w/w (760 g in 7600 mL of water) was added, the mixture was stirred and then the phases were separated.

- 10 The aqueous phase was back-extracted twice with EtOAc (2 x 7600 mL) then the combined organic layers were concentrated under vacuum to about 4500 mL. EtOAc (7600 mL) was added and the solution concentrated again under vacuum to about 4500 mL. The suspension was filtered to remove some inorganic solid and washed with EtOAc (1500 mL). HCl 5-6 N in isopropanol (7600 mL) was added obtaining a thick suspension. The suspension was heated to 50-55°C (internal temperature) for about 1.5 hours then cooled to 20°C. The suspension was stirred overnight and then the solid was collected by filtration, washed with isopropanol (2 x 4500 mL) and dried under vacuum at 50°C for several hours to obtain 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride (1930 g) as a white solid, overall yield 97% theoretical.

Stage 5: N'-[(2,4-Dimethyl-1,3-thiazol-5-yl)acetyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide

1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide dihydrochloride (1200g) was charged under nitrogen followed by dichloromethane (9.600 mL) and ⁱPr₂EtN (2760 mL). The mixture was stirred at 20°C for about 15 minutes. (2,4-dimethyl-1,3-thiazol-5-yl)acetic acid (660 g) was added to the suspension and the mixture was cooled to 5°C (internal temperature) to add slowly, in about 40 minutes, commercial T3P solution 50% w/w in EtOAc (2400 mL) keeping the temperature below 10°C. The suspension was heated to 20°C and a solution of sodium hydroxide 2N (6000 mL) was added. A solid immediately precipitates and the suspension was heated to 40°C for about 1 hour, then cooled to 20°C and aged overnight. The suspension was filtered and the solid washed with sodium bicarbonate 2% w/w solution (4800 mL) and then three times with water (4800 mL). The solid was dried in the oven at 50°C overnight to obtain 826 g of N'-[(2,4-dimethyl-1,3-thiazol-5-yl)acetyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide as a white solid, overall yield 63% theoretical.

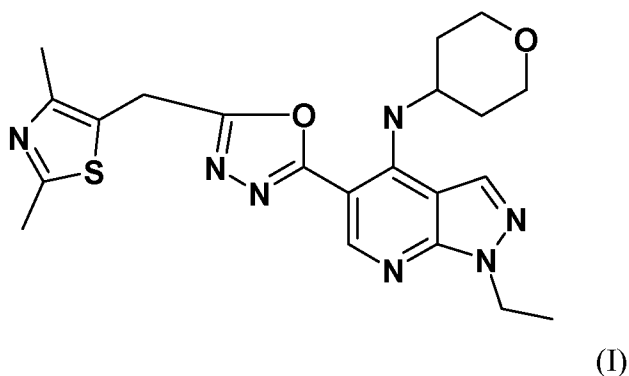
Stage 6: 5-{5-[(2,4-Dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine

Solid N'-[(2,4-dimethyl-1,3-thiazol-5-yl)acetyl]-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carbohydrazide (820g) was suspended in

- dichloromethane (8200 mL). i -Pr₂EtN (900 mL) and Tosyl chloride (508 g) were added and the mixture was heated to reflux for about 1.5 hours. The mixture was cooled down to 20°C and sodium hydroxide 2N (4100 mL) was added and the mixture stirred, the layers were separated and the organic layer was washed with sodium hydroxide 2N (4100 mL) and water (2 x 4100 mL). The resulting organic layer was concentrated to about 4900 mL, dichloromethane (1640 mL) was added then the solution was filtered to remove inorganics, the filter washed with dichloromethane (400 mL) and concentrated again to about 4900 mL. The solution was seeded at 20°C (4.1 g of 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine suspended in 82 mL of acetone), then acetone (10660 mL) was added in about 1 hour and the slurry was aged for 2 hours, then the solid was collected by filtration, washes with acetone (3 x 2400 mL) and dried under vacuum at 50°C for about 24 hours to obtain 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (581 g) as a white solid, overall yield 73.7% theoretical.

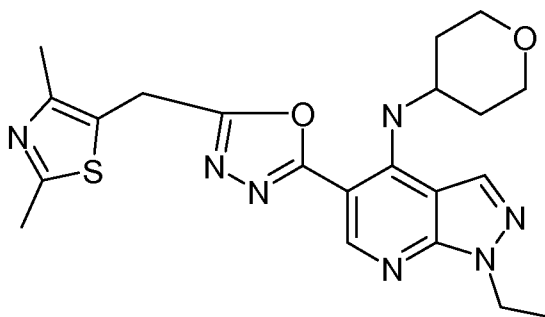
Claims

1. Use of a compound of formula (I): 5-{5-[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]-1,3,4-oxadiazol-2-yl}-1-ethyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine



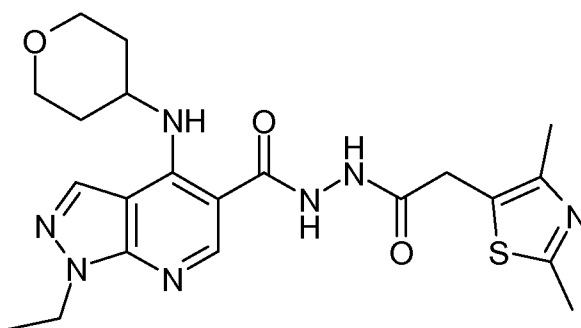
- or a pharmaceutically acceptable salt thereof for the treatment of anxiety disorders.
2. Use of a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of anxiety disorders.
3. A method for the treatment of an anxiety disorder, in a subject in need thereof, comprising administering to said subject an effective amount of the compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof.
4. A compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of an anxiety disorder.
5. The use, method or compound as claimed in anyone of claims 1 to 4 wherein anxiety disorder is comorbid with depression.
6. The use or method or compound as claimed in any one of claims 1 to 5 wherein the anxiety disorder is selected from Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia, and Panic Disorder with Agoraphobia; Agoraphobia; Agoraphobia Without History of Panic Disorder, Specific Phobia including the subtypes Animal Type, Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type, Social Phobia (Social Anxiety Disorder), Obsessive-Compulsive Disorder, Posttraumatic Stress Disorder, Acute Stress Disorder, Generalized Anxiety Disorder, Anxiety Disorder Due to a General Medical Condition, Substance-Induced Anxiety Disorder, Separation Anxiety Disorder, Adjustment Disorders with Anxiety and Anxiety Disorder Not Otherwise Specified.

7. A process for the preparation of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; comprising cyclising a compound of formula (II);



(II)

using tosyl chloride and a soluble organic base in a non protonic solvent; and optionally preparing a pharmaceutically acceptable salt of a compound of formula (I).

8. The process as claimed in claim 7 wherein the soluble organic base is diisopropylethylamine or analine.
9. The process as claimed in claim 7 wherein the non protonic solvent is dichloromethane or acetone or a mixture thereof.
10. The process as claimed in claim 7 wherein the soluble organic base is diisopropylethylamine and/or the non protonic solvent is a mixture of dichloromethane and acetone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/052753

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/052753

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4162 A61P25/22
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI YUN-FENG ET AL: "Antidepressant- and anxiolytic-like effects of the phosphodiesterase-4 inhibitor rolipram on behavior depend on cyclic AMP response element binding protein-mediated neurogenesis in the hippocampus.", NEUROPSYCHOPHARMACOLOGY : OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY OCT 2009 LNKD-PUBMED:19516250, vol. 34, no. 11, October 2009 (2009-10), pages 2404-2419, XP002636154, ISSN: 1740-634X page 2404, abstract page 2405, left-hand column, paragraph 2 page 2413, right-hand column, Discussion ----- -/-	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

22 July 2011

Date of mailing of the international search report

05/08/2011

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Authorized officer

Baurand, Petra

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/052753

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERNARD P ET AL: "Application of drug repositioning strategy to TOFISOPAM.", CURRENT MEDICINAL CHEMISTRY 2008 LNKD-PUBMED:19075663, vol. 15, no. 30, 2008, pages 3196-3203, XP002636155, ISSN: 0929-8673 page 3196, right-hand column, paragraph 1 -----	1-6
Y	WO 2004/056823 A1 (GLAXO GROUP LTD [GB]; ALLEN DAVID GEORGE [GB]; COE DIANE MARY [GB]; CO) 8 July 2004 (2004-07-08) example 98 page 70, line 26 -----	1-6
Y	DAVIS T GREGG ET AL: "The Identification of a Novel Phosphodiesterase 4 Inhibitor, 1-Ethyl-5-{5-[(4-methyl-1-piperazinyl)methyl]-1,3,4-oxadiazol-2-yl}-N-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-b]pyridin-4-amine (EPPA-1), with Improved Therapeutic Index using Pica Feeding in Rats as a Measure of Emetogenicity", JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 330, no. 3, September 2009 (2009-09), pages 922-931 URL, XP002636156, ISSN: 0022-3565 figure 1 page 925, right-hand column, paragraph 2 -----	1-6
Y,P	GUERCIO G. ET AL.: "Overall synthesis of GSK35627: Quick delivery of a PDE4 inhibitor using a fit-for-purpose approach", ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 14, no. 5, 1 July 2010 (2010-07-01), pages 1153-1161, XP002636157, the whole document -----	1-6
Y	CHOI YOUNGGI ET AL: "Total synthesis of (-)- and ent-(+)-vindoline.", ORGANIC LETTERS 29 SEP 2005 LNKD-PUBMED:16178578, vol. 7, no. 20, 29 September 2005 (2005-09-29), pages 4539-4542, XP002652555, ISSN: 1523-7060 page 4540, left-hand column, paragraph 1 Scheme 1 ----- -/--	7-10

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/052753

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAMPBELL E L ET AL: "Total synthesis of (+)-fendleridine (aspidalbidine) and (+)-1 acetylaspidalbidine", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 20100310 AMERICAN CHEMICAL SOCIETY USA LNKD- DOI:10.1021/JA908819Q, vol. 132, no. 9, 11 February 2010 (2010-02-11), pages 3009-3012, XP002652556, ISSN: 0002-7863 page 3010, right-hand column, paragraph 2 Scheme 1 -----	7-10
Y	DOLMAN SARAH J ET AL: "Superior reactivity of thiosemicarbazides in the synthesis of 2-amino-1,3,4-oxadiazoles.", THE JOURNAL OF ORGANIC CHEMISTRY 8 DEC 2006 LNKD- PUBMED:17137395, vol. 71, no. 25, 8 December 2006 (2006-12-08), pages 9548-9551, XP002652557, ISSN: 0022-3263 Schemes 1 and 2 -----	7-10
Y	JOHNS B A ET AL: "The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 19, no. 6, 15 March 2009 (2009-03-15), pages 1802-1806, XP026005883, ISSN: 0960-894X, DOI: DOI:10.1016/J.BMCL.2009.01.090 [retrieved on 2009-01-30] page 1805, right-hand column, paragraph 1 Scheme 6 -----	7-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/052753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2006252790 A1	09-11-2006
		ZA 200605901 A	27-12-2007

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

The use of the compound of formula (I) for the treatment of anxiety disorders

2. claims: 7-10

Process for the preparation of the compound of formula (I)
