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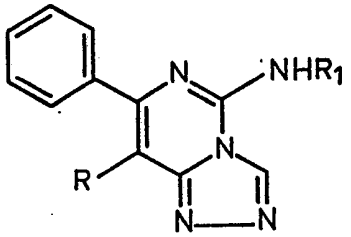
(54) 8-substituted 7-phenyl-1,2,4-triazolo[4,3-c] pyrimidine-5-amines and amides

(57) Compounds corresponding to the following general formula:



(I)

wherein R represents hydrogen, C_1—C_4 alkyl, C_2—C_4 alkoxyalkyl, C_2—C_4 alkenyl or C_2—C_4 alkynyl; and R_1 represents hydrogen or C_1 or C_2 1-oxoalkyl, are pharmaceutically active and may be used as diuretic agents, e.g. in pharmaceutical compositions.

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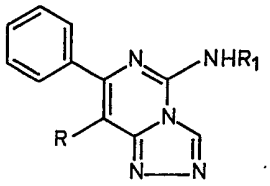
SPECIFICATION

8-substituted 7-phenyl-1,2,4-triazolo [4,3-c] pyrimidines-5-amines and amides, preparation and pharmaceutical use thereof

This invention relates to 8-substituted 7-phenyl-1,2,4-triazolo[4,3-c]pyrimidines-5-amines and amides, preparation and pharmaceutical use thereof.

The present invention provides a compound corresponding to the following general formula:



wherein R represents hydrogen, alkyl containing from 1 to 4 carbon atoms, or alkoxyalkyl, alkenyl or alkynyl containing from 2 to 4 carbon atoms; and R_1 represents hydrogen or 1-oxoalkyl containing 1 or 2 carbon atoms.

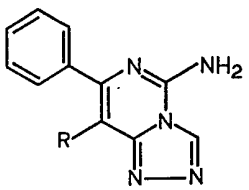
Those alkyl radicals containing from 1 to 4 carbon atoms and represented by R are typified by methyl, ethyl, propyl and butyl and the corresponding branched-chain isomers.

Those alkoxyalkyl radicals containing from 2 to 4 carbon atoms and represented by R are typified by methoxymethyl, methoxyethyl, 2-methoxypropyl, 3-methoxypropyl, ethoxymethyl, 1-ethoxyethyl, 2-ethoxyethyl, ethoxymethyl, propoxymethyl and (1-methylethoxyethyl).

Those alkenyl and alkynyl radicals containing from 2 to 4 carbon atoms and represented by R are typified by ethenyl, 1-propenyl, 2-propenyl, 1-butenyl 2-butenyl, 3-butenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl and the corresponding branched chain isomers.

The 1-oxoalkyl radicals containing 1 or 2 carbon atoms and represented by R_1 are carbonyl and acetyl.

Such compounds corresponding to the following general formula:



wherein R is defined above; are preferred. It is particularly preferred that R should represent alkyl containing from 1 to 4 carbon atoms or alkoxyalkyl containing from 1 to 4 carbon atoms.

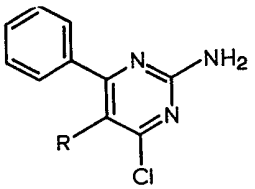
The present compounds are useful because of the valuable pharmacological properties thereof. For example, they are potent diuretics. When assayed for the capacity to increase urine volume as described by Lipschitz *et al.* [J. Pharmacol. Exp. Therap., *7997* (1943)] and assigned potencies based upon parallel dose response curves in accordance with Finney (Statistical Method in Biological Assay, 2nd ed., Charles Griffin & Company, Limited, London, 1964]. 8-methyl-7-phenyl-1,2,4-triazolo[4,3-c]pyrimidine-5-amine and 8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo [4,3-c] pyrimidine-5-amine were found to be 1.2 and 2.7 times as potent as hydrochlorothiazide, respectively. The latter compound is particularly preferred. The typical dosage of hydrochlorothiazide as a diuretic for use in humans is 25 or 50 mg per oral administration.

For therapeutic purposes, the present compounds are generally combined with one or more pharmaceutically acceptable carriers, diluents or adjuvants appropriate to the indicated route of administration. If *per os,* they may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrolidone, and/or polyvinyl alcohol, and thus tableted or encapsulated for convenient administration; alternatively, they may be dissolved in water or a comparably innocuous liquid. Parenteral administration may be effected via sterile fluid admixture with water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art; see, for example F. W. Martin *et al.*, "Remington's Pharmaceutical Sciences", 14th ed., Merck Publishing Co., Eaton, Pa., 1965.

Appropriate dosages, in given instances of course depend upon the nature and severity of the condition treated, the route of administration and the species of mammal involved, including its size and individual idiosyncrasies which obtain.

The present invention also provides such compositions and such pharmaceutical use.

The amines according to the present invention may be prepared by reacting 4-chloro-6-phenylpyrimidin-2-amines corresponding to the following general formula:

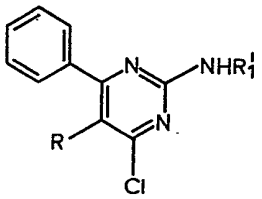


wherein R is defined as above; with formylhydrazine in dimethylformamide. The resulting amines may be crystallized in water and recrystallized from methanol.

The amides according to the present invention may be prepared by reacting the corresponding amines with formic or acetic anhydride, depending upon the desired amide.

Alternatively, the present amides may be

prepared by reacting appropriate N-(4-chloro-6-phenylpipimidin-2-yl)amides corresponding to the following general formula:



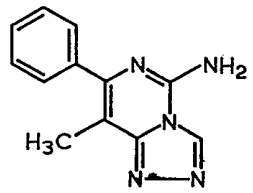
wherein R is defined as above; and R_1' represents formyl or acetyl; for formylhydrazine in dimethylformamide. The solid product is obtained by the addition of water.

The present invention also provides such a process for the preparation of the above compounds.

The following Examples illustrate the present invention. Unless otherwise indicated, temperatures are given in degrees centigrade and amounts in parts, by weight.

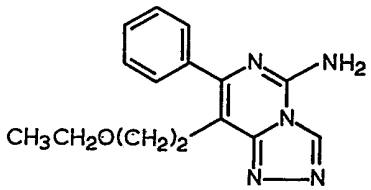
EXAMPLE 1

5.5 parts of 4-chloro-5-methyl-6-phenylpyrimidin-2-amine and 3.0 parts of formylhydrazine are added to 50 parts, by volume of dimethylformamide containing 5.0 parts of molecular sieve 3A and refluxed under nitrogen for 2 hours. After standing for 16 hours at room temperature, the solution is poured into cold water. The yellow crystalline product is filtered off, washed with water and dried. The product is recrystallised from methanol to give, as bright yellow needles melting at 258—260°C, 8-methyl-7-phenyl-1,2,4-triazolo[4,3-c]pyrimidin-5-amine:



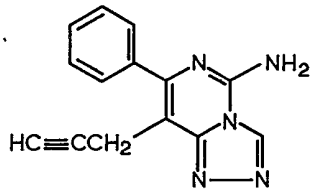
EXAMPLE 2

10.0 parts of 4-chloro-5-(2-ethoxyethyl)-6-phenylpyrimidin-2-amine and 3.0 parts of formylhydrazine are added to 80 parts, by volume, of dimethylformamide containing 8.0 parts of molecular sieve 3A and refluxed under nitrogen for 2 hours. After standing for 16 hours at room temperature, the solution is poured into cold water. The crystalline product is filtered off, washed with water and dried. The product is recrystallized from methanol to give 8-(2-ethoxyethyl)-7-phenyl-]1,2,4]triazolo[4,3-c]pyrimidin-5-amine melting at 154°C:



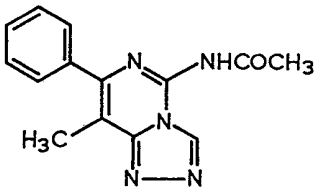
EXAMPLE 3

1.7 parts of 4-chloro-6-phenyl-5-(2-propynyl) pyrimidin-2-amine and 0.84 part of formylhydrazine are added to 20 parts, by volume, of dimethylformamide containing 2.0 parts of molecular sieve 3A and refluxed under nitrogen for 2 hours. The solution is allowed to cool and is poured into cold water. The crystalline product is filtered off, washed with water and dried. The product is recystallized from methanol to give 7-phenyl-8-(2-propynyl) [1,2,4]triazolo[4,3-c]pyrimidin-5-amine melting at 240°C:



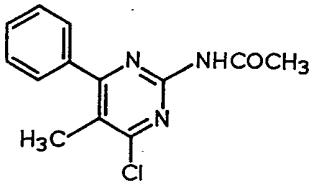
EXAMPLE 4

6.6 parts of 8-methyl-7-phenyl-1,2,4-triazolo[4,3-c]pyrimidin-5-amine (Example 1) is suspended in 50 parts, by volume, of pyridine and 10 parts, by volume, of acetic anhydride. The solution is stirred at room temperature for about 18 hours until a clear solution is formed. After about 21 hours, turbidity develops and a solid gradually forms. After standing for about 40 hours, most of the solvent is removed *in vacuo*. The residue is stirred in water, filtered, washed with water and dried. The product is recrystallized from methanol to give N-(8-methyl-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl]acetamide melting at 210°C:



EXAMPLE 5

Alternatively, the product of Example 4, N-(8-methyl-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidine-5-yl] acetamide, may be obtained using the appropriate chlorinated pyrimidine. 7.85 parts of N-(4-chloro-5-methyl-6-phenylpyrimidine-2-yl)acetamide:

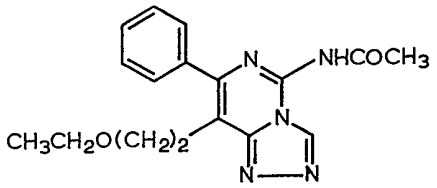


is added to 6.0 parts of formylhydrazine and 60 parts, by volume, of dimethylformamide. The solution is heated to reflux under nitrogen for 2.5 hours. The solution is allowed to cool and stand at room temperature for 16 hours. The clear solution is poured into cold water with stirring. A bright yellow crystalline material is obtained. The

material is filtered, washed with water, dried and recrystallized from methanol to give the desired product.

EXAMPLE 6

6.4 parts of N-[4-chloro-5-(2-ethoxyethyl)-6-phenylpyrimidin-2-yl]acetamide and 2.4 parts of formylhydrazine are added to 60 parts, by volume, of dimethylformamide containing 6.0 parts of molecular sieve 3A and refluxed under nitrogen for 1 hour. The golden orange solution is then allowed to cool and is poured into water. A bright yellow material is obtained, which is then filtered off, washed with water and dried to give N-[8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-2-yl) acetamide melting at 75—76°C:



Having illustrated the preparation of the present compounds, the pharmaceutical use thereof will now be illustrated.

Pharmaceutical formulations were prepared in the following manner, amounts indicating the relative amounts per tablet, capsule, suppository or parenteral product.

Tablets

25 mg of a representative compound, *e.g.* 8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidine-5-amine were dissolved in isopropyl alcohol and distributed on 191.2 mg. of lactose. The mixture was air-dried and passed through a 40 mesh screen. 25 mg of corn starch and 7.5 mg of polyvinylpyrrolidone were added to the drug substance lactose mixture, mixed thoroughly and passed through a 40 mesh screen. The mixture was then granulated using isopropyl alcohol, spread on trays and dried at about 49°C (120°F.) for 16 hours. The dried granulation was then screened. The granules were mixed thoroughly with 1.3 mg of magnesium stearate and the mixture compressed into tablets of the appropriate size. There was thus obtained a tablet having a concentration of active ingredient of 25 mg/tablet.

CAPSULES

25 mg of 8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidine-5-amine were mixed thoroughly with 177.5 mg of corn starch and 177.5 mg of lactose, screened through a 40 mesh screen and remixed. 20 mg of talc were added and the mixture was thoroughly mixed and filled into the appropriate hard gelatin capsule by hand or machine using 400 mg fill per capsule. There was thus obtained a capsule having a concentration of active ingredients of 25 mg capsule.

In the preparation of tablets and capsules using the present compounds, a variety of excipients may be used. For example: Sugars, such as lactose, sucrose, mannitol, or sorbitol; starches, such as corn starch, tapioca starch, or potato starch; cellulose derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, or methyl cellulose; gelatine; calcium phosphates, such as dicalcium phosphate or tricalcium phosphate; sodium sulphate; calcium sulphate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate; stearic acid vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil; surfactants (non-ionic, cationic, anionic); ethylene glycol polymers; betacyclodextrin; fatty alcohols; hydrolyzed cereal solids; as well as other non-toxic compatible fillers, binders, disintegrants, and lubricants commonly used in pharmaceutical formulations.

PARENTERAL PRODUCTS

10 mg of 8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-5-amine was dissolved in 2 ml. of ethanol and 5 ml of sesame oil, filtered and filled into an ampoule and sealed. the ampoule was then sterilized by an appropriate procedure. There was thus obtained an ampoule having a concentration of active ingredient 10 mg/5ml.

In the preparation of parenteral products using the present compounds a variety of vehicles and solublizers may be used. For example: Vegetable oils, such as peanut, corn, cottonseed, sesame oil, benzyl alcohol, saline, phosphate buffer, water, ethylene glycol polymers, urea, dimethylacetamide, "Triton" (Registered Trade Mark), dioxolanes, ethyl carbonate ethyl lactate, glycerol formal, isopropyl myristate, surfactants (non-ionic, cationic, anionic), polyalcohols and ethanol.

SUPPOSITORIES

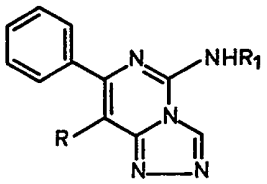
975 mg of cocoa butter were melted, preferably using a water or steam bath to avoid local overheating, then 25 mg of 8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-5-amine was either emulsified or suspended in the melt.

The mass was then poured into cooled chrome-plated metal moulds and the suppository was readily solidified. The total weight of the suppository was 1000 mg.

In the preparation of suppositories using the present compounds a variety of vehicles and bases for suppository application may be used. For example; Triglycerides of oleic, palmitric, and stearic acids (cocoa butter), partially hydrogenated cottonseed oil, branched saturated fatty alcohols, such as Suppository base G, Hydrogenated coconut oil triglycerides of C_{12}—C_{18} fatty acids, water dispersible vehicles, such as the polyethylene glycols, glycerin, gelatin, polyoxyl 40 sterarates, and polyethylene-4-sorbitan monostearates, and materials which may raise the melting point of the suppository base, such as beeswax and spermaceti.

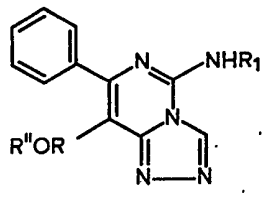
CLAIMS

1.A compound corresponding to the following general formula:



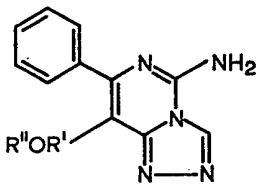
wherein R represents hydrogen, C_1—C_4 alkyl C_2—C_4 alkoxyalkyl, C_2—C_4 alkenyl or C_2—C_4 alkynyl; and R_1 represents hydrogen or C_1—C_2 1-oxoalkyl.

2. A compound as claimed in claim 1 corresponding to the following general formula:



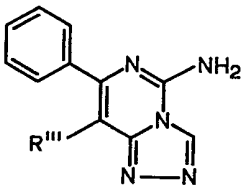
wherein R′ represents C_1 or C_2 alkylene; R″ represents C_1 or C_2 alkyl; and R_1 represents hydrogen or C_1 or C_2 1-oxoalkyl.

3. A compound as claimed in claim 2 corresponding to the following general formula:



wherein R′ represents C_1 or C_2 alkylene; and R″ represents C_1 or C_2 alkyl.

4. A compound as claimed in claim 1 corresponding to the following general formula:



wherein R‴ represents hydrogen, methyl, ethyl, ethyenyl or ethynyl.

5. N-(8-methyl-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl]acetamide.

6. N-(8-(2-ethoxyethyl)-7-phenyl-[1,2,4]triazolo[4,3-c]pyrimidin-5-amine.

7. 8-methyl-7-phenyl-1,2,4-triazolo[4,3-c]pyrimidin-5-amine.

8. A process for the preparation of a compound as claimed in claim 1 substantially as herein described.

9. A process for the preparation of a compound as claimed in claim 1 substantially as herein described with reference to any one of the Examples.

10. A compound as claimed in claim 1 when prepared by a process as claimed in claim 8 or claim 9.

11. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 7 or 10 and a pharmaceutically-acceptable carrier or diluent.

12. A composition as claimed in claim 11 substantially as herein described.

13. The use of a compound as claimed in any of claims 1 to 7 or 10 as a pharmaceutical.

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