DESCRIPTION CN104739839

The present application relates to a new medical use of a triazine derivative. The compounds of formula (1), in particular when R is optionally substituted alkyl, aralkyl or heterocyclyl - alkyl, a sodium channel blockers exhibit as antifolates or activity. Discloses that when R is an aryl group or a heterocyclic group - group when some of the new compounds.

New Medical Uses of triazine derivative

This application is filed on July 13, 2007, Application No. 200780034119.9, titled "New medical purposes triazine derivative" of Divisional application of application.

TECHNICAL FIELD

The present invention relates to triazine compounds as sodium channel blockers and antifolates in And a medicament for the treatment of a disease associated with preparation.

Background technique

U.S. Patent No. 4,649,139 discloses the formula (A) compounds:

[Image]

Wherein R <1> is C 1-10 alkyl, C 2-10 alkenyl, C 2-10 alkynyl or C 3-10 cycloalkyl group, which Any one can be optionally substituted, R <2> to R <6> are independently selected from hydrogen, halo, C 1-6 alkyl More than one group, an alkenyl group, an alkynyl group, or an alkoxy group (by a halogen, hydroxyl and aryl Optionally substituted), amino, mono- or di-substituted amino, alkenyloxy, acyl, acyloxy Group, a cyano group, a nitro group, an aryl group and an alkylthio group, or connect R <2> to R <6> of any adjacent Two to form (-CH = CH-CH = CH-) group. Which discloses: these compounds Treatment of cardiac dysfunction is active, particularly useful in the treatment of arrhythmia.

The present invention is based on the finding that: formula (A) in some of the new compounds and their derivatives Is effective sodium channel blockers, and therefore displayed as in the treatment of diseases in a mammal The voltage-dependent sodium channel blockers is useful in the treatment of the following diseases in particular It is valuable: epilepsy, multiple sclerosis, glaucoma and uveitis, brain damage Injury and cerebral ischemia, stroke, head injury, spinal cord injury, surgical trauma, neurodegenerative Line disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammation Pain, neuropathic pain, migraine, bipolar disorder, paranoia, anxiety and recognition Cognitive disorders, schizophrenia and trigeminal autonomic nervous headache. Some of the compounds also significantly It shows antifolates activity, thus indicating a antifolate formulations for the treatment of a mammal As the price was cancer and Plasmodium vivax and Plasmodium falciparum malaria confrontation between antimalarials value.

SUMMARY OF THE INVENTION

Thus, a compound or a salt or solvate of the present invention provides compounds of formula (I) below use:

(a)

(A) as a voltage-dependent sodium channel blocker for the treatment of a mammalian disease Disease, in particular, especially humans following diseases: epilepsy, multiple sclerosis, Green Light eye and uveitis, brain damage and cerebral ischemia, stroke, head injury, spinal cord damage Injury, surgical trauma, neurodegenerative diseases, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, neuropathic pain, migraine, bipolar disorder, Paranoia, anxiety and cognitive disorders, schizophrenia and trigeminal autonomic head pain;

(b)

(B) as an anti-folate agents for the treatment of disease in a mammal, particularly for the treatment of

Treatment of mammals against cancer and as an anti-malarial Plasmodium vivax and Plasmodium falciparum malaria Disease, especially in humans;

[Image]

among them

R <1> is hydrogen, C 1-10 alkyl, C 2-10 alkenyl, C 1-3 alkyl - aryl, C 1-3 alkyl - Miscellaneous Cycloalkyl group or a C 3-10 cycloalkyl group, an optionally any of its halogen, halo C 1-6 alkyl, C 1-6 alkyl or C 1-6 alkoxy;

R <2> to R <6> are independently selected from hydrogen, halo, C 1-6 alkyl, alkenyl, alkynyl or alkoxy Group (by a halogen, a hydroxyl group and an aryl group optionally substituted with one or more), amino, mono- or Di-substituted amino, alkenyloxy, acyl, acyloxy, cyano, nitro, aryl And alkylthio.

The present invention further comprises a compound of formula (1) is used to prepare the sodium channel Antifolate agents or blockers or antimalarials, particularly for the treatment of each of these diseases drug.

About C 1-10 alkyl, R <1> is suitably an unsubstituted C 1-6 alkyl, typically methyl, Ethyl, isopropyl, n-propyl, isobutyl or n-butyl.

About C 2-10 alkenyl, R <1> may be unsubstituted C 2-6 alkenyl, such as allyl.

About C 3-10 cycloalkyl group, R <1> is typically a cyclohexyl group, by one or more of the following Group optionally substituted with: halo, haloalkyl or alkoxy group such as chloro, fluoro, trifluoromethyl , Methoxy or ethoxy.

About C 1-3 alkylaryl, R <1> is typically benzyl, wherein the phenyl group optionally by the One or more of the following groups: halo, haloalkyl or alkoxy group such as chloro, Fluoro, trifluoromethyl, trifluoromethoxy, methoxy or ethoxy.

About C 1-3 alkyl - heterocyclyl, R <1> is suitably optionally N- substituted piperidinyl - A Group, or a thienyl - methyl or furanyl - methyl.

R <2> to R <6> is suitably substituted benzene ring containing one, two or three substituents.

When other than hydrogen, R <2> to R <6> are preferably selected from halogen, halo C 1-6 alkyl or C 1-7 Alkoxy. Especially preferred substituents are 2,3 or 2,4 or 2,5 or 3,5 or 2,3,5 di- or tri- Halo (especially chloro and / or fluoro).

In the preferred class of compounds, R <1> is not hydrogen.

In another preferred class of compounds, R <2> is not hydrogen.

In a further preferred class of compounds, R <1> and R <2> are not hydrogen.

In preferred class of compounds of formula (1) of:

R <1> is C 1-10 alkyl, C 2-10 alkenyl, C 1-3 alkyl - aryl or C 1-3 alkyl - Miscellaneous Cycloalkyl group, any of which optionally substituted with halogen, halo C 1-6 alkyl, C 1-6 alkyl or C 1-6 Alkoxy; R <2> to R <6> are independently selected from hydrogen and halogen.

In a group of beneficial compounds have neuroprotective properties in, R <1> is C 1-4 alkyl, 3 optionally substituted by the CF, for example, methyl, ethyl, n-propyl, isobutyl, n-butyl Group and trifluoropropyl, R <2> and R <3>, or R <2> and R <4>, or R <2> and R <5>, or R <3> and R <5>, or R <2>, R <3> and R <5> is halo, especially chloro and / or fluoro.

In the formula (I) in the presence of a group of compounds, wherein R <1> is hydrogen, R <2> to R <6> are independently Is selected from hydrogen, halo, haloalkyl and haloalkoxy.

In the formula (I) in the presence of a group of compounds, wherein R <1> is alkyl, hydroxyalkyl, halo Alkyl group, a heterocyclic group, an alkenyl group, an amide group (carboxamido), a benzyl group, by the Halogen, alkyl, alkoxy, hydroxyalkyl, haloalkyl or benzyl substituted amide group, R <2> to R <6> are independently selected from hydrogen and halogen.

In the formula (I) in the presence of a group of compounds, wherein R <2> to R <6> is hydrogen, R <1> is hydrogen or alkyl.

The new compounds of formula (I), form a further aspect of the present invention.

In particular, that where R <1> is an optionally substituted C 1-3 alkyl group - heterocyclyl or an optionally Substituted C 1-3 alkyl - aryl compound (excluding an unsubstituted benzyl group) of the formula (I) is New compounds.

The compounds of formula (I) as exemplary:

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-isopropyl- -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-n-propyl- -l, 2,4- triazine;

5-Amino-6- (2-pentyloxy-phenyl) -2,3-dihydro-3-amino-2-methyl -l, 2,4- Triazine;

5-Amino-6- (2,3,5-trichlorophenyl) -2,3-dihydro-3-amino-2-methyl- -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-methyl -l, 2,4- Triazine; and

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-benzyl -l, 2,4- Triazine.

In addition, the compounds of formula (I) include:

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-ethyl -l, 2,4- Triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-isopropyl- -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-n-propyl- -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-isobutyl- -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-n-butyl -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-allyl-2- -l, 2,4- triazine;

5-Amino-6- (2,3,5-trichlorophenyl) -2,3-dihydro-3-amino-2-methyl- -l, 2,4- triazine;

5-Amino-6- (2,3,5-trichlorophenyl) -2,3-dihydro-3-imino-2-propyl -l, 2,4- triazine;

5-Amino-6- (2-fluoro-3-chlorophenyl) -2,3-dihydro-3-amino-2-methyl -l, 2,4- Triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3,3,3-trifluoro- Propyl) -l, 2,4- triazine;

5 (3) - amino-6- (2,4-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine;

5 (3) - amino-6-phenyl-2,3 (2,5) - dihydro-3 (5) - methyl-2- -l, 2,4- Triazine;

5 (3) - amino-6-phenyl-2,3 (2,5) - dihydro-3 (5) - ethyl-2- -l, 2,4- Triazine;

5 (3) - amino-6- (2,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine;

5 (3) - amino-6- (2,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine;

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine;

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (2-fluoroethyl) -l, 2,4- triazine;

5 (3) - amino-6- (3,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine;

5 (3) - amino-6- (3,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine;

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (2-fluoroethyl) -l, 2,4- triazine;

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (3,3,3-trifluoropropyl) -l, 2,4- triazine;

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (2,2-difluoro-ethyl) -l, 2,4- triazine.

Another group of compounds of formula (I) include:

3,5-diamino-6- (2,5-dichlorophenyl) -l, 2,4- triazine,

3,5-diamino-6- (3,5-dichlorophenyl) -l, 2,4- triazine,

3,5-diamino-6-phenyl -l, 2,4- triazine,

3,5-diamino-6- (2,4-dichlorophenyl) -l, 2,4- triazine,

3,5-diamino-6- (2-trifluoromethoxyphenyl) -l, 2,4- triazine.

The novel compounds of formula (I) include:

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2'-fluorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3'-fluorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (4'-fluorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2 ', 3'-difluoro- Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3'-chlorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (4'-chlorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (4'-methyl-benzene Yl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2'-methoxy- Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3'-methoxy- Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (4'-methoxy- Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2'-chlorophenyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2'-trifluoromethanesulfonyloxy Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3'-trifluoromethyl Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (4'-trifluoromethanesulfonyloxy Phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (2'-fluoro-3'-three Fluoromethyl-phenyl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3-thienyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (3-furyl - Methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-imino -2- (N- tert Carbonyl - piperidin-4-yl - methyl) -l, 2,4- triazine;

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2- (piperidin-4-yl - Methyl) -l, 2,4- triazine.

Salt Use of a compound of formula (I) formed on one aspect of the present invention. Preferred salts Pharmaceutically acceptable acid adduct. Suitable pharmaceutically acceptable acid addition salts Including the use of organic and inorganic acids as those, for example from hydrochloric acid, sulfuric acid, lemon Acid, tartaric acid, phosphoric acid, lactic acid, pyruvic acid, acetic acid, propionic acid, succinic acid, Oxalic acid, fumaric acid, maleic acid, oxaloacetic, methanesulfonic acid, p-toluenesulfonic, benzene - Sulfonic acid, glutamic acid, naphthoic acid and isethionic. Ethyl sulfonate (Esylate) (ethane Sulfonate), edisylate (1,2-ethane sulfonate), malate, tonsil acid , Benzoate and salicylate salts are also suitable.

In the preparation of compounds of formula (I), the compound or a salt thereof can be used as the reaction solvent Agent or crystalline compound obtained solvent or components thereof. The purpose of the formation of the solvate Another aspect of the invention. Suitable pharmaceutically acceptable solvates include hydrates.

The present invention includes within its scope a compound of formula (I) and its salts and solvates All tautomers thereof, enantiomers and polymorphs of use.

The compounds of formula (I) may suitably be disclosed in the aforementioned U.S. Patent by 4,649,139 steps to prepare, in the entire disclosure of this patent is introduced to make reference.

Conveniently, the compound of formula II with a compound (III) Reaction:

[Image]

Wherein R <2> -R <6> as defined in formula (I) defined above,

R <1> -Q ( )

Wherein R <1> as defined in formula (I) are defined, Q is a leaving group.

Suitable leaving groups include halogen and sulfonic acid derivatives, such as methylsulfonyl, methyl Benzenesulfonyl and the like.

The reaction occurs in a suitable solvent, under conventional conditions, in the solvent of formula II The compound at a suitable temperature (for example, between 0 and 100 ° C, most conveniently at room temperature Below) is soluble.

The compounds of formula II can be prepared by disclosed in EP 0 021 121 A Method to the system Equipment, the entire disclosure of this patent is introduced by reference.

Salt of the compound of formula (I) can be obtained by the presence of residual Q acid obtained. Optional , The salts can be prepared by the following: a suitable solvent in the free base formula as Mixed acid compound (I) with a pharmaceutically acceptable solvent was removed to recover the salt, or Make salt crystals from the solvent.

In another aspect, the present invention provides a pharmaceutical composition for the treatment of e.g. The following diseases: epilepsy, multiple sclerosis, glaucoma and uveitis, brain damage and Cerebral ischemia, stroke, head injury, spinal cord injury, surgical trauma, neurodegenerative Disease, motor neuron disease, Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, Neuropathic pain, migraine, bipolar disorder, paranoia, anxiety and cognitive impairment Hinder, schizophrenia and trigeminal autonomic nervous headache; for treating cancer Disease; for the treatment of malaria; in combination with a pharmaceutically acceptable carrier mixture, package Including compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The compounds of formula (I) in effective unit dosage form will be, that is effective Against the disease in vivo a sufficient amount present in the compositions of the present invention.

Present in the compositions of the present invention, pharmaceutically acceptable carriers can be commonly used In the drug application material purposes. These may be liquid or solid material which is inert or Sexual or medically acceptable and are compatible with the active ingredient.

These pharmaceutical compositions can be administered by oral or parenteral administration, for example as a suppository, Ointments, creams, powders, or transdermal patch. However, oral administration is preferred and intravenous The composition.

For oral administration, fine powders or granules will contain diluents, dispersing agents, and / or table Surface active agents may be present in the gas stream, water, or slurry, in a dry state in a capsule or Bags, which may include suspending agents or non-aqueous suspension, or in water or slurry Suspension. When it is desired or required, it may include flavoring agents, preservatives, suspension Or thickening agents. Dry powder or granules may be compressed to form a tablet or contained in a capsule.

For injection, the compounds may be present in sterile aqueous injection, said injection Liquid may contain antioxidants or buffers.

Capsule or pouch in the case of the preferred carrier, may be the free base or a salt thereof Solvate or no contact with the other additives in its pure form is administered.

Alternatively, the active compounds can be used as an effective unit dose of pure form, Such as compressed tablets, etc. exist.

Other compounds may include, for example, medically inert ingredients, e.g., for Solid and liquid diluent, such as tablets or capsules, lactose, starch, or calcium phosphate; for Olive oil soft capsules

or ethyl; and water or plant for suspensions or emulsions Oils; lubricants such as talc or magnesium stearate; gelling agents such as colloidal clays; thickening Such as tragacanth or sodium alginate; and other pharmaceutically acceptable additional ingredients such as moisturizing Agents, preservatives, buffers and antioxidants, the ingredients can be used in this recipe Carrier.

Tablets or other forms of presentation in discrete units may comprise suitably provided Under the effective dose or as a multiple of the amount of the same dose of a compound of formula I, or As many same example contain 5mg to 500mg, usually around 10mg to 250mg Units.

Pharmaceutical compositions of the present invention may be a compound of formula with a pharmaceutically acceptable (I) Carrier mixture are prepared. When necessary, mixing the usual pharmaceutical excipients. Examples of suitable formulations are given in the aforementioned U.S. Patent 4,649,139.

The present invention provides a method of treating a mammal sodium channel blockers And antifolates sensitive diseases, especially of the following diseases: epilepsy, multiple sclerosis Technology, glaucoma and uveitis, brain damage and cerebral ischemia, stroke, head injury, Spinal cord injury, surgical trauma, neurodegenerative diseases, motor neuron disease, Ards Alzheimer's disease, Parkinson's disease, chronic inflammatory pain, neuropathic pain, migraine headaches, double Phase disorder, paranoia, anxiety and cognitive disorders, schizophrenia and trigeminal autonomic Nervous headache; for the treatment of cancer in a mammal; and for the treatment of malaria; the Said treatment by administering an effective amount of a non-toxic formula (I), a compound or a pharmaceutically acceptable By salt or solvate thereof, or a composition as defined above to treat.

As indicated above the compounds of formula (I) are usually used by oral administration or intravenous injection Radiation therapy of such diseases.

Daily 0.01mg / kg to 20mg / kg, preferably from 0.1 to daily 5.0mg / kg of agent The compound administered normally formula (I) in an amount lower. Thus dose range for adult humans is generally It is 0.7mg to 1400mg / day, preferably 7 to 350mg / day.

Taking into account the structurally similar compounds such as lamotrigine known in humans with Way, the use of the compounds of formula (I) are expected no major toxicity issues. However, temporary Appropriate test procedures should be carried out before bed.

As reported below, the following compound of Example display Formula (I) of the exemplary embodiment and Other compounds prepared for testing.

DETAILED DESCRIPTION

Example 1 - lamotrigine

Proof lamotrigine 5 (3) - amino-6- (2,3-dichloro-phenyl) -2,3 (2,5) - dihydro -3 (5) - imino-1,2,4-triazine - as anticonvulsants for treating epilepsy in humans, Providers in the name under which LAMICTAL (GSK) commercially available. Rameau preparation disclosed triazine European Patent No. 0021121.

Example 2

5-amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3-amino-2-methyl -l, 2,4- triazine

By 3,5-diamino (2,3-dichlorophenyl) -l, 2,4- triazine with methyl iodide trans-6- Should be prepared the title compound free base is described in U.S. Patent No. 4,649,139 (Example 1). Mesylate from the free base prepared as follows.

Methanesulfonic acid methyl ester (0.50g, 4.5mmol), 3,5- diamino-6- (2,3-dichlorobenzene Yl) -l, 2,4-triazine (0.50g, 2.0mmol) and dimethylformamide (4ml) at 100 ° C under It was stirred and heated 10min. The solution was cooled, toluene (20ml), and the mixture It was stirred for 0.5h. The solid was collected by filtration, from propan-2-ol and recrystallized, Methanesulfonate to give the title compound as a white solid (0.40g), m.p. 274-276 ° C.

Example 3

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - ethyl-2- -l, 2,4- triazine

Ethyl iodide (3.12g, 0.02mol) was added to acetone (200ml) of 3,5-bis Amino-6- (2,3-dichlorophenyl) - l, 2,4- triazine (2.56g, 0.01mol) was stirred suspension of in. The mixture was stirred at room temperature for 5 days, adding more ethyl iodide (1.56g, 0.01mol), and stirring was continued for three days. The solid was collected by filtration, and then Stirred 40ml 18% aqueous ammonia solution. The solid (about 2.5g) was removed by filtration, Dried in a vacuum and recrystallized from methanol to give 1.4g (22%) of the title compound, As a white crystalline solid, m.p. 216-217 ° C.

δ H (500MHz, dmso-d 6) 1.21 (3H, t, J = 7.0Hz, C-CH 3), 3.90 (2H, q, J = 7.0Hz, NCH 2), 4.15 (1H, brpeak, NH), 6.2-7.2 (2H, vbrpeak, NH 2), 7.41 (2H, m, aromatic H), 7.71 (1H, dd, J = 8,2Hz, Aromatic H).

Methanesulfonate mp 255-260 ° C.

Example 4

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - isopropyl-2- Group -l, 2,4- triazine

2- iodopropane (2ml, 3.4g, 0.02mol) was added to acetone (200ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (2.56g, 0.01mol) was stirred Suspension. The mixture was stirred at reflux for 5 days, adding more 2-iodopropane (1ml, 0.01mol), refluxing was continued for 2 days. After cooling, the solid was collected by filtration, Then with 0.88 aqueous ammonia (80ml) was stirred for 0.5h. The solid (about 2.5g) was removed by filtration Go, and dried in vacuo and recrystallized from

methanol to give 1.0g (34%) of the title compound Thereof, as a pale yellow crystalline solid, m.p. 209-212 ° C.

δ H (500MHz, dmso-d 6) 1.21 (6H, t, J = 7Hz, CH 3 -C-CH 3), 3.21 (3H, s, CH 3 OH), 4.15 (1H, brpeak, NH), 4.84 (1H, brpeak, CHN), 7.38-7.46 (2H, m, aromatic H), 7.71 (1H, dd, J = 8,2Hz, aromatic H). The compound is methanol solvate.

Methanesulfonate mp 247-250 ° C.

Example 5

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-hydroxyethyl Ethyl) -l, 2,4- triazine

The 2-iodo-ethanol (3.44g, 0.02mol) was added to acetone (200ml) in 3,5- Diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (2.56g, 0.01mol) was stirred suspension of Solution. The mixture was stirred at reflux for 6 days, cooled and the solid was collected by filtration. The solid and 0.88 aqueous ammonia (100ml) was stirred, and the mixture was stirred for 0.5h. The Solid (about 2.7g) was removed by filtration, and dried in a vacuum and recrystallized from methanol, To give 1.14g (38%) of the title compound as a white crystalline solid, m.p. 217-218 ° C.

δ H (500MHz, dmso-d 6) 3.34 (3H, s, CH 3 OH), 3.68 (2H, brt, J = 6Hz, OCH 2), 3.96 (2H, m, NCH 2), 5.5-7.0 (2H, vbrpeak, NH 2), 7.36-7.46 (2H, m, aromatic H), 7.71 (1H, dd, J = 8,2Hz, aromatic H). The compound is methanol solvate.

Methanesulfonate mp 242-245 ° C.

Example 6

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino-2-propyl -l, 2,4- triazine

1-iodopropane (3.4g, 0.02mol) was added to acetone (200ml) in 3,5- Diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (2.56g, 0.01mol) was stirred suspension of Solution. The mixture was stirred at reflux for 2 days, add more 1-iodopropane (1.7g, 0.01mol), reflux was continued for 24h. After cooling, the solid was collected by filtration, then After the 0.88 ammonia (80ml) was stirred 0.5h. The solid (about 3.1g) was removed by filtration, And dried in a vacuum from methanol - water (about 160ml) was recrystallized to give 1.65g (56%) Of the title compound as a white crystalline solid, m.p. 197-199 ° C.

δ H (500MHz, dmso-d 6) 0.88 and 0.91 (3H, 2x t, J = 7Hz, C-CH 3), 1.64-1.74 (2H, m, C-CH 2 -C), 3.82 and 3.90 (2H, 2x t, J = 7Hz, NCH 2), 6.2-7.4 (1H, vbrpeak, NH), 7.35-7.46 (2H, m, aromatic H), 7.71 (1H, m, aromatic H). Two kinds of tautomers in a ratio of 4: 1 is present.

Methanesulfonate mp 237-240 ° C.

Example 7

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - isobutoxy-2- Yl -l, 2,4- triazine mesylate

The 2-iodo-butane (1.8ml, 2.88g, 0.016mol) was added to the acetone (50ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.28g, 0.005mol) in Stirred suspension. The mixture was stirred and heated at reflux for 4 days. Add more The 2-iodo-butane (0.6ml, 0.005mol), and reflux continued for 1 day. After cooling, the solid Body was collected by filtration, and then with 0.88 aqueous ammonia (80ml) was stirred for 0.5h. The resulting solid (About 0.9g) was removed by filtration, and dried in vacuum. Part (0.31g) in methanol and (3.5ml) of methanesulfonic acid (0.10g) with stirring, the mixture was diluted with ether to afford the title The mesylate compound (0.22g), as a white crystalline solid, m.p. no apparent (Decomposition> 230 ° C).

δ H (500MHz, dmso-d 6) 0.92 (6H, d, J = 5.9Hz, 2x C-CH 3), 2.12 (1H, m, CHMe 2), 2.30 (3H, s, SCH 3), 3.92 (2H, brs, NCH 2), 7.54 (2H, m, aromatic H), 7.86 (1H, dd, J = 7.2,2.5Hz, aromatic H), 8.18 (1H, brs, NH, exchange), 8.2-8.8 (2H, vbrpeak, NH 2, exchange), 9.14 (1H, brs, NH, exchange).

Example 8

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - butyl-2- -l, 2,4- triazine

The 1-iodo-butane (2.3ml, 3.68g, 0.02mol) was added to the acetone (200ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (2.56g, 0.01mol) stir Mix suspension. The mixture was stirred and heated at reflux for 4 days. Adding more 1-iodo-butane (0.6ml, 0.005mol), and reflux continued for 1 day. After cooling, the solid It was collected by filtration, and then with 0.88 aqueous ammonia (80ml) was stirred for 0.5h. The resulting solid (ca. 2.2g) was removed by filtration, dried under vacuum and recrystallized from methanol to give 1.1g (35%) of the title compound as a white crystalline solid, m.p. 175 ° C.

δ H (500MHz, dmso-d 6) 0.89 (3H, t, J = 7Hz, CH 3), 1.31 (2H, hextet, J = 7Hz, CH2Me), 1.64 (2H, pent, J = 7Hz, CH 2 -C-Me), 3.86 (2H, t, J = 7Hz, NCH 2), 6.2-7.2 (2H, vbrpeak, NH 2), 7.38 (1H, dd, J = 8,2Hz, aromatic H), 7.43 (1H, t, J = 8Hz, aromatic H), 7.70 (1H, dd, J = 8,2Hz, aromatic H).

Example 9

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino-2-phenyl Methyl -l, 2,4- triazine half mesylate

The benzyl chloride (0.92ml, 1.01g, 0.008mol) was added to the acetone (50ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.0g, 0.004mol) stir Mix suspension. The mixture was stirred and heated at reflux for 3 days. Adding more Benzyl chloride (0.6ml, 0.005mol), and refluxed for 2 days to continue. After cooling, the solids pass It was collected by filtration, and then with 0.88 aqueous ammonia (80ml) was stirred for 0.5h. The resulting solid (ca. 0.64g) was removed by filtration, and dried in vacuo. Part (0.35g) in methanol and (3.5ml) of methanesulfonic acid (0.10g) with stirring, the mixture was diluted with ether to afford the title The mesylate compound (0.14g), as a white crystalline

solid, m.p. no apparent (Decomposition> 270 ° C).

δ H (500MHz, dmso-d 6) 2.31 (1.5H, s, SCH 3), 5.42 (2H, brs, NCH 2), 7.39 (5H, m, aromatic H), 7.56 (2H, m, aromatic H), 7.86 (1H, dd, J = 7.2,2.4Hz, aromatic H), 8.28 (1H, s, NH, exchange), 8.4-8.8 (2H, vbrpeak, NH 2, exchange), 9.28 (1H, s, NH, exchange).

The spectrum shows the stoichiometric heterocyclic school. 0.5MeSO 3 H m / z 347 (M <+> + 1).

Example 10

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (prop-2 Enyl) -l, 2,4- triazine mesylate half

Allyl bromide (1.8ml, 2.52g, 0.02mol) was added to the acetone (50ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.28g, 0.005mol) in Stirred suspension. The mixture was stirred and heated at reflux for 4 days. Add more Of allyl bromide (0.6ml, 0.007mol), and reflux continued for 1 day. After cooling, the solid Body was collected by filtration, and then with 0.88 aqueous ammonia (80ml) was stirred for 0.5h. The resulting solid (Approx. 0.84g) was removed by filtration, and dried in vacuum. Part (0.30g) in methanol and (3.5ml) of methanesulfonic acid (0.10g) with stirring, the mixture was diluted with ether to afford the title The mesylate compound (0.26g), as a pale brown crystalline solid, no obvious Mp (decomposition> 270 ° C).

δ H (500MHz, dmso-d 6) 2.31 (1.5H, s, SCH 3), 4.74 (2H, d, J = 4.8Hz, NCH 2), 5.28 (2H, m, olefinic H), 5.93 (1H, m, olefinic H), 7.54 (2H, m, aromatic H), 7.86 (1H, m, aromatic H), 8.20 (1H, s, NH, Exchange), 8.2-8.8 (2H, vbrpeak, NH 2, exchange), 9.2 (1H, s, NH, exchange).

The spectrum shows the stoichiometric heterocyclic school. 0.5MeSO 3 H.

Example 11

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -l, 2,4- three Triazin-2-yl] acetamide 2- (amido) A Jila Mo triazine

2- iodoacetamide (1.85g, 0.01mol) was added to the acetone (50ml) in 3,5-diamino-6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.28g, 0.005mol) is stirred Mix suspension. The mixture was stirred and heated at reflux for 4h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia (50ml) was stirred for 0.5h. The resulting solid Body (about 1.1g) was removed by filtration, dried under vacuum and recrystallized from acetonitrile to give To 0.56g (36%) of the title compound as a white crystalline solid, m.p. no apparent (Decomposition greater than 270 ° C).

δ H (500MHz, dmso-d 6) 2.07 (CH 3 CN), 4.44 (2H, brs, NCH 2), 6.0-7.0 (2H, vbrpeak, NH 2), 7.13 (1H, brs, NH, exchange), 7.37 (1H, dd, J = 8,2Hz, aromatic H), 7.44 (1H, t, J = 8Hz, aromatic H), 7.49 (1H, brs, NH, exchange), 7.71 (1H, dd, J = 8,2Hz, aromatic H).

m / z 313 (M <+>).

Example 12

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4- Yl) phenylmethyl -l, 2,4- triazine

A solution of 4-methylbenzyl bromide (0.70g, 4.3mmol) was added to 3,5-diamino-6- (2,3-Dichlorophenyl) -l, 2,4- triazine (0.64g, 2.5mmol), NaI (0.1g) and acetone (25ml) The stirred suspension. The mixture was stirred and heated at reflux for 3h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (40ml, 1: 1) was stirred for 0.5h. The resulting solid (about 0.7g) was removed by filtration, and dried in vacuo. From ethanol Recrystallized product (0.44g), as a white solid, m.p. 180-185 ° C (decomposition).

δ H (500MHz, dmso-d 6) 2.27 (3H, s, CH 3), 5.05 (2H, s, NCH 2), 7.14 (2H, d, J = 8Hz, aromatic H), 7.22 (2H, d, J = 8Hz, aromatic H), 7.38 (1H, dd, J = 7.5,2Hz, aromatic H), 7.44 (1H, d, J = 7.5Hz, aromatic Aromatic H), 7.71 (1H, dd, J = 7.5,2Hz). The spectrum shows the compound contains 0.3EtOH.

m / z 361 (M <+> +1).

Example 13

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2,3- Difluoromethyl) phenylmethyl -l, 2,4- triazine

2,3-difluoro-benzyl bromide (2.07g, 10mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4-triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) was stirred suspension. The mixture was stirred and heated at reflux for 6h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 2g) was removed by filtration, and dried in vacuo. Recrystallization from methanol to give the product (1.2g), as a pale yellow solid, m.p. 208-209 ° C.

δ H (500MHz, dmso-d 6) 5.20 (2H, s, NCH 2), 5.66 (1H, brpeak, NH), 6.63 (1H, brpeak, NH), 7.19 (2H, m, aromatic H), 7.35 (1H, m, aromatic H), 7.44 (2H, m, aromatic H), 7.72 (1H, brd, J = 7Hz, aryl Aromatic H).

m / z 383 (M <+> +1).

Example 14

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-fluoro) Phenylmethyl -l, 2,4- triazine

A mixture of 2-fluoro-benzyl chloride (1.45g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The

mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 2g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (1.2g), as a pale yellow solid, m.p. 201-203 ° C.

δ H (500MHz, dmso-d 6) 5.16 (2H, s, NCH 2), 6-7 (2H, vbr peak, NH 2), 7.18 (2H, m, aromatic H), 7.33 (2H, m, aromatic H), 7.42 (2H, m, aromatic H), 7.72 (1H, dd, J = 7.5,1.5Hz). The spectrum shows the compound Containing 0.5MeOH.

m / z 365 (M <+> +1).

Example 15

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3-fluoro) Phenylmethyl -l, 2,4-triazine

A solution of 3-fluorobenzyl chloride (1.45g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.5g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.42g), as a pale yellow solid, m.p. 189-190 ° C.

δ H (500MHz, dmso-d 6) 5.13 (2H, s, NCH 2), 6-7 (2H, vbr peak, NH 2), 7.14 (3H, m, aromatic H), 7.43 (3H, m, aromatic H), 7.72 (1H, dd, J = 7.5,1.5Hz).

m / z 365 (M <+> +1).

Example 16

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4-fluoro) Phenylmethyl -l, 2,4-triazine

A mixture of 4-fluorobenzyl chloride (1.45g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.6g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (1.1g), as a pale yellow solid, m.p. 189-190 ° C.

δ H (500MHz, dmso-d 6) 5.08 (2H, s, NCH 2), 6-7 (2H, vbr peak, NH 2), 7.17 (2H, t, J = 8Hz, aromatic H), 7.40 (4H, m, aromatic H), 7.71 (1H, dd, J = 7.2Hz, aromatic H). m / z 365 (M <+> +1).

Example 17

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-) Phenylmethyl -l, 2,4- triazine

2-methoxy-benzyl chloride (1.56g, 10mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4-triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.8g) was removed by filtration, and dried in vacuo. Recrystallized from ethanol to give the product (0.95g), as a pale yellow solid, m.p. 194-196 ° C.

δ H (500MHz, dmso-d 6) 3.80 (3H, s, OCH 3), 5.05 (2H, brs, NCH 2), 6.5-7.0 (1H, vbrpeak, NH), 6.92 (1H, t, J = 8Hz, aromatic H), 7.01 (2H, brt, J = 8Hz, aromatic H), 7.26 (1H, brt, J = 8Hz, aromatic Aromatic H), 7.40 (2H, m, aromatic H), 7.69 (1H, brd, J = 8Hz, aromatic H).

m / z 377 (M <+> +1).

Example 18

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3-) Phenylmethyl -l, 2,4- triazine

3-Methoxy-benzyl chloride (1.56g, 10mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4-triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.4g) was removed by filtration, and dried in vacuo. Recrystallized from ethanol to give the product (0.64g), as a pale yellow solid, m.p. 192-195 ° C.

δ H (500MHz, dmso-d 6) 3.73 (3H, s, OCH 3), 5.07 (2H, brs, NCH 2), 6.5-7.0 (1H, vbrpeak, NH), 6.84 (1H, brd, J = 8Hz, aromatic Aromatic H), 6.88 (2H, m, aromatic H), 7.26 (1H, t, J = 8Hz, aromatic H), 7.42 (2H, m, aromatic H), 7.71 (1H, d, J = 7Hz, aromatic H).

m / z 377 (M <+> +1).

Example 19

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4-) Phenylmethyl -l, 2,4- triazine

The 4-methoxy benzyl chloride (1.56g, 10mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.6g) was removed by filtration, and dried in vacuo. Recrystallized from ethanol to give the product (0.83g), as a pale yellow solid, m.p. 212-215 ° C.

m / z 377 (M <+> +1).

Example 20

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3-chloro) Phenylmethyl -l, 2,4-triazine

A mixture of 3-chlorobenzyl bromide (2.05g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.2g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.35g), as a pale yellow solid, m.p. 178-180 ° C.

δ H (500MHz, dmso-d 6) 5.11 (2H, brs, NCH 2), 6.5-7.0 (1H, vbrpeak, NH), 7.28 (1H, brd, J = 8Hz, aromatic H), 7.32-7.47 (5H, m, Aromatic H), 7.72 (1H, dd, J = 7,2Hz, aromatic H). The spectrum shows the presence of 0.75MeOH.

m / z 381,383 (M <+> +1).

Example 21

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4-chloro) Phenylmethyl -l, 2,4-triazine

A mixture of 4-chlorobenzyl chloride (1.61g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.5g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.71g), as a pale yellow solid, m.p. 192-193 ° C.

δ H (500MHz, dmso-d 6) 5.09 (2H, s, NCH 2), 5.5 (1H, vbrpeak, NH), 6.5 (1H, vbrpeak, NH), 7.35 (2H, d, J = 8Hz, aromatic H), 7.42 (4H, m, aromatic H), 7.72 (1H, brd, J = 7Hz, aromatic H).

m / z 381,383 (M <+> + l).

Example 22

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-chloro) Phenylmethyl -l, 2,4-triazine

A mixture of 2-chlorobenzyl bromide (2.06g, 10mmol) was added to 3,5-diamino-6- (2,3- Stir-chlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Mix suspension. The mixture was stirred and heated at reflux for 5h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.5g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.71g), as a pale yellow solid, m.p. 205 ° C (decomposition).

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.18 (2H, s, NCH 2), 5.6 (1H, brpeak, NH, exchange), 6.6 (1H, brpeak, NH, exchange), 7.20 (1H, m, aromatic H), 7.32 (2H, m, aromatic H), 7.46 (3H, m, Aromatic H), 7.70 (1H, brd, J = 7Hz, aromatic H).

m / z 381,383 (M <+> + l).

Example 23

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2- Trifluoromethyl) phenylmethyl -l, 2,4- triazine

A mixture of 2-trifluoromethylbenzyl bromide (0.56g, 2.2mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4- triazine (0.56g, 2.2mmol), NaI (0.1g) and acetone (25ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (40ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.5g) was removed by filtration, and dried in vacuo. Recrystallized product (0.42g) from methanol, as a pale yellow solid, m.p. 200-201 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.31 (2H, s, NCH 2), 5.66 (1H, brs, NH, exchange), 6.66 (1H, brs, NH, exchange), 7.31 (1H, d, J = 8Hz, aromatic H), 7.45 (3H, m, aromatic H), 7.5 (1H, br peak, NH, exchange), 7.72 (3H, m, aromatic H).

m / z 414,416 (M <+> + l).

Example 24

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3- Trifluoromethyl) phenylmethyl -l, 2,4- triazine

A solution of 3-trifluoromethylbenzyl bromide (2.0g, 8.7mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.12g, 4.4mmol), NaI (0.1g) and acetone (50ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.2g) was removed by filtration, and dried in vacuo. Recrystallized product (0.52g) from methanol, as a pale yellow solid, m.p. 168-170 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.22 (2H, brs, NCH 2), 5.4-5.8 (1H, vbrpeak, NH, exchange), 6.4-6.8 (1H, brs, NH, Exchange), 7.42 (2H, m, aromatic H), 7.63 (4H, m, aromatic H), 7.73 (1H, brd, J = 7Hz, aromatic H). m / z 414,416 (M <+> +1).

Example 25

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4- Trifluoromethyl) phenylmethyl -l, 2,4- triazine

The 4-trifluoromethyl-benzyl chloride (1.0g, 4.0mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4- triazine (0.56g, 2.2mmol), NaI (0.1g) and acetone (25ml) was stirred suspension. The mixture was stirred and heated at reflux for 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (40ml, 1: 1) Stirring 0.5h. The resulting solid (about 0.7g) was removed by filtration, and dried in vacuo. Recrystallized product (0.42g) from methanol, as a pale yellow solid, m.p. 198-200 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.20 (2H, brs, NCH 2), 5.3-5.8 (1H, vbrpeak, NH, exchange), 6.4-6.8 (1H, brs, NH, Exchange), 7-8 (1H, vbrpeak, NH, exchange), 7.43 (2H, m, aromatic H), 7.53 (2H, brd, J = 8Hz, aromatic H), 7.73 (3H, brd, J = 8Hz, aromatic H). m / z 414,416 (M <+> +1).

Example 26

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-fluoro- -3- Trifluoromethyl) phenylmethyl -l, 2,4- triazine

A mixture of 2-fluoro-3-trifluoromethyl benzyl bromide (1.0g, 4.0mmol) was added to 3,5-diamino -6- (2,3-dichlorophenyl) -l, 2,4- triazine (0.56g, 2.2mmol), NaI (50mg) and Acetone (25ml) was stirred suspension. The mixture was stirred and heated under reflux 5h. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (40ml, 1: 1) was stirred for 0.5h. The resulting solid (about 0.7g) was removed by filtration and in vacuo dry. Recrystallized product (0.40g) from methanol, as a pale yellow solid, melting Point> 250 ° C (decomposition).

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.23 (2H, brs, NCH 2), 5.67 (1H, brs, NH, exchange), 6.5-7.0 (1H, vbrpeak, NH, pay Exchange), 7.42 (3H, m, aromatic H), 7.5 (1H, brpeak, NH, exchange), 7.70 (3H, m, aromatic H).

m / z 432,434 (M <+> +1).

Example 27

4 - {[5 (3) - amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3 (5) - imino -l, 2,4- three Triazin-2-yl] methyl} benzamide

or

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3-acyloxy Amino) phenyl methyl -l, 2,4- triazine

3- (chloromethyl) benzamide According CYWatson et al., Bioorg. & Med Chem., 6,721-734 (1998) by reaction of 3-chloro-step-methylbenzoyl chloride and ammonia Reaction.

(3-chloromethyl) benzamide (1.33g, 7.8mmol) was added to 3,5-diamino- 6- (2,3-dichlorophenyl) -l, 2,4- triazine (1.61g, 6.3mmol), NaI (0.1g) and acetone (70ml) was stirred suspension. The mixture was stirred and heated under reflux overnight. After cooling, the solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) Stirring 0.5h. The resulting solid (about 1.5g) was removed by filtration, and dried in vacuo. Recrystallized product (0.92g) from methanol, as a pale yellow solid, m.p. 228-230 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 5.15 (2H, brs, NCH 2), 5.4-5.8 (1H, vbrpeak, NH, exchange), 6.4-6.8 (1H, vbrpeak, NH, exchange), 7.34 (1H, brs, NH, exchange), 7.38-7.48 (4H, m, aromatic H), 7.70 (1H, brd, J = 8Hz, aromatic H.), 7.76 (1H, brs, J = 8Hz, aromatic Aromatic H), 7.84 (1H, brs, aromatic H), 7.96 (1H, brs, NH, exchange). m / z 389,391 (M <+> +1).

Example 28

4 - {[5 (3) - amino-6- (2,3-dichlorophenyl) -2,3-dihydro-3 (5) - imino -l, 2,4- three Triazin-2-yl] methyl} phenyl methanol

or

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (4-hydroxy- Methyl) phenylmethyl -l, 2,4- triazine

4- (chloromethyl) benzyl alcohol (1.0g, 6.4mmol) was added to 3,5-diamino-6- (2,3- Dichlorophenyl) -l, 2,4- triazine (1.28g, 5mmol), NaI (0.1g) and acetone (50ml) of Stirred suspension. The mixture was stirred and heated at reflux for 10h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (80ml, 1: 1) was stirred for 0.5h. The resulting solid (about 1.3g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.47g), as a pale yellow solid, m.p. 215-217 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, MeOH), 4.47 (2H, d, J = 5Hz, OH, exchange), 5.08 (2H, brs, NCH 2), 5.14 (1H, brt, J = 5Hz, OH, exchange), 5.4-5.8 (1H, vbrpeak, NH, exchange), 6.4-6.8 (1H, vbrpeak, NH, exchange), 7.28 (4H, m, aromatic H), 7.40 (1H, brd, J = 8Hz, aromatic H), 7.45 (1H, t, J = 8Hz, aromatic H), 7.72 (1H, brd, J = 8Hz, aromatic H).

m / z 376,378 (M <+> +1).

Example 29

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3- Thienylmethyl) -l, 2,4- triazine

3- chloromethylthiophene according S.Gronowitz and S.Liljefors, Chemica Scipta, 13,39-45 (1978-79) step by thiophene-3 chloride methanol to the system Equipment.

A mixture of 2-chloromethyl-thiophene (1.04g, 7.8mmol) was added to 3,5-diamino-6- (2,3-

Dichlorophenyl) -l, 2,4- triazine (1.00g, 3.9mmol), NaI (0.07g) and acetone (35ml) The stirred suspension. The mixture was stirred and heated at reflux for 36h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (30ml, 1: 1) was stirred for 5h. The resulting solid (about 0.5g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.22g), creamy solid, m.p. 191-192 ° C (decomposition).

δ H (500MHz, dmso-d 6) 3.32 (3H, s, CH 3 OH), 5.07 (2H, s, NCH 2), 5.2-6.0 (1H, vbrpeak, NH, exchange), 6.5-7.5 (2H, vbrpeak, NH 2), 7.11 (1H, dd, J = 5,1Hz, aromatic H), 7.37-7.45 (3H, m, aromatic Aromatic H), 7.50 (1H, m, aromatic H), 7.72 (1H, dd, J = 7.5,2Hz). The light Spectrum shows the compound contains l.0MeOH. m / z 353 (M <+> +1).

Example 30

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3- furosemide Nan ylmethyl) -l, 2,4- triazine

3- chloromethylfuran according E.Sherman and EDAmstutz, J.Am.Chem. Soc, 72,2195-2199 (1950) of the step by-3-chloride methanol to the system Equipment.

3-Chloro-methylfuran (0.90g, 7.7mmol) was added to 3,5-diamino-6- (2,3- Dichlorophenyl) -l, 2,4- triazine (1.00g, 3.9mmol), NaI (0.07g) and acetone (40ml) The stirred suspension. The mixture was stirred and heated at reflux for 36h. After cooling, The solid was collected by filtration, and then with 0.88 aqueous ammonia - water (30ml, 1: 1) was stirred for 5h. The resulting solid (about 1.1g) was removed by filtration, and dried in vacuo. From methanol Recrystallized product (0.72g), creamy solid, m.p. 191-193 ° C.

δ H (500MHz, dmso-d 6) 3.32 (3H, s, CH 3 OH), 4.92 (2H, s, NCH 2), 5.5-6.4 (1H, vbrpeak, NH, exchange), 6.48 (1H, brs, furan H), 6.5-7.5 (2H, vbrpeak, NH 2), 7.37-7.46 (2H, m, aromatic H), 7.61 (1H, brs, furan-H), 7.64 (1H, brs, furan-H), 7.71 (1H, dd, J = 7.5, 2Hz, aromatic H). The spectrum shows the compound contains l.0MeOH.

m / z 337 (M <+> +1).

Example 31

6- (2,3,5-trichlorophenyl) -l, 2,4- triazine-3,5-diamine

The preparation according to the method described in U.S. Patent No. 4,602,017; m.p. 232-235 ° C.

Example 32

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - methyl-2- -l, 2,4- triazine

Iodomethane (0.40g, 2.8mmol) was added to acetone (15ml) in 3,5- Amino-6- (2,3,5-trichlorophenyl) - l, 2,4- triazine (0.20g, 0.7mmol) was stirred suspension of Solution. The mixture was stirred for 6 days at room temperature, and removed at 40 ° C under vacuum Solvent. The ice (approximately 4g) was added to the residue, followed by stirring 0.88 ammonia (3ml) and The mixture 4h. The solid was removed by filtration, and dried in vacuo from ethanol Recrystallized to give 0.13g of the title compound as an off-white crystalline solid, m.p. 225-226 ° C.

δ H (500MHz, dmso-d 6) 3.47 (3H, s, NCH 3), 5.5-7.4 (3H, vbr peak, NH, exchange), 7.56 (1H, d, J = 2.5Hz, aromatic H), 7.92 (1H, dd, J = 2.5Hz, aromatic H).

m / z 304-306 (M <+> +1).

Example 33

6- (2,3-difluorophenyl) -l, 2,4- triazine-3,5-diamine

Step 1 2,3-difluorobenzoyl chloride

2,3-difluoro-benzoic acid (11.6g, 0.07mol), thionyl chloride (37.5ml, 61.1g, 0.5mol) and toluene (80ml) was heated at reflux for 3h. The solution was cooled in a vacuum The volatiles were removed. The residue with toluene (2 × 30ml) azeotropically to give the product (10.8g), was a clear yellow oil.

Step 2 2,3-difluoro-benzoyl cyanide

Using a Dean - Stark (Dean-stark) means the copper cyanide (I) (6.6g, 0.07mol), potassium iodide (12.2g, 0.07mol) and xylene (70ml) was heated at reflux for 24h. Added in xylene (40ml) in 2,3-difluorobenzoyl chloride (10.8g, 0.06mol) Solution. Using Dean - Stark apparatus and the resulting suspension in N 2 at 165 ° C next time Stream three days. After cooling, the inorganic salt was removed by filtration, the filtrate was concentrated in vacuo. will Residue with toluene (2 × 30ml) azeotropically to give the product (7.2g), as a brown solid.

Step 3 2- (2,3-difluorophenyl) -2- (guanidinoimino) acetonitrile

Concentrated sulfuric acid (43.5ml, 80g, 0.82mol) was slowly added with stirring to water in. The aminoguanidine bicarbonate (4.4g, 0.032mol) was slowly added with stirring to the Hot acid solution (Note! The release of CO 2), and then continue stirring 15min. In acetonitrile (20ml) of 2,3-difluoro - benzoyl cyanide (3.1g, 0.019mol) solution after 0.5h by Dropwise added to the above aminoguanidine sulfate solution, and the mixture was stirred at room temperature for 4 day. Then cooled in an ice bath was carefully added along with aqueous NaOH (4M), straight The mixture is pH 7. The precipitate was collected by filtration, washed with water and dried to give To the product (2.9g), as a yellow solid, m.p. 168-170 ° C.

Step 4

2- (2,3-difluorophenyl) -2- (guanidinoimino) acetonitrile (2.8g, 0.01mol) and Propan-1-ol (30ml) was stirred and heated under reflux for 1.5h. The solution was cooled in a vacuum Concentrated, and the

residue chromatographed on silica (250g) on. With CH 2 Cl 2 -MeOH (95: 5) to give a tan solid. The material is suspended in CH 2 Cl 2, and the residual Insolubles were collected by filtration to give the product (1.3g), creamy solid, m.p. 229-230 ° C.

δ H (500MHz, dmso-d 6) 6.42 (2H, brs, NH 2, exchange), 6.6-7.0 (2H, vbr peak, NH 2, exchange), 7.25 (1H, brt, J = 7.5Hz, aromatic H), 7.30 (1H, m, aromatic H), 7.48 (1H, m, aromatic H). m / z 224 (M <+> + 1).

Example 34

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino-2-propyl -l, 2,4- triazine

The iodopropane (0.51g, 3mmol) was added to acetone (15ml) in 3,5-diamine -6- (2,3,5-trichlorophenyl) -l, 2,4- triazine (0.29g, 1mmol) was stirred suspension of in. The mixture was stirred and heated at reflux for 8 days. After cooling, the precipitate by Collected by filtration, then stirred in a water (4ml) and aqueous ammonia (2ml) in 4h. The solid through It was removed by filtration, dried in vacuo and recrystallized from methanol to give 0.15g of the title Compound was an off-white crystalline solid, m.p. 240-243 ° C.

δ H (500MHz, dmso-d 6) 0.88 (3H, t, J = 7.5Hz, CH 3), 1.67 (2H, hext, J = 7.5Hz, CH 2), 3.82 (2H, t, J = 7.5Hz, NCH 2), 6.3-7.3 (2H, vbr peak, NH 2, exchange), 7.56 (1H, d, J = 2.5Hz, aromatic H), 7.92 (1H, d, J = 2.5Hz, aromatic H).

m / z 332-334 (M <+> +1).

Example 35

3-chloro-2- (fluorophenyl) -l, 2,4- triazine-3,5-diamine

Step 13- chloro-2-fluoro-benzoic acid

3-chloro-2-fluorobenzaldehyde (15.9g, 0.1mol) was dissolved in tert-butanol (60ml), and Stirred and heated at 50 ° C under under N 2. The aqueous solution of 2M NaOH (100ml, 0.2mol) was heated to 50 ° C, and added to the aldehyde solution. The aqueous hydrogen peroxide (H 2 O 2, 30%, 70ml, 0.6mol) was added after 45min, maintaining the temperature at 55-60 ° C. The mixture was then stirred under N 2 and heated 1h, cooled and concentrated in vacuo. will The remaining slurry was filtered. Hydrochloric acid filtrate with toluene (2 ××× ml) washed and treated with a 5N Technology to pH 1 with vigorous stirring. The resulting solid was collected by filtration, washed with water, And dried in vacuo at 50 ° C, to give 11.1g product, mp 179-181 ° C.

Has been reported by different routes [J.Mortier et al., Tetrahedron Lett.36, Samples 881-884 (1995)] was prepared, having a melting point of 179-181 ° C.

Step 2 3-chloro-2-fluorobenzoyl chloride

A solution of 3-chloro-2-fluorobenzoic acid (10.0g, 0.06mol), thionyl chloride (31ml, 50g, 0.4mol) and dry toluene (40ml) was heated at reflux for 3h. The solution was cooled and true The volatiles were removed air. The residue with toluene (2 × 30ml) azeotropically to give the product (11.5g), was a clear yellow oil.

Step 3 3-chloro-2-fluoro-benzoyl cyanide

Using a Dean - Stark apparatus copper cyanide (I) (6.6g, 0.07mol), potassium iodide (12.2g, 0.07mol) and xylene (50ml) was heated under reflux for 24h. Add in dimethyl Benzene (15ml) of 3-chloro-2-fluorobenzoyl chloride (11.5g, 0.06mol) was added. Use Di Ann - Stark apparatus and the resulting suspension was 165 ° C under N 2 at reflux for 3 days. cool down After the inorganic salt was removed by filtration, the filtrate was concentrated in vacuo. The residue and armor Benzene (2 × 30ml) azeotropically to give the product (9.5g), as a brown solid.

Step 4 2- (3-chloro-2-fluorophenyl) -2- (guanidinoimino) acetonitrile

Concentrated sulfuric acid (43.5ml, 150g, 1.6mol) was slowly added with stirring to water (45ml) in. The aminoguanidine bicarbonate (5.7g, 0.036mol) was slowly added with stirring Was added to the hot acid solution (Note! Releasing CO 2), and the stirring was continued for 15min. In acetonitrile (31ml) of the 3-chloro-2-fluoro - benzoyl cyanide (4.3g, 0.02mol) solution was Dropwise over 0.5h aminoguanidine sulfate was added to the above solution, and the mixture at room Temperature and stirred for 4 days. Then cooled in an ice bath was carefully added along with an aqueous solution of NaOH (4M), until the mixture is pH 7. The precipitate was collected by filtration, washed with water and Dried to give product (3.2g), a tan solid.

Step 5

2- (3-chloro-2-fluorophenyl) -2- (guanidinoimino) acetonitrile (3.2g, 0.01mol) and Propan-1-ol (30ml) was stirred and heated under reflux for 3h. The solution was cooled in a vacuum Concentrated and the residue chromatographed on silica (250g) on. With CH 2 Cl 2 -MeOH (95: 5) to give a tan solid. The material is suspended in CH 2 Cl 2, and the residual Insolubles were collected by filtration to give the product (1.3g), creamy solid, m.p. 246-247 ° C.

δ H (500MHz, dmso-d 6) 6.99 (2H, brs, NH 2, exchange), 7.28 (1H, t, J = 8Hz, aromatic H), 7.44 (1H, td, J = 8,2Hz, aromatic H), 7.65 (1H, td, J = 8,2Hz, aromatic H), 12.5 (1H, brpeak, NH, exchange).

m / z 240,242 (M <+> +1).

Example 36

5 (3) - Amino-6- (3-chloro-2-fluorophenyl) -2,3 (2,5) - dihydro-3 (5) - methyl-2- -l, 2,4- triazine

Methyl iodide (0.5ml, 1.14g, 8mmol) was added to acetone (25ml) in 3,5-diamino-6- (3-chloro-2-

fluorophenyl) -l, 2,4- triazine (0.48g, 2mmol) was stirred Suspension. The mixture was stirred at 45 ° C under 24h, cooled and collected by filtration solid. The ice (about 10g) was added to the residue, followed by stirring 0.88 ammonia (5ml) And the mixture was 4h. The solid was removed by filtration, and dried in vacuo from methanol Recrystallized, to give 0.23g of the title compound as an off-white crystalline solid, m.p. 194-196 ° C.

δ H (500MHz, dmso-d 6) 3.48 (3H, s, NCH 3), 6.2-7.2 (2H, vbr peak, NH 2, exchange), 7.27 (1H, t, J = 8Hz, aromatic H), 7.40 (1H, td, J = 8,2Hz, aromatic H), 7.64 (1H, td, J = 8,2Hz, aromatic H).

m / z 254,256 (M <+> +1).

Example 37

l, l- dimethylethyl 4- [5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro- -3 (5) - imino -l, 2,4- triazin-2-yl-methyl] piperidine-1-carboxylate

or

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (tert- Oxycarbonyl-piperidin-4-yl) methyl -l, 2,4- triazine

The l, l- dimethylethyl 4-iodo-methyl-piperidine-1-carboxylate [according to A. Villalobos et al., J.Med. Chem., 37,2721-2734 (1994) by a method Three-step method (ethyl isonipecotate) was prepared from 4-ethyl-piperidine] (3.25g, 10mmol) was added to the acetone (50ml) of 3,5-diamino-6- (2,3-dichlorobenzene Yl) -l, 2,4- triazine (1.28g, 5mmol) was stirred suspension. The mixture back It was stirred and heated under a stream of nine days. After cooling in ice, the solid (2.5g) collected by filtration set. This material was stirred in water (10ml) and 0.88 ammonia (10ml) in 12h. The solid Body was removed by filtration, and dried in a vacuum and recrystallized from methanol to give 0.60g The polyurethane, was off-white crystalline solid, m.p. no apparent.

m / z 453,455 (M <+> +1).

δ H (500MHz, dmso-d 6) 1.05 (2H, ddd, J = 25,12,4Hz, CCH 2 C), 1.38 (9H, s, C (CH 3) 3), 1.59 (2H, brd, J = 12Hz, CCH 2 C), 2.06 (1H, m, CH), 2.69 (2H, m, CH 2 N), 3.76 (2H, m, CH 2 N), 3.92 (2H, brd, J = 7Hz, NNCH 2), 5.0-6.0 (1H, vbr peak, NH, exchange), 6.4-7.0 (2H, vbrpeak, NH 2, exchange), 7.39 (1H, d, J = 7.5Hz, aromatic H), 7.44 (1H, t, J = 7.5Hz, aromatic H), 7.70 (1H, d, J = 7.5Hz, aromatic Aromatic H).

Example 38

4- [5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -l, 2,4- Triazin-2-yl-methyl] piperidine dimesylate

or

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (piperidin- 4-yl) methyl -l, 2,4- triazine

1,1-dimethylethyl 4- [5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - Dihydro-3 (5) - imino -l, 2,4- triazin-2-yl-methyl] piperidine-1-carboxylate (0.5g, 1.1mmol) was dissolved in CH 2 C1 2 (10ml) and add trifluoroacetic acid (TFA, 10ml). The mixture was stirred for 0.5h, then concentrated in vacuo. By residual TFA Toluene was removed azeotropically. The residue was saturated NaHCO 3 solution (10ml) was stirred, then Addition of ammonia (d = 0.88) until the pH was 12. The mixture was stirred for 2h, and the deposited solid pass It was collected by filtration and dried. This material (0.12g, 0.3mmol) was dissolved in methanol (3ml) And add methanesulfonic acid (70mg, 0.7mmol). The solution was stirred for 2h, then treated with Ether was slowly diluted until precipitated oily solid. Pulverized, was removed by filtration And dried under vacuum to give the product (0.18g), was an off-white solid, m.p. 180-200 ° C.

m / z 353,355 (M <+> +1).

δ H (500MHz, dmso-d 6) 1.30 (2H, brddd, J = 25,12,4Hz, CCH 2 C), 1.79 (2H, brd, J = 12Hz, CCH 2 C), 2.07 (1H, m, CH), 1.59 (2H, brd, J = 12Hz, CCH 2 C), 2.07 (1H, m, CH), 2.31 (6H, m, CH 3 S), 2.76 (2H, td, J = 12,4Hz, CH 2 N), 3.20 (2H, brd, J = 12Hz, NCH 2), 3.22-3.40 (7H, brpeak, NH, exchange), 4.00 (2H, brd, J = 7Hz, NNCH 2), 7.53 (1H, dd, J = 7.5,2Hz, aromatic H), 7.56 (1H, t, J = 7.5Hz, aromatic H), 7.86 (1H, dd, J = 7.5,2Hz, aromatic H).

Example 39

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (3,3,3- Trifluoro-propyl) -l, 2,4- triazine

No sharp melting point (decomposition).

δ H (500MHz, dmso-d 6) 2.76-2.86 (2H, m, CH 2 CF 3), 4.31 (2H, t, J = 7Hz, NCH 2), 7.47 (1H, dd, J = 8,1.5Hz, aromatic H), 7.53 (1H, t, J = 8Hz, aromatic H), 7.84 (1H, dd, J = 8,1.5Hz, aromatic H), 8.30 (3H, brpeak, NH, exchange). m / z 352,354 (M <+> +1).

Example 40

2-chloro-3-fluorophenyl -l, 2,4- triazine-3,5-diamine

The intermediate compound was prepared by the following procedure as in Example 35 analogous manner Preparation:

step 1

3-chloro-2-fluorobenzoic acid according B.Bennetau et al., J.Chem. Soc. Perkin Trans 1,1265-1271 (1995) method by chlorination of 3-fluoro-benzoic acid Obtained.

Step 2

3- chloro-2-fluorobenzoyl chloride

Step 3

3-chloro-2-fluoro-benzoyl cyanide

Step 4

2- (3-chloro-2-fluorophenyl) -2- (guanidinoimino) acetonitrile

Step 5

2-chloro-3-fluorophenyl -l, 2,4- triazine-3,5-diamine, m.p. 244-246 ° C, m / z 240,242 (M <+> +1).

δ H (500MHz, dmso-d 6) 6.4-7.0 (4H, s + brpeak, 2x NH 2, cross Exchange), 7.25 (1H, m, aromatic H), 7.47 (2H, m, aromatic H).

Example 41

3,5-diamino-6- (2,5-dichlorophenyl) -l, 2,4- triazine, m.p. 228-230 ° C, The method according to U.S. Patent No. 4,602,017 was prepared as described.

Example 42

3,5-diamino-6- (3,5-dichlorophenyl) -l, 2,4- triazine, m.p. 223-225 ° C, 3,5-dichlorobenzoic acid was prepared from 33 using similar procedure as for Example.

Example 43

3,5-diamino-6-phenyl -l, 2,4- triazine, m.p. 218-219 ° C, using a JA Settepani and A.B.Borkovec, J.Heterocyl. Chem., 3,188-190, (1966) be prepared.

Example 44

3,5-diamino-6- (2,4-dichlorophenyl) -l, 2,4- triazine and according RWARees P.B.Russell et al, J.Med. Chem., 15,859-861 (1972) approach to system Equipment.

Example 45

5 (3) - amino-6- (2,4-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine mesylate, m.p. 283-285 ° C, as in Example 2 Similar Manner, but using ethanol as a solvent, by 3,5-diamino-6- (2,4-dichlorophenoxy Yl) -l, 2,4- triazine is reacted with methyl methanesulfonate prepared. The compound is described in US Patent No. 4,649,139 in.

Example 46

5 (3) - amino-6-phenyl-2,3 (2,5) - dihydro-3 (5) - methyl-2- -l, 2,4- Triazine mesylate, m.p. 230-232 ° C, as in Example 2 in a similar manner, but Is the use of ethanol as a solvent, by 3,5-diamino-6-phenyl -l, 2,4- triazine with methanesulfonamide Methyl reaction. The free base is described in U.S. Patent No. 4,649,139 in.

Example 47

5 (3) - amino-6-phenyl-2,3 (2,5) - dihydro-3 (5) - ethyl-2- -l, 2,4- Triazine mesylate, m.p. 230-232 ° C, as in Example 2 in a similar manner, but Is the use of ethanol as a solvent, by 3,5-diamino-6-phenyl -l, 2,4- triazine with methanesulfonamide Ethyl reaction.

Example 48

5 (3) - amino-6- (2,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine mesylate, m.p. 297-298 ° C, according to U.S. Pat. 4,649,139 describes methods to prepare.

Example 49

5 (3) - amino-6- (2,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine mesylate, m.p. 264-265 ° C, with the described in Example 2 In a similar manner, but using ethanol as a solvent, by 3,5-diamino-6- (2,5- Dichlorophenyl) -l, 2,4- triazine and ethyl methanesulfonate prepared.

Example 50

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine, m.p. 269-271 ° C, with the described in Example 2, similar Manner, but using ethanol as a solvent, by 3,5-diamino-6- (2,3,5-trichlorophenyl Phenyl) -l, 2,4- triazine and ethyl methanesulfonate prepared.

Example 51

3,5-diamino-6- (2-trifluoromethoxyphenyl) -l, 2,4- triazine, m.p. 148-150 ° C, using a similar method used for Example 33 from 2- embodiment trifluoromethoxyphenoxy Formic acid.

Example 52

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2-fluoro- Ethyl) -l, 2,4- triazine mesylate

step 1

2-fluoroethyl methanesulfonate

Methane sulfonyl chloride (12.6g, 0.11mol) added after 10min to remain in Containing triethylamine (12.1g, 0.12mol) in dichloromethane at 0-5 ° C (100ml) in 2-fluoro-ethanol (6.40g, 0.10mol) was stirred. The mixture was stirred for 1h, After that time and allowed to warm to room temperature. The mixture was extracted with dichloromethane (25ml) Diluted, and then with ice - water (40ml), followed

by cold 10% hydrochloric acid (40ml), saturated Sodium bicarbonate solution (40ml) and brine (40ml) and washed. The dichloromethane solution was passed through a sulfur Sodium sulfate, and the solvent was removed in vacuo to give the product (11.4g), as a pale yellow oil. This material was used in the following reaction without further purification.

Step 2

A mixture of 2-fluoro-ethanol (0.50g, 3.5mmol), 3,5- diamino-6- (2,3-dichlorobenzene Yl) -l, 2,4-triazine (0.50g, 2.0mmol) and dimethylformamide (4ml) at 120 ° C under It was stirred and heated 24h. The solution was cooled, added ether (30ml), stirred and pulverizing the The mixture was 0.5h. After the mixture was precipitated, the solvent was decanted from the oily precipitate with boiling 2-butanone (25ml, 2x) Proton extraction residue to remove impurities. From methanol - ether knot The residue to give crystals of the title compound (0.40g), was a light tan solid, m.p. 253-255 ° C (decomposition, rapid heating).

δ H (500MHz, dmso-d 6) 2.31 (3H, s, SCH 3), 4,46 (2H, brdt, J = 26.4,5Hz, NCH 2), 4.76 (2H, brd, J = 47.2Hz, FCH 2), 7.55 (2H, m, aromatic H), 7.86 (1H, m, aromatic H), 8.28 (1H, s, NH, exchange), 8.3-9.0 (2H, vbrpeak, NH 2, exchange), 9.24 (1H, s, NH, exchange).

Example 53

5 (3) - amino-6- (3,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Methyl -l, 2,4- triazine mesylate, m.p. 234-236 ° C, as in Example 2 Similar Manner, but using ethanol as a solvent, by 3,5-diamino-6- (3,5-dichlorophenoxy Yl) -l, 2,4- triazine is reacted with methyl methanesulfonate prepared.

Example 54

5 (3) - amino-6- (3,5-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- Ethyl -l, 2,4- triazine mesylate, m.p. 217-219 ° C, as in Example 2 Similar Manner, but using ethanol as a solvent, by 3,5-diamino-6- (3,5-dichlorophenoxy Yl) -l, 2,4- triazine and ethyl methanesulfonate prepared.

Example 55

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (2-fluoroethyl) -l, 2,4- triazine mesylate, m.p. 212-214 ° C, with the embodiment 52 in a similar manner, by dimethyl formamide 2-fluoroethyl methanesulfonate and 3,5-diamino -6- -l, 2,4- triazine reaction (2,3,5-trichlorophenyl) is prepared.

Example 56

5 (3) - amino-6- (2,3,5-trichlorophenyl) -2,3 (2,5) - dihydro-3 (5) - imino -2- (3,3,3-trifluoropropyl) -l, 2,4-triazine mesylate

step 1

3,3,3-trifluoro-propyl methanesulfonate by the procedure of Example 52 Step 1 and used to implement Prepared by a procedure similar to 3,3,3-trifluoro-propanol is reacted with methanesulfonyl chloride.

Step 2

In a similar manner as in Example 52 in dimethyl formamide 3,3,3-trifluoropropyl Yl methanesulfonate and 3,5-diamino-6- (2,3,5-trichlorophenyl) -l, 2,4- triazine reaction Get no clear melting point (hygroscopic) of the title compound.

Example 57

5 (3) - amino-6- (2,3-dichlorophenyl) -2,3 (2,5) - dihydro-3 (5) --2- (2,2- Difluoroethyl) -l, 2,4- triazine

step 1

2,2-difluoro-ethyl triflate according WGReifenrath et al., J. Med. Chem., 23,985-990 (1980) by a step of 2,2-difluoro-trifluoro-ethanol and Methanesulfonic anhydride (triflic anhydride) in the reaction.

Step 2

2,2-difluoro-ethyl triflate (1.40g, 6.5mmol) was added to 3,5- Diamino-6- (2,3-dichlorophenyl) -l, 2,4-triazine (0.50g, 2.0mmol) and dimethyl Formamide (3.5ml) in. The temperature of the mixture was stirred and heated at 100 ° C 2h, and then So at room temperature overnight. Add ether (35ml), the mixture was stirred for 0.5h. That After the mixture was precipitated, the solvent was decanted from the oily precipitate, and the residue was water (10ml) And aqueous ammonia solution (5ml, d = 0.88) was stirred for 6h. The tan solid was removed by filtration, Washed with water (3ml) was washed and air dried. To give the title product recrystallized from propan-2-ol in (0.25g), was a light tan solid, m.p. 179-181 ° C (decomposition, rapid heating).

δ H (500MHz, dmso-d 6) 4.30 (2H, brt, J = 13.8Hz, NCH 2), 5.6-7.0 (2H, vbrpeak, NH 2, exchange), 6.39 (1H, brt, J = 56Hz, CHF 2), 7.3-7.7 (1H, vbrpeak, NH, exchange), 7.41 (1H, d, J = 7.7Hz, aromatic H), 7.45 (1H, t, J = 7.7Hz, aromatic H), 7.74 (1H, d, J = 7.7Hz, aromatic Aromatic H).

Bioassay

The compound of formula (I) is the following test various activity:

Screening strategies:

Screening strategies designed to choose a suitable sodium channel blocking activity and low side effects Compound with tendency. Purposes, will do this initially by all of the compounds sodium channel check Measurement (veratridine-induced [<14> C] guanidine enter rat forebrain synaptosomes uptake) to office Management, and the impact curve IC 50 values generated from concentration. To accomplish this data, Inhibition of selected compounds was also measured [<3> H]

BTX-B binding IC 50 's.

Previous studies have shown: substituted triazine dihydrotestosterone reductase (DHFR) Activity of potential inhibitors (McCullough and Bertino 1971, Cashmore etc. People, 1975, Booth et al., 1987) and Sapse et al., 1994). DHFR (such as methyl Aminopterin) inhibitor has been used to treat various cancers (Suster et al., 1978 and Niculescu-Duvaz et al., 1982), because the inhibition of cell growth by interfering enzyme Long, but because this influences (for cell growth), DHFR inhibitor may Teratogenic (Skalko and Gold, 1974, Feldcamp and Carey, 1993 and Buckley et al., 1997). The compound is a potential inhibitor of DHFR shall find, Then this compound itself may have potential as anticancer agents. Several methods are available Measuring inhibition of DHFR activity, for this study, we have detected inhibiting compound System [<3> H] methotrexate binding effect (Myers et al., 1975 and Rothenberg, etc. Al., 1977).

Another side effect is usually labeled human Ether-a-go-go related gene (HERG) potassium channel (inward rectifier, I kr) inhibitory activity, which can be fatal, because To lead to heart failure through the development of long QT syndrome. Useful initial screening by Measurement of [3H] astemizole (astemizole) binding to the plasma membrane expression of hERG inhibition To evaluate, to evaluate the potential impact of this channel. By measuring the inhibition at 10μM under The active compound to test the system of choice. Inhibition values assumed at 10% and 90% Between can be extrapolated IC 50 for each compound.

He said screening cascade (cascade) has identified a suitable sodium channel blocking activity Compound, said compound having a (relatively) low tendency aforementioned side effects. To enter a Further development of these compounds, they need some knowledge of the efficacy of pharmacological effects.

Sodium channel blockers, for example, in the rat middle cerebral artery occlusion reduces nerve damage Injury and infarct volume SIPA song near (Sipatrigine) (Smith et al., 1997), and Phenytoin (protection from retinal ganglion cells die in glaucoma experimental model Death) (Hains and Waxman, 2005), show nerves in neurodegenerative model range Protection effect. Because oxygen failure endanger glycolysis and oxidative phosphorylation, ischemic damage Harm resulting in electrical failure (nerve signal) and pump failure (membrane potential recovery). This These failures (electrical and ion pump activity) and decrease the local concentration of ATP related (Astrup Et al., 1981). Thus the following effects of compounds able to show, in a serious new Chen After the concentration of metabolic damage in the hippocampus of rats maintain 0.4mm slices ATP (having Training metabolism inhibition factor, iodine acetate).

Experimental procedure:

Preparation of rat forebrain synaptosomes and homogenized:

Experimental use of heavy 175-250g male Wistar rat forebrain (without cerebellum / pith The quality of the entire brain) to carry out. Make all efforts to reduce the number of animals used Amount, all experiments according to UK Animals (Scientific Procedures) Act, 1986 And the European Community Council Directive of 24November 1986 (86/609 / EEC) performed. The following animals were sacrificed by stunning and decapitation, the former Brain (without cerebellum / medulla of the entire brain) and quickly cut and transferred to contain the cold 0.25M sucrose weighing tube.

Synaptosomes (including heavy and light mitochondrial part synaptosomes) through the front brain metastasis (Known net weight) to the glass vessel and using teflon potter mortar homogenization to the system Equipment, the vessel has been added to 9 volumes of ice-cold 0.25M sucrose, the homogenization through It had set to 900rpm of Braun Potter S motor driven homogenizer 8 "upper and lower punches Cheng "to carry out. The resulting homogenate was centrifuged at 4 ° C under 10min at 1036x g, collected Supernatant. As above, the remaining pellet was resuspended in fresh ice-cold 0.25M sucrose, And repeat the centrifugation step. The supernatant fraction collection and 40,000x g (average) at 4 ° C Centrifuged 15min, the resulting pellets in a suitable detection buffer 20-25mg per milliliter wet Heavy concentration in a suitable assay buffer and resuspended.

The homogenate by transferring to a known weight of the forebrain containing 9 volumes of ice-cold 50mM HEPES buffer at pH 7.4 coolant tube prepared. The mixture at 4 ° C By setting the maximum speed at 3x5sec pulse Ultra-Turrax <TM> homogenizer are Homogenized. The resulting homogenate was centrifuged at 40,000x g at 4 ° C under 15min (average), the cast The supernatant was discarded. The resulting pellet was resuspended in 9 volumes of ice-cold fresh buffer at pH 7.4 Medium (as above), repeat centrifugation step, the resulting beads per ml assay buffer 20-25mg wet weight concentration of [<3> H] BTX-B resuspended in binding buffer.

[<14> C] guanidine flow and [<3> H] BTX-B binding:

Two tests were conducted using a 14ml polypropylene test tube to the test tube Adding a range of concentrations of test compound. The test compounds were dissolved in DMSO And added to detect liquid, so that the maximum concentration of DMSO does not exceed 2% v / v.

[<14> C] guanidine flow:

Test compounds in the following incubation buffer at 30 ° C under the pre-incubated 10min: The incubation buffer (50mM pH 7.4HEPES (with Tris base adjusted to pH 7.4), 130mM choline chloride, 5.5mM D- glucose, 0.8mM MgSO 4 and 5mM KC1) Net starting contains 7.5mg of tissue and l00μg hydrochloric acid in a final volume of 0.5ml Veratrine. By adding 0.5ml [<14> C] guanidine (incubation buffer l.0μCi / ml) initiator Intake and 2.5 minutes after the addition of 10ml ice-cold wash buffer (5mM pH in 7.4HEPES buffer 163mM choline chloride, 1.8mM CaCl 2 and 0.8mM MgSO 4) terminate, followed immediately by using Brandel <TM> cell harvester through a Whatman GF / C glass fiber filters by vacuum filtration. Separately 2x 5ml ice-cold wash buffer Was added to each tube, vacuum filtration step repeated. The GF / C glass fiber filters transfected Move to trace the vial (mini vials), and

using Brandel <TM> sedimentary / distribution system Tim Plus 4ml Picofluor <40> liquid scintillator. Radioactive liquid scintillation counting using Beckman Measurements.

[<3> H] BTX-B binding:

Triggered by the following combination: Add 5mg initial wet weight of tissue to be included in the Final volume of 0.25ml of incubation buffer (see above, but instead chloride containing 134mM Choline and lmM KC1) of [<3> H] BTX-B (single measurement temperature by measuring the radioactivity Fertility concentration), test drugs and 25μgα- scorpion venom (scorpion venom). The sample was mixed Co-cultured for 90 minutes at 25 ° C, and by the addition of 5ml ice-cold wash buffer (see Termination above) detection, and then immediately use Brandel <TM> cell harvester through Whatman GF / C glass fiber filters by vacuum filtration. Also 5ml of ice-cold wash Buffer was added to each tube, vacuum filtration step repeated. The GF / C glass fiber over Filters were transferred to trace the vial and use Brandel <TM> sedimentary / distribution system added 4ml Picofluor <40> liquid scintillator. Radioactivity measured using a Beckman liquid scintillation counter Amount, by referring to the appropriate quenching parameters directly into cpm dpm.

[<3> H] combination of methotrexate

All steps at 4 ° C (or on ice) were. The new cut cut rat liver Ice-cold 0.25M sucrose, the subsequent containing 50mM pH 15mM dithiothreitol in 6.0 phosphate buffer (10ml / g tissue) homogenization (U-turrax). The resulting uniform Centrifuged at 47,500x g pulp 20min, before using the supernatant (filtered through cotton To remove fat mass) stored at -80 ° C under (Rothenberg et al.).

[<3> H] methotrexate to inhibit the binding of rat liver homogenate supernatant fraction substantially On such Arons et al., Conducted the 1975. Briefly, the compound at room temperature, In mercaptoethanol (60mM) presence in the final volume 410μL of 50mM pH 6.0 Of phosphate buffer, with NADPH (480μM), liver supernatant (DHFR enzyme) And [<3> H] methotrexate (50nM) were incubated for 15 minutes. The binding reaction by adding 50μl wood Charcoal suspension (made in phosphate buffer 50mM pH 6.0 in a weight ratio of suspended 100: 4: 1 is present in charcoal, bovine serum albumin and dextran) and stops. The sample Product rotation, allowed to stand for 2 minutes at full speed by the charcoal microcentrifugation 5min To precipitate. Transfer the sample aliquot to contain a clear supernatant liquid for use Liquid scintillation counting vials scintillation spectrometry radioactivity measured.

The [<3> H] specific binding methotrexate determined to be 200μM "cold" Methotrexate Difference combination of presence and absence. Percent inhibition values by comparing this value Calculations.

Calculated IC 50 value:

Data as shown in parentheses mean ± sem number of experiments to represent.

IC 50 values from the relative binding by the ligand / guanidine concentration according to the following equation 10 plotted log Uptake of the radioligand displacement or guanidine flow inhibition curves obtained:

y = Rmin + Rsp / {1 + exp [-n (x-C)]}

Wherein y = binding (dpm)

x = log concentration of compound 10

Rmin = lower asymptote (ie 100% inhibition)

Rsp = upper asymptote -Rmin (ie, specific binding)

n = slope (log e)

And C = IC 50 (inhibitory concentration 50% is required for specific binding)

Hippocampal slice detection:

The following animals were sacrificed by stunning and decapitation, the forebrain (without cerebellum / medulla whole A brain) and quickly cut and transferred to contain the cold pre-charge (pre-gassed) of Artificial cerebrospinal fluid (aCSF) container. The hippocampus fast cutting, use Mcllwain Tissue sections were prepared 0.4mm slices. The sections were randomly distributed in 50ml containing ACSF Erlenmeyer flask 25-30ml cold pre-release gas. When the media through true Air sucked out is removed, the flask with 95% O 2/5% CO 2 in a continuous inflatable (continued gassing) at 30 ° C incubated for 30 minutes. Add freshly aCSF, the sections such as Before the further incubated for 30 minutes. Medium is aspirated again removed by vacuum, and dried 25ml pre-warmed (30 ° C) without Ca <2+> in aCSF instead. Inflatable under continuous warm again After educating 10min, by immediately transferred to contain 0.4ml ice cold 0.5M TCA (TCA) in each microcentrifuge tube was removed 2-3 tablets (using Eppendorf pipette in 100μl volume) for measuring the ATP and protein. Iodine acetate (25μl 0.4M in Solution) was added to the flask, and stop inflation. After just 11min, to 3-4 slices It was removed and transferred to a microfuge tube in the previously described.

Measurement of ATP and protein:

Ultrasound will be destroyed by a single slice, and the resultant homogenized at 10000x g in 4 ° C and centrifuged 5min. The supernatant was poured into a new tube, any remaining supernatant by Vacuum aspiration removed. The pellets were resuspended by sonication in 0.5ml 0.1M KOH in With the slow-stirring the resulting suspension was incubated at 37 ° C for 30 minutes.

By luciferase reagent (commercially available from Perkin Elmer of ATPLite) were mixed and Then in 96-well plates measuring luminescence counter, measurement of ATP in the supernatant 6μl concentration.

The protein concentration using bovine serum albumin as the reference standard using the BCA <TM> protein Quality testing (puncture) to measure.

ATP concentration is expressed as nmoles / mg protein, and by the effect of 1μM TTX Neuroprotective index (% protection) directly comparing the calculated results.

hERG:

Performing an assay to measure the effect of 10μM under compound. Conduct putative binding oblique Was 1, the compound having the inhibition values of 10% and 90% between the IC 50 value Extrapolation.

result:

Table 1

[Image]

Data as shown in parentheses in the number of experiments average IC 50 (μM) ± standard error of the presentation

Table 2: compound name and structure:

[Image]

[Image]

Table 3: [<14> C] guanidine Traffic Summary

[Image]

[Image]

Table 4: [<3> H] BTX-B binding summary

[Image]

Table 5: inhibition from a single point of study and the [K] (hERG): [Na] channel selective extrapolation IC 50 's (hERG)

MDS Results

[Image]

<*> Synaptosomes data

Table 6: [<3> H] methotrexate binding summary data

[Image]

[Image]

<*> From methotrexate Displacement curve The% inhibition

Table 7: Summary of hippocampal slice data

[Image]

Table 8: [<14> C] influence uptake guanidine compound

[Image]

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