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(54) Title: A PHENYL TRIAZOLE DERIVATIVE AND ITS USE FOR MODULATING THE GABA_A RECEPTOR COMPLEX

(57) Abstract: This invention relates to a novel phenyl triazole derivative, pharmaceutical compositions containing this compound, and methods of treatment therewith. The compound of the invention is in particular considered useful for the treatment of central nervous system diseases and disorders which are responsive to modulation of GABA_A receptors containing the $\alpha 5$ subunit.

A PHENYL TRIAZOLE DERIVATIVE AND ITS USE FOR MODULATING THE GABA_A RECEPTOR COMPLEX

TECHNICAL FIELD

5

This invention relates to a novel phenyl triazole derivative, pharmaceutical compositions containing this compound, and methods of treatment therewith. The compound of the invention is in particular considered useful for the treatment of central nervous system diseases and disorders which are responsive to modulation
10 of GABA_A receptors containing the α 5 subunit.

BACKGROUND ART

The GABA_A receptor protein complex is the molecular target of a number
15 of ligands, including the benzodiazepine class of tranquilizer drugs. Multiple isoforms of the GABA_A receptor exist; each receptor is a pentameric complex comprising subunits drawn from α ₁₋₆, β ₁₋₃, γ ₁₋₃, δ , ϵ , and θ subunit isoforms. However, the classical benzodiazepines show no subtype selectivity. Moreover it is believed that one of the key elements responsible for the drawbacks of the classical
20 benzodiazepines (such as sedation, dependency and cognitive impairment) has to do with the α 1 subunit of the GABA_A receptors.

Further, it has been suggested that the GABA_A α 5 subunit represents a therapeutic target for treatment of various diseases and disorders of the central nervous system, and literature has established a nexus between the GABA_A α 5 subunit
25 as therapeutic target, and various acute and chronic neurological disorders, chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis,
30 dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive compulsive disorders, acute stress disorder, drug addictions,

movement disorders, Parkinson's disease, restless leg syndrome, cognition
deficiency disorders, multi-infarct dementia, mood disorders, depression,
neuropsychiatric conditions, psychosis, attention-deficit hyperactivity disorder,
neuropathic pain, stroke, attentional disorders, eating disorders, anorexia, anorexia
5 nervosa, cachexia, weight loss, muscle atrophy, pain conditions, chronic pain,
nociceptive pain, post-operative pain, osteoarthritis pain, rheumatoid arthritis pain,
musculoskeletal pain, burn pain, ocular pain, pain due to inflammation, pain due to
bone fracture, hyperalgesia, neuropathic pain, herpes-related pain, HIV-related
neuropathic pain, traumatic nerve injury, post-stroke pain, post-ischemia pain,
10 fibromyalgia, chronic headache, migraine, tension-type headache, diabetic
neuropathic pain, phantom limb pain, visceral pain and cutaneous pain, and
compounds capable of modulating GABA_A receptors containing the $\alpha 5$ subunit are in
particular expected to be useful candidates for the treatment of i.a. cognitive
disorders, Alzheimer's disease, schizophrenia, positive, negative and/or cognitive
15 symptoms associated with schizophrenia, and cognitive deficits associated with
Down syndrome, with autism, with neurofibromatosis type I, or after stroke.

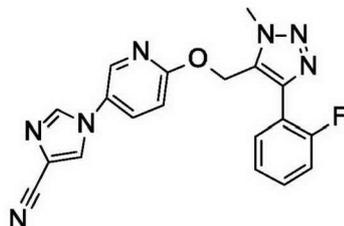
Isoxazole derivatives capable of modulating the GABA_A receptor complex
are known from e.g. WO 2007/039389, WO 2007/042420, WO 2007/054444, WO
2007/071598, WO 2007/074078, WO 2007/074089, WO 2007/137954, WO
20 2009/000662, WO 2009/071464, WO 2009/071476, WO 2009/071477, WO
2010/097368, WO 2010/112475, WO 2010/125042, WO 2010/127968, WO
2010/127974, WO 2010/127975, WO 2010/127976 and WO 2010/127978, and
triazole derivatives capable of modulating the GABA_A receptor complex are known
from e.g. WO 2012/062687. Moreover WO 2008/025539, WO 2008/025540, WO
25 2009/149795 and WO 2011/020615 describe heterocyclic compounds, including
certain phenyl triazole derivatives, useful as agonists of the NR1 H4 (FXR) receptor.
However, the triazole derivatives of the present invention have not been reported.

SUMMARY OF THE INVENTION

30

In its first aspect, the invention provides a phenyl triazole derivative of
the following structure (I):

- 3 -



Formula (I)

i.e. 1-[6-[[5-(2-fluorophenyl)-3-methyl-triazol-4-yl]methoxy]-3-pyridyl]imidazole-4-carbonitrile, and pharmaceutically acceptable salts thereof.

In its second aspect, the invention provides a pharmaceutical composition,
5 comprising a therapeutically effective amount of the phenyl triazole derivative of formula (I) of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention relates to the use of the phenyl triazole derivative of formula (I) of the invention, or a pharmaceutically acceptable salt thereof,
10 for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of GABA_A receptors containing the α 5 subunit.

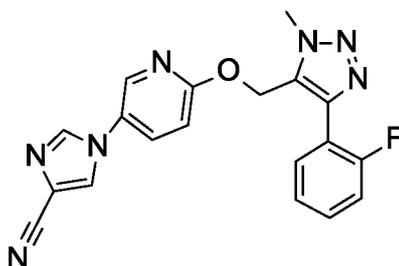
In a still further aspect, the invention provides a method for treatment,
15 prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of GABA_A receptors containing the α 5 subunit, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the phenyl triazole derivative of formula (I) of the invention, or a
20 pharmaceutically acceptable salt thereof.

Other aspects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Phenyl triazole derivatives

In its first aspect the present invention provides a phenyl triazole
5 derivative of the following structure (I):



i.e. 1-[6-[[5-(2-fluorophenyl)-3-methyl-triazol-4-yl]methoxy]-3-
pyridyl]imidazole-4-carbonitrile;

or a pharmaceutically acceptable salt thereof.

10

Pharmaceutically Acceptable Salts

The phenyl triazole derivative of formula (I) of the invention may be
provided in any form suitable for the intended administration. Suitable forms
include pharmaceutically (i.e. physiologically) acceptable salts of the compound of
15 the invention.

Examples of pharmaceutically acceptable salts include, without
limitation, the non-toxic inorganic and organic acid addition salts such as the
hydrochloride derived from hydrochloric acid, the hydrobromide derived from
hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from
20 perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived
from sulphuric acid, the formate derived from formic acid, the acetate derived from
acetic acid, the aconate derived from aconitic acid, the ascorbate derived from
ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the
benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid,
25 the citrate derived from citric acid, the embonate derived from embonic acid, the
enantate derived from enanthic acid, the fumarate derived from fumaric acid, the
glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the
lactate derived from lactic acid, the maleate derived from maleic acid, the

malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Such pharmaceutically acceptable salts and common methodology for preparing them are known in the art. Further details may be found in *Stahl P et al, Handbook of Pharmaceutical Salts: Properties, Selection and Use*; Wiley-VCH, 2002.

In addition, the phenyl triazole derivative of formula (I) of the invention may exist in the form of a polymorph, or the compound may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

20

Labelled Compounds

The phenyl triazole derivative of formula (I) of the invention may be used in its labelled or unlabelled form. In the context of this invention a labelled compound has one or more atoms replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. The labelling will allow easy quantitative detection of said compound.

The labelled compounds of the invention may be useful as diagnostic tools, radio tracers, or monitoring agents in various diagnostic methods, and for *in vivo* receptor imaging.

The labelled isomer of the invention preferably contains at least one radionuclide as a label. Positron emitting radionuclides are all candidates for usage. In the context of this invention the radionuclide is preferably selected from ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{131}I , ^{125}I , ^{123}I and ^{18}F .

30

The physical method for detecting the labelled isomer of the present invention may be selected from Position Emission Tomography (PET), Single Photon Imaging Computed Tomography (SPECT), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), and Computed Axial
5 X-ray Tomography (CAT), or combinations thereof.

Deuterated analogs

The phenyl triazole derivative of formula (I) of the invention may be provided in the form of their deuterated analogs. Deuterium forms bonds with
10 carbon that vibrate at a lower frequency and are thus stronger than C-H bonds. Therefore "heavy hydrogen" (deuterium) versions of drugs may be more stable towards degradation and last longer in the organism.

Methods of Preparation

15 The phenyl triazole derivative of formula (I) of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the process described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

20 The end product of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

25 The phenyl triazole derivative of formula (I) of the invention are capable of modulating GABA_A receptors containing the $\alpha 5$ subunit. Thus in further aspect, the phenyl triazole derivative of formula (I) of the invention is considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to modulation of GABA_A receptors containing the $\alpha 5$ subunit, in particular in the central
30 nervous system.

In one embodiment, the phenyl triazole derivative of formula (I) of the invention is considered useful for the treatment, prevention or alleviation of a disease, disorder or condition which is selected from the group of acute

neurological disorders, chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian
5 rhythms, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's
10 dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit hyperactivity disorder, neuropathic pain, stroke, attentional disorders, and for use as cognitive enhancers.

In another embodiment, the phenyl triazole derivative of formula (I) of the invention is considered useful for the treatment, prevention or alleviation of a
15 disease, disorder or condition which is selected from the group of eating disorders, anorexia, anorexia nervosa, cachexia, weight loss, muscle atrophy, pain conditions, chronic pain, nociceptive pain, post-operative pain, osteoarthritis pain, rheumatoid arthritis pain, musculoskeletal pain, burn pain, ocular pain, pain due to inflammation, pain due to bone fracture, hyperalgesia, neuropathic pain, herpes-
20 related pain, HIV-related neuropathic pain, traumatic nerve injury, post-stroke pain, post-ischemia pain, fibromyalgia, chronic headache, migraine, tension-type headache, diabetic neuropathic pain, phantom limb pain, visceral pain and cutaneous pain.

In a third embodiment, the phenyl triazole derivative of formula (I) of the
25 invention is considered useful for the treatment, prevention or alleviation of a disease, disorder or condition selected from the group of cognitive disorders, Alzheimer's disease, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, and cognitive deficits associated with Down syndrome, with autism, with neurofibromatosis type I, or after stroke.

30 In a fourth embodiment, the phenyl triazole derivative of formula (I) of the invention is considered useful for the treatment, prevention or alleviation of a disease, disorder or condition selected from the group of Alzheimer's disease, schizophrenia and Down syndrome.

In a fifth embodiment, the phenyl triazole derivative of formula (I) of the invention is considered useful as a cognitive enhancer.

Further, the phenyl triazole derivative of formula (I) of the invention may be useful as a radioligand in assays for detecting compounds capable of
5 modulating GABA_A receptors containing the $\alpha 5$ subunit.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API), that is the compound of formula (I) or a pharmaceutically acceptable salt thereof, including solvates and anhydrides, is within the range of from about 0.1 to about 1000 mg API per day, more preferred
10 of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

15

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the phenyl triazole derivative of formula (I) of the invention.

20 While the phenyl triazole derivative of formula (I) of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary
25 pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the phenyl triazole derivative of formula (I) of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other
30 therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular
5 injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or
10 microcapsules.

The phenyl triazole derivative of formula (I) of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in
15 particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles,
20 and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The phenyl triazole derivative of formula (I) of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as
25 the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of formula (I) of the invention.

For preparing pharmaceutical compositions from a phenyl triazole derivative of formula (I) of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills,
30 capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and
5 size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, cellulose, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax,
10 cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as
15 solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

20 Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection
25 liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled
30 syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient

may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example

dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

5 Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for
10 example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be
15 obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate
20 quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

25 In one embodiment, the invention provides tablets or capsules for oral administration.

In another embodiment, the invention provides liquids for intravenous administration and continuous infusion.

Further details on techniques for formulation and administration may be
30 found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of

administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by
5 titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient of formula (I) per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for
10 therapeutic treatments.

The active ingredient of formula (I) may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g}/\text{kg}$ i.v. and 1 $\mu\text{g}/\text{kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o.
15 Preferred ranges are from about 0.1 $\mu\text{g}/\text{kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g}/\text{kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment,
20 prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of GABA_A receptors containing the $\alpha 5$ subunit, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of the phenyl triazole derivative of formula (I) of the
25 invention, or a pharmaceutically acceptable salt thereof.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the
30 subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

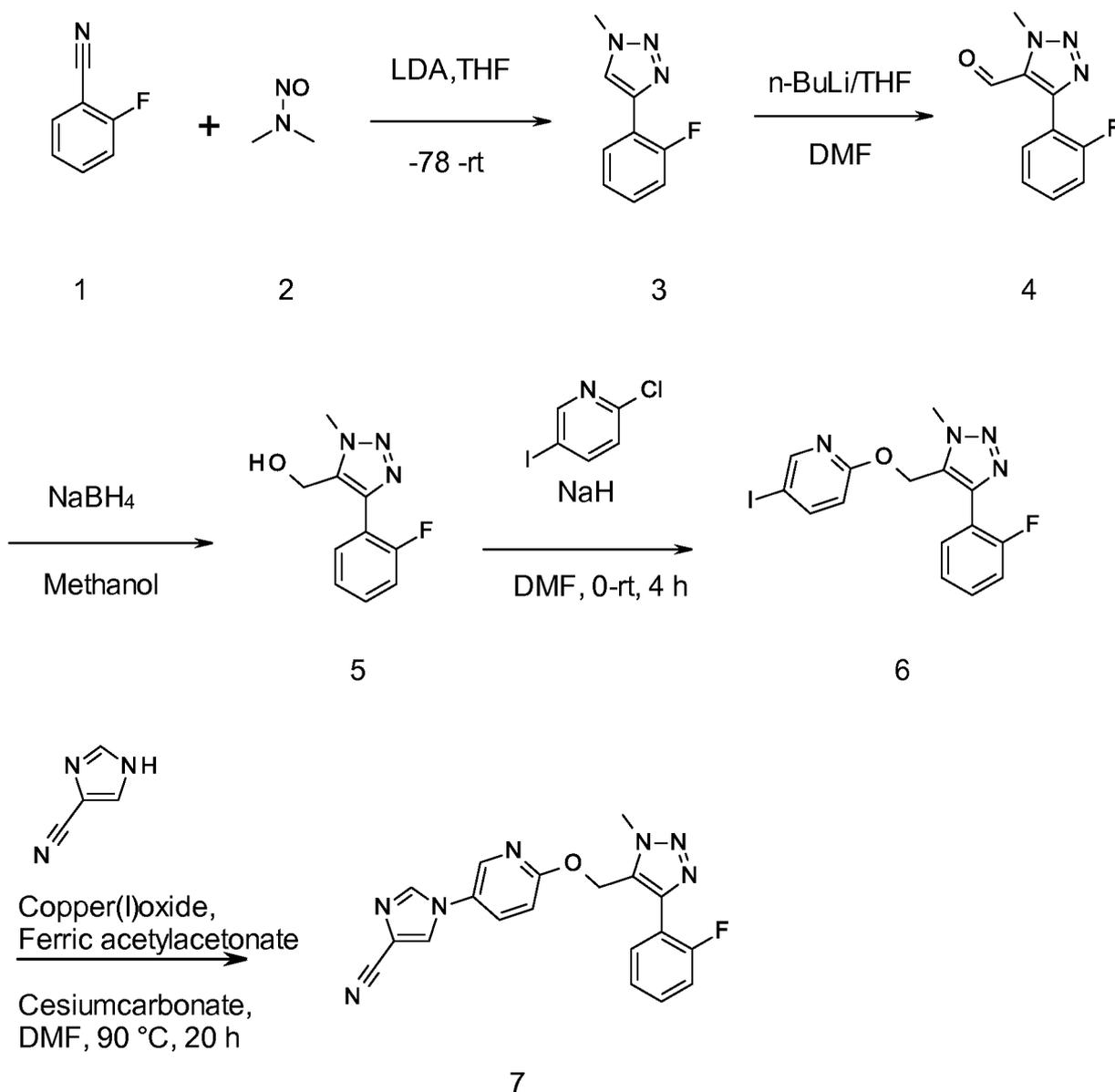
EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

Preparative Example

Preparation of 1-{6-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3] triazol-4-ylmethoxy]-pyridin-3-yl}-1H-imidazole-4-carbonitrile (Compound 7)



Preparation of 4-(2-fluorophenyl)-1-methyl-1H-1,2,3-triazole (Compound 3)

To a pre cooled (-78°C, internal temp. -70°C) solution of diisopropyl amine (193.13 g, 1899.04 mmol) in THF (1500 ml) under nitrogen atmosphere was added n-Butyllithium (759.617 ml, 1899.04 mmol, 2.5 M solution in hexane) and stirred for 90 min. Then N, N-dimethyl nitrous amide **2** (134.57 g, 1816.48 mmol) in THF (500 ml) was cannulated portion wise during a period of 30 min. and stirred for 1 h. Then a solution of 2-Fluorobenzonitrile **1** (100.0 g, 825.671 mmol) in THF (500 ml) was cannulated portion wise during a period of 30 min and stirred at -78°C (internal temp. -70°C) for 1 h. Then cooling bath was removed and stirred at room temperature for 2 h. The reaction was monitored by TLC and UPLC. The above reaction mass was slowly quenched with saturated solution of ammonium chloride (2000 ml) at room temperature and the aqueous layer was extracted with dichloromethane (5 X 2000 ml). The combined organic layer was dried over sodium sulphate, filtered and concentrated to afford crude mass (170.0 g, 116.21% mass balance). It was purified by gravity column using 30% ethyl acetate in pet ether as an eluent to furnish desired product 4-(2-fluorophenyl)-1-methyl-1H-1,2,3-triazole (64.52 g, 44.10% mass balance) as reddish gum. Then it was triturated with methyl tert-butyl ether (1000 ml) and hexane (500 ml), the supernat layer was decanted and the solid was dried to furnish desired product 4-(2-fluorophenyl)-1-methyl-1H-1,2,3-triazole (32.9 g, 22.49%) as yellowish solid.

¹H NMR (400 MHz, CDCl₃): δ 8.30 (t, *J* = 7.64 Hz, 1H), 7.94 (d, *J* = 3.72 Hz, 1H), 7.34-7.24 (m, 2H), 7.15 (t, *J* = 6.72 Hz, 1H), 4.17 (s, 1H); MH⁺ = 178.1/179.2.

Preparation of 4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-carbaldehyde (Compound 4)

To a pre cooled (-70°C to -78°C) solution of 4-(2-fluorophenyl)-1-methyl-1H-1,2,3-triazole **3** (51 g, 287.84 mmol) under nitrogen atmosphere in THF (1200 ml) was added n-Butyllithium (138.16 ml, 345.41 mmol, 2.5M solution in hexane) and stirred for 2h. Then DMF (1200 ml, 14794.844 mmol) was added and stirred at -78°C for 30 min. The reaction was monitored by TLC and UPLC. The reaction mixture was slowly quenched with ice cold water (1000 ml) and the aqueous layer was extracted with ethyl acetate (5 X 1000 ml). The combined

organic layer was dried over sodium sulphate, filtered and concentrated to afford crude mass (50 g, 84.66% mass balance). It was purified by gravity column using 20% ethyl acetate in pet ether as an eluent to afford desired product 4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-carbaldehyde (40 g, 67.72%)
5 as reddish solid. Then it was triturated with methyl tert-butyl ether (1000 ml) and hexane (500 ml), the supernatant layer was decanted and the solid was dried to furnish desired product 4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-carbaldehyde (32 g, 54.18% yield) as white solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.00 (d, $J = 3.4$ Hz, 1H), 7.80 (td, $J =$
10 7.6 & 1.6 Hz, 1H), 7.51 (td, $J = 7.6$ & 0.8 Hz, 1H), 7.37-7.33 (m, 1H), 7.28 (t, $J =$
9.88 Hz, 1H), 4.40 (s, 3H); $\text{MH}^+ = 206.1/207.1$; IR: 1686.3 cm^{-1} .

Preparation of (4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-yl) methanol (5)

To a stirred solution of 4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-
15 carbaldehyde **4** (38 g, 185.19 mmol) under nitrogen atmosphere in methanol (300 ml) was added sodium borohydride (8.407 g, 222.23 mmol) in portion wise at 0°C and the reaction mass stirred for 20 min. The reaction was monitored by TLC and UPLC. The reaction mixture was quenched with water (500 ml) and concentrated to remove methanol and water. Then it was extracted with ethyl acetate (4 X 500
20 ml), combined organic layer was washed with brine (50 ml), dried over sodium sulphate, filtered and concentrated to afford crude mass (34 g, 88.6% mass balance). The above solid was triturated with hexane (3 X 100 ml), the supernatant layer was decanted and the solid was dried to afford desired product (4-(2-Fluorophenyl)-1-methyl-1H-1,2,3-triazole-5-yl) methanol (31 g, 80.77%) as off-
25 white solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.67 (dt, $J = 7.60$ & 1.76 Hz, 1H), 7.40-
7.37 (m, 1H), 7.26 (dt, $J = 7.50$ & 1.00 Hz, 1H), 7.17 (t, $J = 8.32$ Hz, 1H), 4.76 (s,
2H), 4.717 (s, 3H), 2.60 (s, 1H, exchangeable with D_2O); UPLC (m/z): 208 (MH^+);
HPLC Purity: 99.44%; IR: 3201.3 cm^{-1} ; MP: $99.1-102.2^\circ\text{C}$.

Preparation of 2-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3]triazol-4-ylmethoxy]-5-iodo-pyridine (Compound 6)

To a suspension of NaH (0.73 g, 18.1 mmol, 60% in mineral oil) in DMF (10 ml) under N₂ atmosphere at 0°C was added [5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3]triazol-4-yl]-methanol (2.5 g, 12.06 mmol) and stirred for 1 h. Then 2-chloro-5-iodopyridine (3.17 g, 13.27 mmol) was added and reaction mixture was slowly warmed to room temperature and stirred for 4 h. The reaction was monitored by TLC. The reaction mixture was quenched with ice-water, extracted with ethylacetate (50 ml), washed with brine (10 ml), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude mass (4.4 g, 88.9% mass balance). It was triturated with hexane and the solid was filtered and dried under vacuum to furnish 2-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3]triazol-4-ylmethoxy]-5-iodo-pyridine (2.4 g, 48.48%) as yellow solid.

¹H NMR (400 MHz, DMSO-D₆): δ 8.28 (d, *J* = 2.00 Hz, 1H), 8.00 (q_{ab}, *J* = 8.64 & 2.16 Hz, 1H), 7.58 (t, *J* = 7.44 Hz, 1H), 7.49 (q, *J* = 5.68 Hz, 1H), 7.32 (q, *J* = 7.32 Hz, 2H), 6.70 (d, *J* = 8.68 Hz, 1H), 5.44 (s, 2H), 4.15 (s, 3H).

Preparation of 1-{6-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3] triazol-4-ylmethoxy]-pyridin-3-yl}-1H-imidazole-4-carbonitrile (Compound 7)

The mixture of 2-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3]triazol-4-ylmethoxy]-5-iodo-pyridine (0.5 g, 1.22 mmol), 1H-imidazole-4-carbonitrile (0.170 g, 1.82 mmol), cesium carbonate (0.79 g, 2.43 mmol), copper(I)oxide (0.017 g, 0.122 mmol), ferric acetylacetonate (0.129 g, 0.365 mmol) in DMF (10 ml) was heated at 90°C for 20 h. The reaction was monitored by TLC and UPLC. The reaction mixture was concentrated under reduced pressure, water was added and extracted with ethylacetate (3 X 50 ml). The organic layer was washed with brine (15 ml), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude mass (500 mg, 109% mass balance). It was purified in grace column using 2% methanol in chloroform as an eluent to furnish desired 1-{6-[5-(2-Fluoro-phenyl)-3-methyl-3H-[1,2,3]triazol-4-ylmethoxy]-pyridin-3-yl}-1H-imidazole-4-carbonitrile (0.180 g, 39.38%) as off-white solid.

¹H NMR (400 MHz, DMSO-D₆): δ 8.68 (d, *J* = 1.16 Hz, 1H), 8.46 (d, *J* = 2.8 Hz, 1H), 8.42 (d, *J* = 1.12 Hz, 1H), 8.06 (dd, *J* = 8.88 & 2.8 Hz, 1H), 7.61 (dt, *J*

= 7.4 & 1.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.35 (q, $J = 9.2$ Hz, 2H), 7.05 (d, $J = 8.84$ Hz, 1H), 5.53 (s, 2H), 4.18 (s, 3H). UPLC (m/z): 375/377(MH⁺); HPLC purity: 96.96%; MP: 178.0-181.5°C.

5 Example 2

***In vitro* inhibition of ³H-flumazenil (³H-Ro 15-1788) binding HEK cells expressing the human GABA_A $\alpha_5\beta_3\gamma_2$ s receptor**

The benzodiazepine modulator unit can selectively be labelled with the antagonist ³H-flumazenil.

10 The affinity of ³H-flumazenil for different subunit combinations have been reported to be 1.0 nM, 1.1 nM, 1.5 nM and 0.4 nM for $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_2\gamma_2$, $\alpha_3\beta_2\gamma_2$, and $\alpha_5\beta_2\gamma_2$ receptors, respectively, and 107 nM and 90 nM for $\alpha_4\beta_2\gamma_2$ and $\alpha_6\beta_2\gamma_2$ receptors (see *Sieghart; Pharmacol. Rev.* 1995 **47** 181-234).

The pharmacology of the mutated $\alpha_5\beta_3\gamma_2$ s GABA_A receptor is similar to
15 that of the wild type receptor with respect ³H-flumazenil binding.

Cell cultures and membrane preparation

HEK-293 cell lines with stable expression of recombinant human GABA_A $\alpha_5\beta_3\gamma_2$ s receptors (plasmid H46/E9/B10) are seeded in T175 polystyrene
20 flasks or roller bottles (1700 cm², Fisher Scientific CCI-431191), and cultured (37°C, 5% CO₂) in Dulbecco's Modified Eagle Medium (DMEM) with GlutaMAX™ supplemented with 10% fetal bovine serum and one or both of the following antibiotics: hygromycin B (50 µg/ml; γ_2 subunit) or G418 (0.5 mg/ml; α_5 subunit).

When the cultures reach confluency, the DMEM is removed and the
25 cells are washed (10 ml for T175 flasks; 50 ml for roller bottles) once in Dulbecco's Phosphate Buffered Saline (DPBS). Following addition of DPBS to the cultures (10 ml for T175 flasks; 100 ml for roller bottles) for approximately 5 min cells are easily detached from the surface by shaking or tapping the flask gently. The cell suspension is transferred to Falcon tubes and centrifuged at 23,500 x g for 10 min
30 at 2°C. The pellet is washed once in 15 ml Tris-citrate buffer (50 mM, pH 7.1) using an Ultra-Turrax homogenizer and centrifuged at 2°C for 10 min at 27,000 x

g. The washed pellet is re-suspended in 15 ml Tris-citrate buffer and frozen at -80°C until the day of the binding experiment.

Assay

5 On the day of the experiment the cell membrane preparation is thawed and centrifuged at 2°C for 10 min at 27,000 x g. The pellet is re-suspended, using an Ultra-Turrax homogenizer in Tris-citrate buffer, to 15-50 µg protein per assay and then used for binding assays.

Aliquots of 500 µl cell suspension are added to 25 µl of test compound
10 solution and 25 µl of ³H-flumazenil (1 nM, final concentration), mixed and incubated for 40 min at 2°C. Non-specific binding is determined using clonazepam (1 µM, final concentration).

All dilutions of test compounds and incubation of assay are performed in glass vials / 96-vial plates. Solutions of test compounds and ³H-flumazenil are
15 prepared 22x the desired final concentration. Compounds are dissolved in 100% DMSO (10 mM stock), diluted in 48% ethanol-water, and tested in triplicate in serial 1:3 or 1:10 dilutions. When screening large numbers of compounds only one concentration of each compound is tested in single wells. Reference compounds are not included routinely, but for each experiment performed total and non-
20 specific binding is compared to data obtained during validation of the assay.

Binding is either terminated by rapid filtration onto

1) Whatman GF/C glass fibre filters using a Brandel Cell harvester, followed by 5 washes with 1 ml ice-cold buffer or onto

2) UniFilter GF/C glass fibre filter plates using a Tomtec cell harvester,
25 followed by washing with approximately 5 ml ice-cold buffer.

The amount of radioactivity on the filters is determined by conventional liquid scintillation counting using a

1) Tri-Carb™ counter (PerkinElmer Life and Analytical Sciences) for separate large filters or

30 2) Topcount™ counter (PerkinElmer Life and Analytical Sciences) for 96-well filter plates. Specific binding is total binding minus non-specific binding.

Calculations

25-75% inhibition of specific binding must be obtained before calculation of an IC₅₀ (the concentration (μM) of the test compound which inhibits the specific binding of ³H-flumazenil by 50%).

5 The IC₅₀ value for a test compound is determined based on the equation:

$$B = 100 - (100 * C^n / (IC_{50}^n + C^n))$$

where *B* is the binding in percentage of total specific binding; *C* is the concentration of test compound; and *n* is the Hill coefficient. For screening
10 purposes *n* is set to 1. The IC₅₀ value is calculated from the concentration response curves by the non-linear regression method using the curve-fitting program GraphPad Prism.

The K_i value for a test compound can be calculated from the IC₅₀ value using the equation by Cheng and Prusoff:

15
$$K_i = IC_{50} / (1 + L/K_d)$$

where the K_d for ³H-flumazenil is 0.36 nM, and L is the measured concentration of ³H-flumazenil in the inhibition assay.

Test result from this experiment is shown in Table 1 below.

20 Table 1

In vitro inhibition of ³H-flumazenil

Test compound	K _i (μM)
Compound 7	0.02

25 **Example 3**

Pharmaceutical Compositions

The phenyl triazole derivative of formula (I) of the invention may be put on any desirable form of composition, and may be dosed in any desired amount. This example shows the preparation of a standard capsule formulation.

Standard Capsule Formulation

Capsules containing 1 mg active pharmaceutical ingredient (API) of formula (I) per capsule are obtained using the following composition:

Ingredient	Function	Amount (mg/capsule)
API	Active ingredient	1
Starch 500	Filler	117

5

The calculated amount of drug substance and filler corresponding to 1 mg of active drug substance and 117 mg of filler per capsule are weighed out and dry-mixed. The blend is subsequently filled into the calculated number of capsules (preferably size 4).

10

Example 4

Figure 1 shows modulation of $\alpha_5\beta_2\gamma_2$ GABA_A receptor currents by the compound of formula (I) in *Xenopus laevis* oocytes. Modulatory efficacy of compound (1) (the compound of formula (I) as the free base) was determined by techniques similar to those described in Mirza et al. (*J Pharmacol Exp Ther.* 2008; 327:954-68). In brief, oocytes were injected with cRNA for human GABA_A receptor subunits α_5 , β_2 and γ_2 in a 1:1:2 ratio and modulatory efficacy was evaluated by co-applications with a submaximal EC₅₋₂₀ GABA concentration (0.5 μ M) termed GABAcontrol. The compound was tested in five concentrations (3.16, 0.316, 0.0316, 0.00316 and 0.000316 μ M) on each oocyte starting with the lowest concentration. Background subtracted peak current amplitudes were normalized to the respective GABAcontrol current, converted to % change and depicted \pm S.E.M. as a function of increasing compound concentrations. Plotted datapoints were fitted to the empirical Hill equation using non-linear regression. 95 % confidence intervals for maximal efficacy (Bottom) and potency (LogEC₅₀) are derived from this fitting routine.

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5 Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

10 The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A phenyl triazole derivative which is
1-[6-[[5-(2-fluorophenyl)-3-methyl-triazol-4-yl]methoxy]-3-pyridyl]imidazole-4-carbonitrile;
or a pharmaceutically acceptable salt, a polymorph or a hydrate thereof.
2. A pharmaceutical composition, comprising a therapeutically effective amount of the phenyl triazole derivative of claim 1, or a pharmaceutically acceptable salt, a polymorph or a hydrate thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.
3. A phenyl triazole derivative which is 1-[6-[[5-(2-fluorophenyl)-3-methyl-triazol-4-yl]methoxy]-3-pyridyl]imidazole-4-carbonitrile; or a pharmaceutically acceptable salt, a polymorph or a hydrate thereof for use in a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of GABA_A receptors containing the α 5 subunit.
4. The compound of claim 3 for use in a method for the treatment of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of GABA_A receptors containing the α 5 subunit.
5. The compound of any one of claims 3-4, wherein the disease, disorder or condition is selected from the group of acute and chronic neurological disorders, chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis, dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional

disorder, obsessive compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit hyperactivity disorder, neuropathic pain, stroke, attentional disorders, eating disorders, anorexia, anorexia nervosa, cachexia, weight loss, muscle atrophy, pain conditions, chronic pain, nociceptive pain, post-operative pain, osteoarthritis pain, rheumatoid arthritis pain, musculoskeletal pain, burn pain, ocular pain, pain due to inflammation, pain due to bone fracture, hyperalgesia, neuropathic pain, herpes-related pain, HIV-related neuropathic pain, traumatic nerve injury, post-stroke pain, post-ischemia pain, fibromyalgia, chronic headache, migraine, tension-type headache, diabetic neuropathic pain, phantom limb pain, visceral pain and cutaneous pain.

6. The compound of any one of claims 3-4, wherein the disease, disorder or condition is selected from the group consisting of Alzheimer's disease, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, and Down syndrome.

7. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of GABA_A receptors containing the $\alpha 5$ subunit, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the phenyl triazole derivative of claim 1, or a pharmaceutically acceptable salt, a polymorph or a hydrate thereof.

8. The method of claim 7, wherein the disease, disorder or condition is selected from the group of acute and chronic neurological disorders, chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I,

sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis, dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit hyperactivity disorder, neuropathic pain, stroke, attentional disorders, eating disorders, anorexia, anorexia nervosa, cachexia, weight loss, muscle atrophy, pain conditions, chronic pain, nociceptive pain, post-operative pain, osteoarthritis pain, rheumatoid arthritis pain, musculoskeletal pain, burn pain, ocular pain, pain due to inflammation, pain due to bone fracture, hyperalgesia, neuropathic pain, herpes-related pain, HIV-related neuropathic pain, traumatic nerve injury, post-stroke pain, post-ischemia pain, fibromyalgia, chronic headache, migraine, tension-type headache, diabetic neuropathic pain, phantom limb pain, visceral pain and cutaneous pain.

9. The method of claim 7, wherein the disease, disorder or condition is selected from the group consisting of Alzheimer's disease, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, and Down syndrome.

10. Use of the phenyl triazole derivative of claim 1 or a pharmaceutically acceptable salt, a polymorph or a hydrate thereof in the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of GABA_A receptors containing the $\alpha 5$ subunit.

11. The use of claim 10, wherein the disease, disorder or condition is selected from the group of acute and chronic neurological disorders, chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with

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schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis, dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit hyperactivity disorder, neuropathic pain, stroke, attentional disorders, eating disorders, anorexia, anorexia nervosa, cachexia, weight loss, muscle atrophy, pain conditions, chronic pain, nociceptive pain, post-operative pain, osteoarthritis pain, rheumatoid arthritis pain, musculoskeletal pain, burn pain, ocular pain, pain due to inflammation, pain due to bone fracture, hyperalgesia, neuropathic pain, herpes-related pain, HIV-related neuropathic pain, traumatic nerve injury, post-stroke pain, post-ischemia pain, fibromyalgia, chronic headache, migraine, tension-type headache, diabetic neuropathic pain, phantom limb pain, visceral pain and cutaneous pain.

12. The use of claim 10, wherein the disease, disorder or condition is selected from the group consisting of Alzheimer's disease, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, and Down syndrome.

Figure 1

