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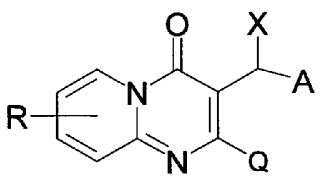

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(57) Abstract: The present invention concerns novel compounds possessing the general formula (I), pharmaceutical preparations containing such active ingredients, as well as the process for manufacture thereof, where R, X, A and Q are defined in the claims. The novel compounds are efficient in the prevention and/or treatment of diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

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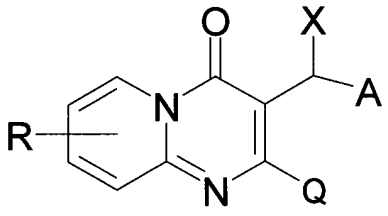
NOVEL MEDICINAL COMPOUNDS

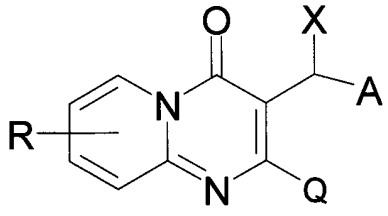
The present invention concerns novel compounds possessing the general formula (I),



(I)

pharmaceutical compositions containing an active substance possessing the general formula (I), and preparation thereof. The novel compounds are effective in prevention and treatment of diseases caused by the bacterium *Mycobacterium tuberculosis* or other Mycobacteria.

More precisely, the invention concerns compounds possessing the general formula (I),



(I)

where

R stands for any of the followings: hydrogen atom, halogen atom, nitrile group, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxy carbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide

group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkyl amine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives;

X stands for hydrogen atom(s), oxo group or hydroxyl group;

A stands for any of the followings: oxo group, hydroxyl group, OR', NR' or NHR', where R' stands for hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxycarbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives;

Q stands for halogen atom, or NR''R''', where R'' és R'''stands for any of the followings: hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy

carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryl oxycarbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkylcarboxamide group, cycloalkylcarboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, arylcarboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives, or in given cases R'' and R''' constitutes unsubstituted or substituted aromatic or unsubstituted or substituted heteroaromatic ring or cycloalkyl or heterocyclic group;

and organic or inorganic salts of compounds possessing the general formula (I).

The invention moreover concerns the procedure for preparation of compounds possessing the general formula (I), as well as the application of compounds possessing the general formula (I) and its pharmaceutically applicable organic or inorganic salts and pharmaceutical compositions containing one or more of these compounds and its salts for prevention and/or treatment of diseases caused by the bacterium *Mycobacterium tuberculosis* or other Mycobacteria.

Most species of the Mycobacterium genus inhabit the surface waters and the upper levels of the soil; they are important, mostly saprophyte microorganisms that contribute to

biodegradation of organic materials in the environment. Some Mycobacterium species, however, became pathogenic in the course of the evolution: in this respect, one should mention *Mycobacterium tuberculosis* and *Mycobacterium bovis* as the most important pathogens in the Mycobacterium tuberculosis complex, that also contains the following other species: *M. bovis bacillus Calmette-Guerin, M. africanum, M. microti, M. canetti, M. caprae*. These bacteria differ substantially by their virulence and host organisms, but their DNA is very similar: these bacteria show a 99.9% similarity at the DNA level (*Brosch R. et al. Molecular genetics of Mycobacteria. Washington, D.C.: American Society for Microbiology, 2000:19-36; Brosch R. et al. Proc Natl Acad Sci U S A 2002; 99:3684-3689.; Zumla, A. et al. Pulmonary Medicine. 8(3):166-172, May, 2002*).

The tuberculosis disease and the human race have existed together for a very long time. The eradication of tuberculosis is still far away, and newly appearing multi-drug resistant and extremely multi-drug resistant tuberculosis strains cause new difficulties in therapy (*Gergely, R. Medicina Thoracalis 1998; 51:185-188; Hutás I. HIPPOCRATES Vol. I. (5) 260, 1999*).

The global health challenge, caused by tuberculosis, can be characterized by the following numbers: every year 8 million new TB cases are diagnosed, and 2 million casualties are caused by tuberculosis. One third of the human population carries the tuberculosis bacterium (*WHO Report, 2007, Genova*).

From the 1980's, numerous AIDS patients developed tuberculosis as a co-infection, increasing the number of new

cases worldwide. About 15% of all AIDS sufferers die from tuberculosis.

At the end of the twentieth century, drug-resistant tuberculosis strains appeared, causing further difficulties in the therapy: the multi-drug resistant (MDR) strains (that are resistant to the two first-line TB drugs, isoniazid and rifampicin) should be mentioned primarily, and the less frequent, but very hard to cure, extensively drug resistant (XDR) strains secondly.

When the *Mycobacterium tuberculosis* bacterium enters the lung by inhalation, it becomes internalized by phagocytosis into macrophages of the lung, i.e. the alveolar macrophages. The bacteria will survive in the macrophages, and may remain in the lung for years or disperse in the body of the host organism. The tuberculosis bacterium surviving in the macrophage can be in an active, dividing, or in a passive sleeping, or dormant state with very low metabolism.

Timely started therapy will cease further infections in the population of the host organism, and will prevent secondary drug resistance and later relapses by eradicating the bacteria. The appearance of resistant *M. tuberculosis* strains requires the revision of the current therapy protocols (*William K. J. and Duncan K. Curr Mol Med. 2007 May;7(3):297-307*).

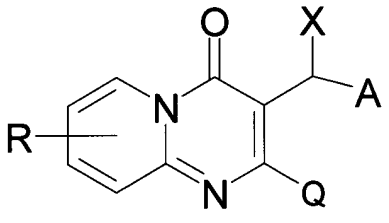
In neutral and slightly basic media, isoniazid, rifampicin and streptomycin are very efficient against M. tuberculosis. Pyrazinamide is efficient in the more acidic intra-cellular space.

The most anti-tuberculotic drugs have bacteriostatic or bactericide effects in the inter-cellular space. By the prior art, the known anti-tuberculotic drugs enter the macrophages through diffusion, in a limited rate. Additionally, non-specific toxicity and too fast metabolism may cause pharmacodynamic difficulties, and decrease the effects of the drugs. Usually, anti-tuberculosis therapies apply multiple drugs through a period of 6 to 9 months in non-MDR strains, and up to 24 months in the case of MDR or XDR strains.

Most anti-tuberculotic drugs have limited effects against dormant bacilli. Increasing the metabolism or the diffusion of the drugs into the infected macrophages may speed up the therapy and would allow the decrease of drug concentration applied, yielding fewer side effects.

The aim of the present invention is to overcome the above mentioned difficulties with new anti-tuberculotic drug preparations efficient in diseases caused by *Mycobacterium tuberculosis*, and other Mycobacteria in the lung and in other organs. The drug molecules will be efficient in the prevention and/or therapy of tuberculotic diseases.

Surprisingly, we found that the above goal can be potentially achieved by using new compounds possessing the general formula (I)



(I)

where

R stands for any of the followings: hydrogen atom, halogen atom, nitrile group, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxy carbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkyl amine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives;

X stands for hydrogen atom(s), oxo group or hydroxyl group;

A stands for any of the followings: oxo group, hydroxyl group, OR', NR' or NHR', where R' stands for hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxycarbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group,

alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives;

Q stands for halogen atom, or NR''R''', where R'' és R'''stands for any of the followings: hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryl oxycarbonyl group, heterocyclic oxycarbonyl group and its derivatives, alkylcarboxamide group, cycloalkylcarboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, arylcarboxamide group, heterocyclic carboxamide group and its derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives, or in given cases R'' and R''' constitutes unsubstituted or substituted aromatic or unsubstituted or substituted heteroaromatic ring or cycloalkyl or heterocyclic group;

and pharmaceutically applicable organic or inorganic salts of compounds possessing the general formula (I).

The invention specifically concerns those compounds possessing the general formula (I) that we selected from the compounds listed below:

2-Chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,

7-Bromo-2-chloro-8-methyl-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,

2-Allylamino-3-allyliminomethyl-pyrido[1,2-a]pyrimidin-4-one,

2-Allylamino-3-allyliminomethyl-7-methylpyrido[1,2-a]pyrimidin-4-one,

2-Allylamino-3-allyliminomethyl-9-methylpyrido[1,2-a]pyrimidin-4-one,

2-Propylamino-3-propyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Isopropylamino-3-isopropyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Prop-2-ynylamino-3-prop-2-ynyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclopentylamino-3-cyclopentyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclohexylamino-3-cyclohexyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-(2-Hydroxyethyl)amino-3-(2-hydroxyethyl)iminomethyl-pyrido[1,2-a]pyrimidin-4-one,

2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]-iminomethyl-pyrido[1,2-a]pyrimidin-4-one,

2-[2-(Thiophen-2-yl)-ethyl]amino-3-[2-(thiophen-2-yl)-ethyl]iminomethyl-pyrido[1,2-a]pyrimidin-4-one,

2-Cyclopropylamino-3-cyclopropyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclopropylmethylamino-3-cyclopropylmethyl-iminomethylpyrido[1,2-a]pyrimidin-4-one,

2-[2-(Pyrrolidin-1-yl)ethyl]amino-3-[2-(pyrrolidin-1-yl)ethyl]-iminomethylpyrido[1,2-a]pyrimidin-4-one,
2-[2-(Tetrahydropyran-4-yl)ethylamino]-3-[2-(tetrahydropyrano-4-yl)ethyliminomethyl]pyrido[1,2-a]pyrimidin-4-one,
2-(2-Dimethylaminoethylamino)-3-(2-dimethylaminoethyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one,
2-Phenylamino-3-phenyliminomethylpyrido[1,2-a]pyrimidin-4-one,
2-(2-Bromophenylamino)-3-(2-bromophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Morpholin-4-yl-phenylamino)-3-(4-morpholin-4-yl-phenyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Acetylaminophenyl)amino-3-(4-acetylaminophenyl)-iminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Trifluoromethylphenylamino)-3-(4-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(2-Trifluoromethylphenylamino)-3-(2-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(4-Fluorophenylamino)-3-(4-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(2-Fluorophenylamino)-3-(2-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(4-Methoxyphenylamino)-3-(4-methoxyphenylimino)-methylpirimido[1,2-a]pyrimidin-4-one,
2-(2-Methoxyphenylamino)-3-(2-methoxyphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-Allylamino-3-allylaminomethyl-pyrido[1,2-a]pyrimidin-4-one,
2-Propylamino-3-propylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclopropylamino-3-cyclopropylaminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclopropylmethylamino-3-cyclopropylmethylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclohexylamino-3-cyclohexylaminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Tetrahydropyran-4-yl)-ethyl]-amino-3-[2-(tetrahydropyran-4-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one trihydrochloride,
2-[2-(Thiophen-2-yl)-ethyl]-amino-3-[2-(thiophen-2-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Pyrrolidin-1-yl)-ethyl]-amino-3-[2-(pyrrolidin-1-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one trihydrochloride,
2-Cyclopentylamino-3-cyclopentylaminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-phenylamino-3-phenylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Dimethylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(Allylmethylamino)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
4-Oxo-2-(pyrrolidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
4-Oxo-2-(piperidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(Morpholin-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(2-Hydroxymethylpiperidine-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde-hydrate,

4-Oxo-2-propylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-tertiary butoxycarbonylmethylamino-4-oxopyrido[1,2-a]-pyrimidine-3-carbaldehyde,
4-Oxo-2-phenylaminopyrido[1,2-a]pyrimidine-3-carbaldehyde-hydrate,
4-Oxo-2-phenylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde,

and the pharmaceutically applicable organic and inorganic salts of these compounds.

In addition, the invention concerns all such pharmaceutical compositions which contain as active substance one or more compounds possessing the general formula (I) and/or their pharmaceutically applicable organic or inorganic salt(s) at pharmaceutically applicable concentrations together with one or more pharmaceutically applicable diluting agent(s), excipient(s), and/or inert carrier(s).

The term „alkyl" stands for substituents possessing acyclic straight or branched chains of at most 20 carbon atoms, such as methyl, ethyl, n-propyl, n-butyl, 1-methyl-ethyl, i-propyl, tertiary butyl. The alkyl group may be further substituted, i.e. it may contain any of the following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The term „cycloalkyl" stands for substituents possessing cycloalkyl groups with 3-12 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl group may be further substituted, i. e. it may contain any of the

following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The term „aryl" stands for substituents possessing either an aromatic monocyclic group of 6 carbon atoms or a aromatic bicyclic group of 10 carbon atoms, e.g. phenyl, 1-naphtyl or 2-naphtyl. The aryl group may be further substituted, i. e. it may contain any of the following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The term „alkenyl" stands for substituents possessing branched, or non-branched or cyclic alkylene groups containing 2-10 carbon atoms and at least one double bond, such as e.g. ethenyl, propenyl, butenyl, cyclohexenyl, including the potential isomers, as well. The alkenyl group may be further substituted, i. e. it may contain any of the following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The term „alkynyl" stands for substituents possessing branched, or non-branched or cyclic alkynyl groups containing 2-10 carbon atoms and at least one triple bond, such as ethynyl, propalgyl, butynyl és pentynyl, including the potential isomers, as well. The alkynyl group may be further substituted, i. e. it may contain any of the following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The term „halogen" stands for any of the following substituents: fluorine, chlorine, bromine or iodine.

The term „heterocyclic" stands for substituents possessing cyclic groups where one or more carbon atoms are substituted with nitrogen, oxygen or sulphur atoms, e.g. pyrrole, pyrrolidine, pyrazole, imidazole, piridine, thiophene,

benzodioxane. The heterocyclic group may be further substituted, i.e. it may contain any of the following substituents: F, Cl, Br, OH, OMe, methyl, ethyl, CN, COOH, COOMe, $CONH_2$, and NH_2.

The compounds possessing the general formula (I) and the pharmaceutically applicable compositions containing their inorganic or organic salts in either solid or fluid forms may be administered by any of the following routes: peroral, parenteral (including subcutaneous, intramuscular, intravenous), buccal, sublingual, nasal or rectal, or *via* topical administration.

The solid compositions to be administered by peroral route may be in the form of powder, capsule, pill (tablet), film tablet, microcapsule, etc, and may contain as carrier materials like binders (e.g. gelatin, sorbitol, polyvinyl-pirrolidone); fillers (e.g. lactose, glucose, starch, calcium-phosphate, etc); auxiliary materials (e.g. magnesium-stearate, talcum, polyethylene-glycol, silicon-dioxide, etc); lubrication agents (e.g. sodium-lauryl-sulphate, etc), etc.

The fluid compositions to be administered by peroral route may be in the form of solutions, suspensions or emulsions which may contain as carrier materials e.g. suspending agents (e.g. gelatin, carboxy-methyl-cellulose, etc); emulgation agents (e.g. sorbitane monooleate, etc) stb.; solvents (e.g. water, oils, glycerol, propylene glycol, ethanol); preservatives (e.g. p-hydroxy-benzoate methyl-ester, etc), etc.

Representative forms of parenteral compositions constitute solutions or suspensions, which contain the compounds possessing the general formula (I) and/or their

pharmaceutically applicable organic and inorganic salts as sterile solutions in aqueous solutions or parenterally applicable non-aqueous solutions e.g. in polyethylene glycol, polyvinyl pirrolidone, lecithin, peanut oil or sesame oil. As an alternative application, the solution may be lyophilized and re-dissolved in an adequate solvent just before administration.

The compositions applicable *via* the nasal route covered by the present inventions may contain the compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts in the form of aerosols, drops, gels and powders.

The aerosol compositions covered by the present invention may contain the compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts in the form of a sterile solution or fine suspension prepared using a pharmaceutically adequate aqueous or non-aqueous solvent. The sterile aerosol may be present in a container containing one dose or multiple doses, where the dosage or the refill is provided, and which is usually equipped with a vaporizer. As an alternative, the closed container may also be adequate for dosage of unit doses; such as the single-dose nasal inhalator or the aerosol-container equipped with a dosing valve, disposable when emptied. If the aerosol-container is equipped with a dosing valve, then it contains some form of carrier gas, e.g. compressed gas (e.g. compressed air) or organic carrier gas (chlorinated or fluorinated hydrocarbon). Dosage of the aerosol may also be administered by a vaporizer pump.

The compositions applicable *via* the buccal route covered by the present invention may contain the compounds possessing

the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts in the form of pills, lozenges, or pastille, where the active ingredient is formulated together with a carrier (e.g. sugar, gum arabic, gum tragacanth, gelatin, glycerol, etc).

The compositions covered by the present invention may also be administered *via* the rectal route. Such compositions are usually in the form of suppositories, which contain the active ingredient mixed in a suppositorial carrier material, e.g. cocoa butter (theobroma cacao) or other known carrier. The suppositories are produced in the usual manner by first mixing the components with the melted carrier, then molding the mixture using adequate mould forms.

In addition, the pharmaceutical compositions covered by the present invention is also applicable as transdermal preparation, e.g. in the form of ointment, gel or patch.

The administration routes mentioned above as examples are described in the art (literature) by themselves as well (c.f. e.g. Remington's Pharmaceutical Sciences, Edition 18th, Mack Publishing Co., Easton, USA (1990)).

The pharmaceutical compositions covered by the present invention are produced by i) mixing the active ingredient (containing the compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts) and the carrier material(s) and ii) formulating the produced mixture into the form of any already described pharmaceutical preparation. The methods to be applied for producing such pharmaceutical preparations are described in the

art (e.g. in the above mentioned handbook ([Remington's Pharmaceutical Sciences]).

In addition, the present invention also covers the application of one or more pharmaceutical compositions, containing the compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts in the form of any pharmaceutically applicable formulations in order to prevent and/or treat diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

In addition, the present invention also covers procedure(s) to prepare pharmaceutically applicable compositions containing the compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts to prevent and/or treat diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

In addition, the present invention also covers pharmaceutical protocols to prevent and/or treat diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria (such as tuberculotic diseases of the lung and other tissues) during which protocols patients suffering from such diseases are administered efficient, non-toxic doses of compounds possessing the general formula (I) and/or their pharmaceutically applicable organic and inorganic salts.

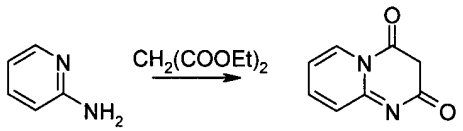
The compounds covered by the present inventions were identified by using high-throughput *in silico* (i.e. computer-driven and -modeled) docking screen on the whole surface of the dUTPase enzyme from Mycobacterium tuberculosis, which is essential for viability of the bacterium. The starting compound

database contained over one million small molecular compounds present and described in electronic catalogues of chemical companies. This compound database was docked on the surface of the *Mycobacterium tuberculosis* dUTPase protein using our computer cluster and the docking software Frigate, developed by us. Results were evaluated using mathematical optimization by the Frigate software to reveal fitting data of the compounds to the surface of the *Mycobacterium tuberculosis* dUTPase protein.

During *in silico* docking, the small molecular compounds were treated as flexible molecules and their locations in the three-dimensional space and their three-dimensional structures (considering all possible rotations along the rotatable chemical bonds) were optimized. The compounds characterized with the best binding profiles were further screened based on important pharmacological properties (e.g. log P).

Preparation of compounds possessing the general formula (I)

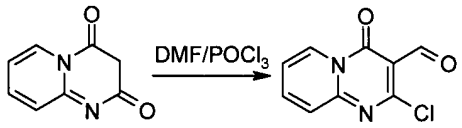
During preparation of compounds possessing the general formula (I) covered in the present invention, we used 2-aminopyridine as starting material, and reacted it in a condensation reaction with diethylmalonate as shown in reaction scheme 1.



Reaction scheme 1

The reaction was generalized for substituted derivatives of 2-aminopyridine as well.

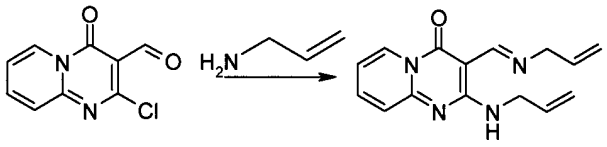
In the next step, the product of the condensation reaction, pyrido[1,2-a]pyrimidin-2,4-dione was formylated at position 3 *via* Vilsmeier-Haack reaction, and was also chlorinated at position 2 using phosphoryl chloride, as shown in reaction scheme 2. Using this procedure, we produced 2-chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde.



Reaction scheme 2

The reaction was generalized for pyrido[1,2-a]pyrimidin-2,4-dione compounds produced using substituted derivatives of 2-aminopyridine as well.

The compound 2-R-amino-3-R-iminomethylpyrido[1,2-a]pyrimidin-4-one can be generated by reacting 2-chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde in adequate polar solvent with primer amines as shown in reaction scheme 3. The produced hydrochloric acid may be neutralized using either excess amines or tertiary amines.



Reaction scheme 3

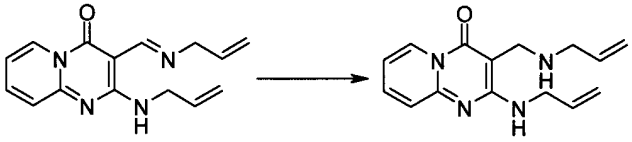
The reaction was generalized for

a) primary amines,

b) secondary amines, and

d) aromatic amines.

The 3-iminomethyl-group of the Schiff-base generated from primary amines may be reduced (using e.g. sodium borohydride) into aminomethyl-group (c.f. reaction scheme 4).



Reaction scheme 4

The Schiff-base, containing 3-iminomethyl-group, generated from primary (also aromatic) amines can be split into carbaldehyde using aqueous acid in alcoholic solvent (c.f. reaction scheme 5). In several cases, the carbaldehyde group can be hydrated to generate carbaldehyde-hydrate (geminal diol).

Generated compounds

Using the above described procedures and based on the examples below, the compounds possessing the general formula (I) covered in the present invention are summarized in Tables 1-7.

The compounds were characterized using thin layer chromatography (Merck TLC Silica gel 60 F_{254}) and NMR (11.7

Tesla Bruker Avance-500 (double channel) spectrometer, 300K, d6-DMSO solvent).

Table 1: Chloro-carbaldehydes

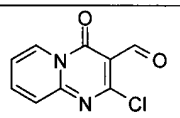
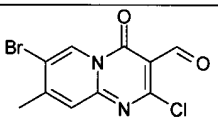
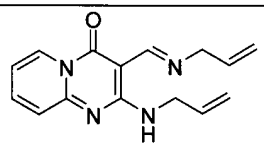
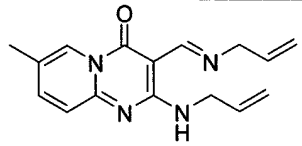
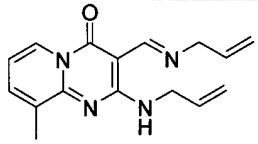
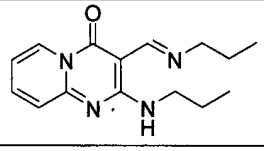
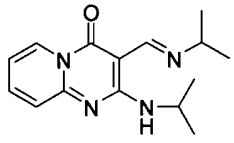
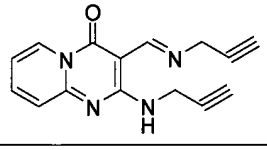
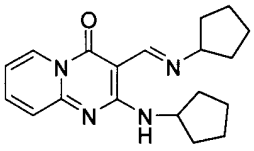
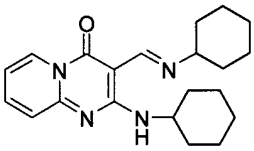
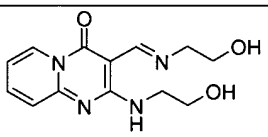
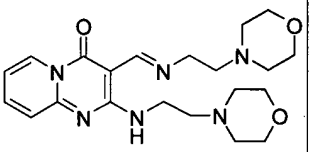
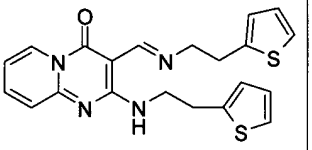
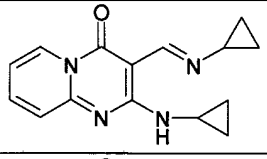
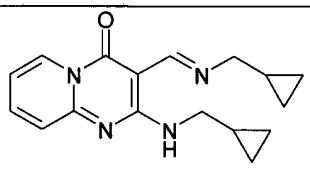
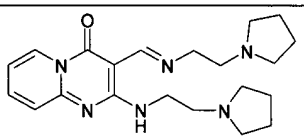
Code	name	Structure	TLC
TB 818	2-Chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,35
TB 856	7-Bromo-2-chloro-8-methyl-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : MeOH 4:1 Rf= 0,62

Table 2: Aliphatic Schiff-bases

Code	name	Structure	TLC
TB 801	2-Allylamino-3-allyliminomethyl-pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,45
TB 810	2-Allylamino-3-allyliminomethyl-7-methylpyrido[1,2-a]-pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,60
TB 811	2-Allylamino-3-allyliminomethyl-9-methylpyrido[1,2-a]-pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,60
TB 804	2-Propylamino-3-propyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,55
TB 805	2-Isopropylamino-3-isopropyliminomethyl pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,50
TB 806	2-Prop-2-ynylamino-3-prop-2-ynyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,50

Code	name	Structure	TLC
TB 807	2-Cyclopentylamino-3-cyclopentyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,60
TB 808	2-Cyclohexylamino-3-cyclohexyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,55
TB 809	2-(2-Hydroxyethyl)amino-3-(2-hydroxyethyl)imino-methylpyrido[1,2-a]-pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,30
TB 812	2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]iminomethyl-pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,30
TB 813	2-[2-(Thiophen-2-yl)-ethyl]amino-3-[2-(thiophen-2-yl)-ethyl]iminomethyl-pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,65
TB 814	2-Cyclopropylamino-3-cyclopropyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,50
TB 815	2-Cyclopropylmethylamino-3-cyclopropylmethyl-iminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,50
TB 817	2-[2-(Pyrrolidin-1-yl)ethyl]amino-3-[2-(pyrrolidin-1-yl)-ethyl]-iminomethyl-pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,2

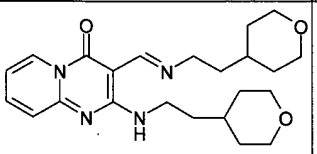
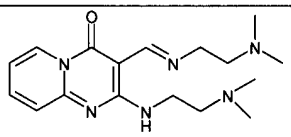
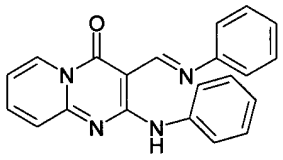
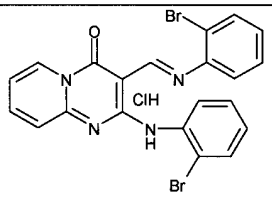
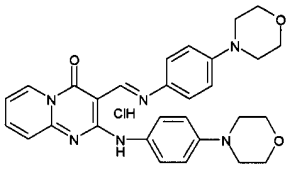
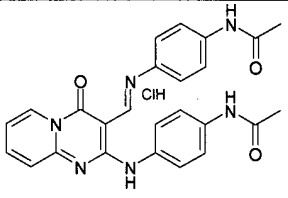
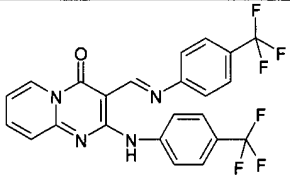
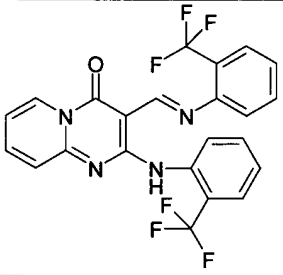
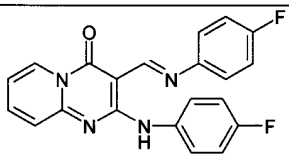
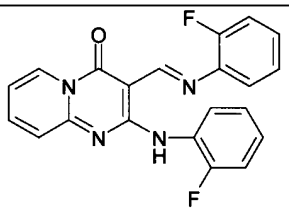
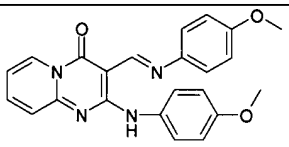
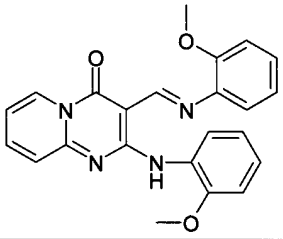
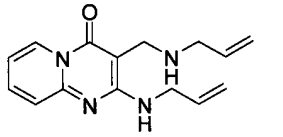
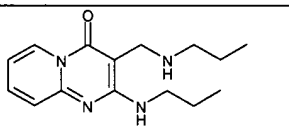
Code	name	Structure	TLC
TB 816	2-[2-(Tetrahydropyran-4-yl)ethylamino]-3-[2-(tetrahydropyran-4-yl)-ethyliminomethyl]pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,35
TB 859	2-(2-Dimethylaminoethylamino)-3-(2-dimethylaminoethyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one		MeOH : TEA 9:1 Rf= 0,50

Table 3: Aromatic Schiff-bases

Code	name	Structure	TLC
TB 827	2-Phenylamino-3-phenyliminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,6
TB 858	2-(2-bromophenylamino)-3-(2-bromophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one hydrochloride		T:MeOH 4:1 Rf= 0,80
TB 860	2-(4-Morpholin-4-yl-phenylamino)-3-(4-morpholin-4-yl-phenyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one hydrochloride		T:MeOH 4:1 Rf= 0,55
TB 863	2-(4-Acetylaminophenyl)amino-3-(4-acetylaminophenyl)-iminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride		T:MeOH 4:1 Rf= 0,75
TB 866	2-(4-Trifluoromethylphenylamino)-3-(4-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,44

Code	name	Structure	TLC
TB 867	2-(2-Trifluoromethylphenylamino)-3-(2-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,65
TB 871	2-(4-Fluorophenylamino)-3-(4-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,75
TB 872	2-(2-Fluorophenylamino)-3-(2-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,75
TB 868	2-(4-Methoxyphenylamino)-3-(4-methoxyphenylimino)-methylpirimido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,55
TB 869	2-(2-Methoxyphenylamino)-3-(2-methoxyphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one		Toluene : MeOH 4:1 Rf=0,59

Tabl2 4: Aliphatic amines

Code	name	Structure	TLC
TB 802	2-Allylamino-3-allylaminomethyl-pyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,15-0,3
TB 821	2-Propylamino-3-propyl-aminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,12

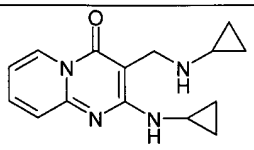
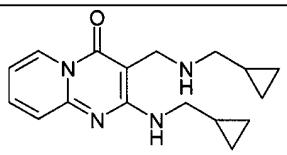
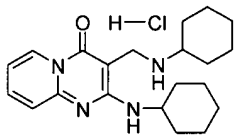
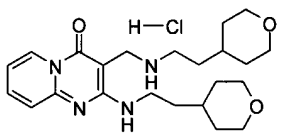
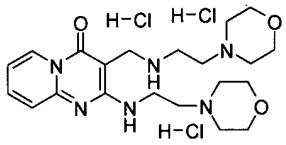
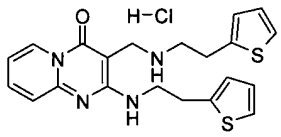
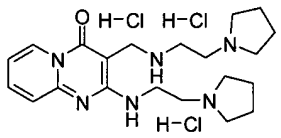
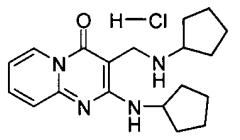
Code	name	Structure	TLC
TB 826	2-Cyclopropylamino-3-cyclopropylaminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,15
TB 829	2-Cyclopropylmethylamino-3-cyclopropylmethylaminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,15
TB 831	2-Cyclohexylamino-3-cyclohexylaminomethylpyrido[1,2-a]pyrimidin-4-one x 1HCl		Toluene : methanol 4:1 Rf= 0,25
TB 832	2-[2-(Tetrahydropyran-4-yl)-ethyl]-amino-3-[2-(tetrahydropyran-4-yl)-ethyl]-aminomethyl-pyrido[1,2-a]pyrimidin-4-one x 1HCl		Toluene : methanol 4:1 Rf= 0,2
TB 833	2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one x 3HCl		Toluene : methanol 4:1 + 1 csepp NH_3 Rf= 0,65
TB 834	2-[2-(Thiophen-2-yl)-ethyl]-amino-3-[2-(thiophen-2-yl)-ethyl]-aminomethyl-pyrido[1,2-a]pyrimidin-4-one x 1HCl		Toluene : methanol 4:1 Rf= 0,35
TB 835	2-[2-(Pyrrolidin-1-yl)-ethyl]-amino-3-[2-(pyrrolidin-1-yl)-ethyl]-aminomethyl-pyrido[1,2-a]pyrimidin-4-one x 3HCl		Toluene : methanol 4:1 Rf= 0,2-0,4
TB 838	2-Cyclopentylamino-3-cyclopentylaminomethylpyrido[1,2-a]pyrimidin-4-one x HCl		Toluene : methanol 4:1 Rf= 0,15

Table 5: Aromatic amines

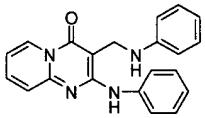
TB 836	2-phenylamino-3-phenylaminomethylpyrido[1,2-a]pyrimidin-4-one		Toluene : methanol 4:1 Rf= 0,5

Table 6: Secondary amine derivatives

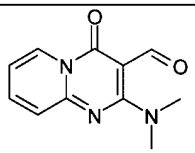
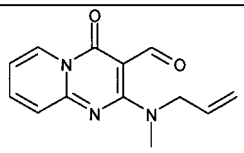
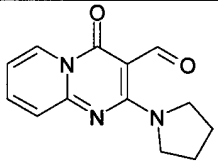
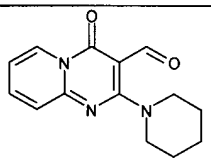
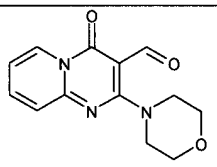
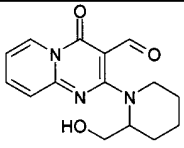
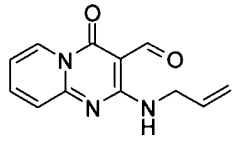
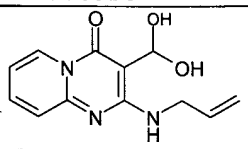
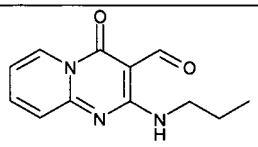
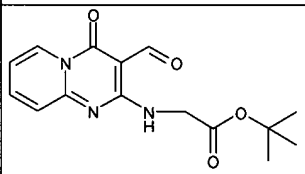
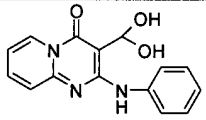
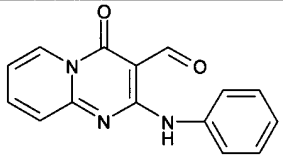
Code	name	Structure	TLC
TB 828	2-Dimethylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,3
TB 852	2-(Allylmethylamino)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		T:MeOH 4:1 Rf= 0,50
TB 820	4-Oxo-2-(pyrrolidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : MeOH 4:1 Rf=0.38
TB 822	4-Oxo-2-(piperidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,35
TB 823	2-(Morpholin-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,35
TB 840	2-(2-Hydroxymethyl-piperidin-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Hexane : EtOAc 1:1 Rf=0,22

Table 7: Amino-carbaldehydes

Code	name	Structure	TLC
TB 803	2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,55

Code	name	Structure	TLC
TB 876	2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde-hydrate		Toluene : MeOH 4:1 Rf=0,32
TB 825	4-Oxo-2-propylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : methanol 4:1 Rf= 0,3
TB 830	2-tertbutoxycarbonylmethylamino-4-oxopyrido[1,2-a]-pyrimidine-3-carbaldehyde,		Toluene : methanol 4:1 Rf= 0,40
TB 837	4-Oxo-2-phenylaminopyrido[1,2-a]pyrimidine-3-carbaldehyde hydrate		Toluene : methanol 4:1 Rf= 0,25
TB 874	4-Oxo-2-phenylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde		Toluene : MeOH 4:1 Rf=0,28

In all cases where the names and the structures of any compound presented in the tables above disagree, the structure (structural formula) has to be considered to be authoritative.

The invention will be specifically illustrated using the examples below, however, the invention is not limited to the examples below.

EXAMPLES

Example 1: Production of 2-chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde (TB 818)

To 321 ml (3.45 mol) phosphoroxychloride, 55.4 ml (0.71 mol) dimethylformamide is added at a temperature between -5 - 0 °C.

The reaction mixture is stirred for 10 min, then 80.0 g (0.49 mol) pyrido[1,2-a]pyrimidin-2,4-dione is added, in several doses, while the temperature is kept 5 °C. The reaction mixture is allowed to warm to room temperature, and is then stirred for 3 hours at 100 °C. The excess of phosphoroxychloride is removed by vacuum distillation. To the distillation residue, 400 ml dichlorometane is added and the mixture is poured onto 1000 g ice. The pH of the mixture is set to pH=7 by addition of solid sodium hydroxide. The separated yellow precipitate is filtered and washed with 2x200 ml water and 2x100 ml dichloromethane, dried at 40 °C in vacuum. Yield: 92.7 g (0.44 mol, 91 %); yellow, solid

TLC: Rf=0,35 (toluene:methanol 4:1).

^{1}H-NMR: 10,24 (1H, s), 9,16 (1H, d), 8,35 (1H, t), 7,86 (1H, d), 7,67 (1H, t)

Example 2: Production of 2-allylamino-3-allyliminomethylpyrido[1,2-a]pyrimidin-4-one (TB 801)

25.03 g (120 mmol) 2-chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde is dissolved in 300 ml dichloromethane, and 36 ml (480 mmol) allylamine is added drop by drop during 5 min at room temperature. The reaction mixture is stirred for 3 hours at room temperature. When the reaction is completed, the reaction mixture is washed with 300 ml saturated aqueous solution of Na_2CO_3; the aqueous phase is extracted with 2x50 ml dichloromethane; the combined organic phase is dried on anhydrous Na_2SO_4; and is evaporated down in vacuum. The produced approx. 35 g solidifying yellow oil is recrystallized from iso-propanol. Yield: 24.8 g (92 mmol, 77 %); yellow solid product. TLC: Rf=0,45 (toluene:methanol 4:1).

^{1}H-NMR: 10,73 (1H, t), 8,8 (1H+1H, s+d), 7,86 (1H, t), 7,32 (1H, d), 7,70 (1H, t), 5,98 (2H, m), 5,35-5,15 (4H, m), 4,20 (4H, m).

Example 3: Production of 2-allylamino-3-allylaminomethylpyrido[1,2-a]pyrimidin-4-one (TB 802)

1.50 g (5.6 mmol) 2-allylamino-3-allyliminomethylpyrido[1,2-a]pyrimidin-4-one is dissolved in 50 ml methanol, then 0.26 g (6.7 mmol) sodium borohydride is added to the reaction mixture at room temperature. When the reaction is completed, 15 ml 15 ml 2M hydrochloride acid is added, then the pH is set at pH=12 by addition of 10 % sodium hydroxide (aqueous solution). The aqueous phase is extracted with 2x30 ml dichloromethane, the combined organic phase is dried on anhydrous Na_2SO_4, and is evaporated down in vacuum.

Yield: 0.73 g (2.7 mmol, 48 %), yellow solid product. TLC: 4:1 Rf=0,15-0,3 (toluene : methanol).

^{1}H-NMR: 8,78 (1H, d), 7,90 (1H, s), 7,73 (1H, t), 7,30 (1H, d), 7,05 (1H, t), 5,89 (2 H, m), 5,25-5,05 (4H, m), 4,11 (2H, m), 3,77 (2H, m), 3,13 (2H, m), 2,18 (1H, m).

Example 4: Production of 2-allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde (TB 803)

4,0 g (15 mmol) 2-allylamino-3-allyliminomethylpyrido[1,2-a]pyrimidin-4-one is to be dissolved in 80 ml ethanol, then 5 ml 1:1 hydrochloric acid is added to the mixture. The reaction mixture is refluxed for 6 hours, and cooled to room temperature. The precipitate is filtered, washed with ethanol and dried at 40 °C in vacuum.

Yield: 1.33 g (5.8 mmol, (39 %), pale yellow solid product. An additional amount of 0.78 g (3.4 mmol, 23 %) of the product was precipitated from the mother liquor stored in the refrigerator.
TLC: Rf= 0,55 (toluene : methanol 4:1).
^{1}H-NMR: 10,07 (1H, s), 9,58 (1H, m), 8,78 (1H, d), 7,95 (1H, t), 7,30 (1H, d), 7,14 (1H, t), 5,96 (1H, m), 5,16 (2H, m), 4,20 (2H, t).

Example 5: Production of 2-allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde-hydrate (TB 876)

In several cases, the carbaldehyde group may be hydrated into carbaldehyde hydrate (geminal diol). In another experiment, the product was gained as 2-allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde hydrate (Yield: 55 %, solid yellow product).
TLC: Rf= 0,32 (toluene : methanol 4:1).
^{1}H-NMR: 8,89 (1H, d), between 8,08-6,5, a total of 7 H, sharp peaks 8,08, 7,63, 7,32, wide peaks 7,85, 7,0, 5,86 (1H, m), 5,40 (1H, s), 5,27 (1H, d), 5,16 (1H, d), 3,97 (2H, m).

The biological effects of the compounds covered by the present invention were investigated as follows.

Example 6: Enzyme inhibition

The protein enzymes *Mycobacterium tuberculosis* dUTPase and *Homo sapiens* dUTPase were expressed in *E. coli* expression system and were purified to homogeneity as described previously (*Varga et al. Biochem Biophys Res Commun. 2008 373:p. 8-13.; Varga et al. FEBS Lett. 2007 581: p. 4783-8.*). To investigate

the effects of several compounds, we carried out enzyme assay measurements. The potential dUTPase inhibitory effects of the compounds were investigated using the malachite green assay (*McQuade, T. J. et al., Anal Biochem. 2009 386: p. 244-50.*). The phosphate produced *via* the coupled reaction binds to malachite green and changes its colour. The colour change is detected spectrophotometrically, thus we directly measure the concentration of the produced phosphate, thereby indirectly measuring the velocity of the enzymatic reaction and the extent of the inhibition.

In parallel to the measurements with the *Mycobacterium tuberculosis* dUTPase enzyme, we also carried out similar investigations with the human dUTPase enzyme, as well. Using those methods, we determine the lowest inhibitor concentration where dUTPase inhibition is still observable. In all experiments, the concentration of the enzyme was 50 nM.

We carried out measurements with selected compounds and with two of these compounds, we have observed significant inhibition. In the case of these compounds, we determined the minimal inhibitory concentrations for *Mycobacterium tuberculosis* dUTPase. None of these compounds inhibited the human dUTPase enzyme.

Table 8 summarizes the results.

Table 8

Code of the compound	Minimal inhibitory concentration (mM)
TB 807	1.23
TB 808	1.13

Example 7: Investigation of binding of the compounds to *Mycobacterium tuberculosis* dUTPase by X-ray crystallography

Crystallization:

Crystallization of *Mycobacterium tuberculosis* dUTPase was carried out by co-crystallization in the presence of several compounds. We applied several alterations in the method described in the literature (*Varga et al. Biochem Biophys Res Commun. 2008 373:p. 8-13.*). Hanging-drop vapour diffusion method was applied and the complex of the enzyme and the compound was crystallized in the mixture of 50 mM Tris-HCl buffer, also containing 1.25-1.7 M ammonium-sulphate and 12 % glycerol, at pH=7.5. The compounds TB 807 or TB 808 were present at 2.5 mM concentration in the complex. After 2-4 weeks, several protein crystals appeared.

Under these conditions, *Mycobacterium tuberculosis* dUTPase protein does not form crystals in the absence of bound ligands. Thus, the appearance of protein crystals in the presence of the compounds indicated that crystallization was facilitated by the binding of the compounds TB 807 or TB 808. This also indicates

that the compounds TB 807 or TB 808 are present as bound to the protein in the crystals.

X-ray crystallographic data collection was performed on a Rigaku R-AXIS RAPID diffractometer (*Mycobacterium tuberculosis* dUTPase together with compound TB 807, full data set was collected, resolution 2.5 Å, space group: $P6_3$) and also on synchrotron (ESRF Grenoble, beamline 14-4, *Mycobacterium tuberculosis* dUTPase together with compound TB 807, full data set was collected, resolution: 2 Å or 1,6 Å, space group: $P6_3$).

Structure determination

The XDS program and molecular replacement was used for data analysis and solving the phase problem. The very high resolution structure of a point mutant of *Mycobacterium tuberculosis* dUTPase was used as the model (PDB ID: 3HZA). Refinement was carried out using the Refmac software from the CCP4 software package. Model building was performed using Coot.

The determined structure indicated that the compound TB 807 binds to the *Mycobacterium tuberculosis* dUTPase at a binding site that provides explanation for the enzyme inhibitory and the biological effect.

Example 8: Bacteriologic evaluations of the TB8 derivatives: determination of the minimal inhibitory concentration (MIC) and the colony forming units (CFU) in *M. tuberculosis* and *M. kansasii* cultures

Using 4 week old fresh M. tuberculosis H37Rv (ATCC 27294) and Mycobacterium kansasii (ATCC 35775) cultures, 0.5 Mcfarland (1.5×10^8 CFU/ml) (McFarland, J. Nephelometer J. Amer Med Ass, 1907. 14: p. 1176-1178.) suspensions were prepared in Sauton medium. The bacterial suspensions were diluted 10^3 and 10^4 times. The compounds to be tested were dissolved in DMSO, and after sterile filtration, these were diluted with DMSO to produce ten distinct concentrations in the 0.05 - 100 µg/ml range. The solutions were added to test tubes containing 5 ml Sula liquid medium (pH=6,5) (Sula, L. Bull World Health Organ, 1963. 29(5): p. 589-606; Sula, L. Bull World Health Organ, 1963. 29(5): p. 607-625). The test tubes were then infected with diluted bacterium suspensions (100 µl) and these were incubated for 28 days in 37 °C. After the 28 days incubation period, the minimal inhibitory concentration (MIC) were determined, i.e., the minimal compound concentration that prevents bacterial growth to turn the Sula media turbid was identified by visual inspection. Aliquots from the test tubes potentially containing still surviving bacteria were used to inoculate solid Lövenstein-Jensen medium (Löwenstein, E. Bakteriol Parasitenkd infektionskr hyg Abt I orig, 1931. 120: p. 127; Jensen, K. Bakteriol Parasitenkd infektionskr hyg Agt I Orig, 1932. 125: p. 222), and following an incubation period of 4-6 weeks, the colonies were counted; this way we identified the CFU value (colony forming units). The CFU value, multiplied by the dilution concentration, was compared to the initial bacterium number from the 0.5 McFarland suspension (1.5×10^8 CFU/ml). The MIC and CFU values were determined in at least two independent experiments in each case.

The experiments were conducted in the Bacteriologic Reference Laboratory of Corden International Hungary Ltd. on the campus of the Koranyi Tuberculosis and Pulmonology Institute, Budapest.

The results are given in Tables 9, 10 and 11.

Table 9: MIC values of the TB8 derivatives in *M. tuberculosis*

TB code	*M. tuberculosis* H37Rv MIC (µg/ml)	MIC (µM)
TB 801	1	3.7
TB 802	61	225.6
TB 803	1	4.4
TB 804	2	7.3
TB 805	2	7.3
TB 806	1	3.8
TB 807	2	6.2
TB 808	2	5.7
TB 809	4	14.5
TB 810	22	77.9
TB 811	4	14.2
TB 812	>88	>212.3
TB 813	9	22.0
TB 814	1	3.7
TB 815	4	13.5
TB 816	9	21.8
TB 817	>100	>261.4
TB 818	10	47.9
TB 819	>100	>474.8
TB 820	5	2.1
TB 821	>100	>364.5
TB 822	100	388.7
TB 823	1	3.9
TB 825	40	173.0
TB 826	100	369.9
TB 827	0.05	0.1
TB 828	1	4.6

TB 829	80	268.1
TB 830	60	197.8
TB 831	60	153.5
TB 832	>100	>221.7
TB 833	>100	>190.1
TB 834	40	89.5
TB 836	0.05	0.1
TB 837	5	17.6
TB 838	80	220.4
TB 839	100	325.9
TB 840	40	139.2
TB 842	>100	>494.5
TB 844	80	330.2
TB 852	0.25	1.0
TB 853	60	298.2
TB 854	>100	>554.0
TB 855	>100	>444.3
TB 856	20	66.3
TB 857	>100	>354
TB 858	1	1.9
TB 859	>100	>303
TB 860	10	18.3
TB 861	20	93.2
TB 862	20	38.7
TB 863	0.5	1.0
TB 863	0.5	1.0
TB 864	> 100	>308.3
TB 865	> 100	>323.3
TB 867	> 100	>209.9
TB 868	0.25	0.6
TB 869	0.5	1.2
TB 870	40	149.1

Table 10: MIC values of the TB8 derivatives in *M. kansasii:*

TB code	*M. kansasii* MIC (µg/ml)	MIC (µM)
TB 801	>100	>373
TB 804	>100	>367
TB 805	>100	>367
TB 806	>100	>378
TB 807	60	184.9
TB 817	>100	>261

TB 818	40	191.7
TB 819	>100	>475
TB 820	0.5	2.1
TB 822	>100	>389
TB 823	>100	>386
TB 825	>100	>432
TB 826	>100	>370
TB 827	40	117.5
TB 828	>100	>460
TB 829	>100	>335
TB 830	>100	>330
TB 831	60	153.5
TB 834	40	89.5
TB 838	>100	>276
TB 839	>100	>326
TB 852	>100	>411
TB 853	>100	496.9

Compounds characterized with low MIC values on the *M. tuberculosis* bacterium were also tested on multidrug-resistant bacterium strain (INH, RIF MDR A8 M. tuberculosis). The MIC and CFU values were determined as we described above.

Table 11: MIC values of some TB8 derivatives on multidrug-resistant M. tuberculosis culture

TB code	**MIC (mg/ml) INH. RIF resistant MDR A8 *M. tuberculosis***
TB 807	**5**
TB 808	**5**
TB 813	**2**
TB 820	**5**
TB 823	**5**
TB 827	**<0.5**
TB 831	**60**
TB 836	**<0.5**
TB 864	**80**

Example 9: In vitro cytotoxicity: Examination of cytotoxicity and cytostaticity using colometric tetrazolium test (MTT)

The cytotoxicity of the TB8 derivatives were examined in HepG2 (human hepatoma), MonoMac6 (human monocyte) cell lines, on human PBMC (human peripheral blood monomorphonuclear) cells, and on mouse bone marrow macrophage cells. The cytostatic effects were examined on HepG2, MonoMac6, and PBMC cell lines.

In both types of trials, cell viability were determined by MTT (3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyl tetrazolium bromide) test (*Gerlier, D. J Immunol Methods, 1986. 94(1-2): p. 57-63; Mosmann, T. J Immunol Methods, 1983. 65(1-2): p. 55-63; Slater et al., T. F. Biochim Biophys Acta, 1963. 77: p. 383-93*).

In the case of HepG2 and MonoMac6 cell lines, aliquots from logarithmically dividing cell population were distributed on 96-well tissue-growth plate in 100 µl RPMI-1640 total medium (5×10^3 cell/well). In the case of the isolated human PBMC and the differentiated mouse bone marrow macrophage cells, on the day of the experiment we distributed the cells on the tissue-growth plate; 10^4 cells/well for mouse macrophage and 5×10^4 cells/well for human PBMC, both in serum-free RPMI-1640 medium.

After discarding 50 µl medium, we dissolved the compound to be tested in 150 µl serum-free medium, and after sterile-filtration, it was added to the cells in 4-8 parallel experiments. In the cytotoxicity test, the cells were incubated at 37 °C for three hours, and then the compounds were washed

out from the cells. In the cytostaticity test, the cells were incubated at 37 °C for three days in 5% CO_2 atmosphere.

After the incubation period in both trials, 45 µl MTT solution were added to each wells (c = 2 mg/ml, solved in serum-free medium). Following 3.5 hours of incubation, the tissue culture plate was centrifuged at 2000 rpm for 5 minutes, and the supernatant was carefully aspirated with a G30 needle, then it was discarded. The precipitated purple crystals were solved in 100 µl DMSO, and after 10 minutes agitation, the absorbance were determined at λ = 540 nm and 620 nm using ELISA plate reader spectrometer. The differences in the absorbance values measured at the two wavelengths were averaged (A). The cytotoxicity and the cytostatic effects were computed with the following formula:

$$100 \cdot \left(1 - \frac{A_{\text{treated\_cells}}}{A_{\text{untreated\_cells}}}\right)$$

where A means the difference in the absorbance averaged in the 4-8 parallel experiments.

The measure of the cytotoxicity in percentage as the function of concentration was represented graphically, and by interpolation we gave the IC_{50} values in Table 12.

Table 12: Comparison of the MIC and IC_{50} values for some members of the TB8 family

Compound/ TB code	MIC (mol/dm^3)	IC_{50} (mol/dm^3)
TB 801	3.73×10^{-6}	1.21×10^{-2}
TB 827	1.47×10^{-7}	$>1.88\times10^{-4}$

TB 836	1.47×10^{-7}	$>2.10\times10^{-4}$
TB 852	2.00×10^{-6}	$>1.64\times10^{-4}$
TB 847	5.67×10^{-6}	1.81×10^{-4}

Example 10: Examination of the interaction of drug compounds with lipid layers

Potential penetration of the drug molecules into the cell membrane of macrophages was evaluated by two methods: i) the preparation of lipid mixed films and ii) penetration tests. The lipid mixed film consists of the mixture of the lipid and the drug compound in 5 to 1 molar ratio. In the examination of the penetration of the drug compound into the lipid film, the concentration of the compound was 2×10^{-6} M.

In the first method, addition of the compound TB801 to the lipid did not result in any difference as compared to the drug-free lipid.

In the second method, penetration of drug into the lipid layer was detected by the change of surface pressure. As a first step, pure lipid monolayer was formed and following one compression/expansion cycle, the layer was compressed to a given value of surface pressure (15 and 20 mN/m). After this step, the compound was injected below the lipid layer and interaction between the compound and the lipd layer was evaluated based on eventual changes of surface pressure.

The solubility and the amphiphilicity of the TB 801 compound was also determined by measuring the octanol/water

ratio *log* P_{app} , and by measuring the surface tension of aqueous solutions containing the compound TB 801 (Table 12). The static surface tension was changed only in the 40 times more concentrated solution, than was used in the penetration study.

Table 12: Penetration data for the compound TB 801

Compound	M	charge	A_m (A^2)	*log* P_{app}	$\breve{a}_{stat}$ (mN/m)
TB 801	268.0	-	157.7	0.61 ±0.05	71.6 ±0.4

Legend:

M: relative molecular mass

A_m: molecular space requirement (from the mixed film isotherm)

log P_{app}: the octanol/water quotient

$\breve{a}_{stat}$: static surface tension (mN/m) in $8x10^{-5}$ M aquaeous solution.

Example 11: Production of pharmaceutical preparations

a) Pills:

The following materials are mixed: 0.01-50% drug compound possessing the general formula (I), 15-50% lactose, 15-50% potato starch, 5-15% polyvinyl-pyrrolidone, 1-5% talcum, 0.01-3% magnesium-stearate, 1-3% colloidal silicon-dioxide, and 2-7% ultraamylopectin. The mixture is granulated by the wet granulation method and compressed into tablets.

b) Dragees and film tablets:

The pills produced as described above are coated with entero- or gastrosolvent film coating, or with sugar-containing coating and talcum. Dragees are coated with a mixture of bee wax and carnauba wax.

c) Capsules:

The following materials are mixed thoroughly: 0.01-50% drug compound possessing the general formula (I), 1-5% sodium-lauryl-sulphate, 15-50% starch, 15-50% lactose, 1-3% colloidal silicon-dioxide, and 0.01-3% magnesium-stearate. The mixture is pressed through a filter and is loaded into capsules.

d) Suspensions:

Components: 0.01-15% drug compound possessing the general formula (I), 0.1-2% sodium-hydroxide, 0.1-3% citric acid, 0.05-0.2% nipagin (sodium methyl 4-hydroxy-benzoate), 0.005-0.02% nipasol, 0.01-0.5% carbopol (polyacrylic acid), 0.1-5% 96% ethanol, 0.1-1% flavouring material, 20-70% sorbitol (70 % aqueous solution) and 30-50% distilled water.

Carbopol in small doses is added to an aqueous solution of nipagin and citric acid with extensive stirring of the mixture. The resulting solution is left to stand for 10-12 hours. Then, sodium hydroxide (dissolved in 1 ml distilled water), the aqueous solution of sorbitol and finally the ethanol solution of raspberry-flavor is added during strong stirring. To the such prepared carrier material, the drug compound is added in small doses and is homogenized using immersion homogenizer. Finally the suspension is filled up to the final volume and the suspension syrup is produced in its final form using a colloid mill.

e) Suppositories:

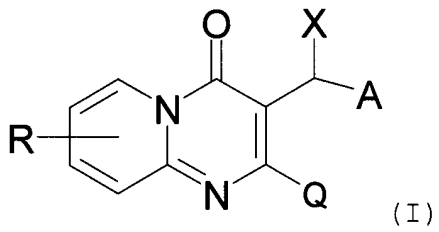
0.01-15% drug compound possessing the general formula (I), and 1-20% lactose is mixed thoroughly, then this mixture is added to a fat preparation (final concentration of the fat in the suppositories will be 50-95%), suitable for production of suppositories (e.g. Witepsol 4), melted and cooled down to 35 °C. The mixture such prepared is homogenized and is filled into cooled forms.

f) Lyophilized powder ampoule preparations:

Using bi-distilled water, adequate for injection, a 5 % aqueous solution of mannitol or lactose is prepared and sterile filtered. Using the same method, a 0.01-5% sterile solution of the drug compound possessing the general formula (I). The two solutions are mixed under aseptic circumstances and 1 ml aliquots are filled into ampoules. The ampoule content is lyophilized and the ampoules are closed under nitrogen atmosphere. The content of the ampoules is dissolved right before use in sterile water or sterile physiological salt solution (0.9% sodium chloride).

Claims

1. Compounds possessing the general formula (I)



(I)

where

R stands for hydrogen atom, halogen atom, nitrile group, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its substituted derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxy carbonyl group, heterocyclic oxycarbonyl group and its substituted derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its substituted derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its substituted derivatives, amine group, alkylamine group, cycloalkyl amine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its substituted derivatives;

X stands for hydrogen atom(s), oxo group or hidroxyl group;

A stands for oxo group, hydroxyl group, OR′, NR′ or NHR′, where R′ stands for hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, heterocyclic group and its substituted derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryloxycarbonyl group, heterocyclic oxycarbonyl group and its substituted derivatives, alkyl carboxamide group, cycloalkyl carboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, aryl carboxamide group, heterocyclic carboxamide group and its substituted derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its substituted derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its substituted derivatives;

Q stands for halogen atom, or NR′′R′′′, where R′′ and R′′′ stands for hydrogen atom, alkyl group, cycloalkyl group, alkenyl group, alkynyl group, aryl group, or heterocyclic group and its substituted derivatives, alkoxy carbonyl group, cycloalkoxy carbonyl group, alkenyl oxycarbonyl group, alkynyl oxycarbonyl group, aryl oxycarbonyl group, heterocyclic oxycarbonyl group and its substituted derivatives, alkylcarboxamide group, cycloalkylcarboxamide group, alkenyl carboxamide group, alkynyl carboxamide group, arylcarboxamide group, heterocyclic carboxamide group and its substituted derivatives, hydroxyl group, alkoxy carbonyl group, cycloalkoxy carbonyl group,

alkenyloxy group, alkynyloxy group, aryloxy group, heterocyclic oxy group and its substituted derivatives, amine group, alkylamine group, cycloalkylamine group, alkenyl amine group, alkynyl amine group, arylamine group, heterocyclic amine group and its derivatives, or in given cases R'' and R''' constitutes unsubstituted or substituted aromatic or unsubstituted or substituted heteroaromatic ring or cycloalkyl or heterocyclic group;

and pharmaceutically applicable organic or inorganic salts of compounds possessing the general formula (I).

2. Compounds possessing the general formula (I) selected from

2-Chloro-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,

7-Bromo-2-chloro-8-methyl-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,

2-Allylamino-3-allyliminomethyl-pyrido[1,2-a]pyrimidin-4-one,

2-Allylamino-3-allyliminomethyl-7-methylpyrido[1,2-a]pyrimidin-4-one,

2-Allylamino-3-allyliminomethyl-9-methylpyrido[1,2-a]pyrimidin-4-one,

2-Propylamino-3-propyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Isopropylamino-3-isopropyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Prop-2-ynylamino-3-prop-2-ynyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclopentylamino-3-cyclopentyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-Cyclohexylamino-3-cyclohexyliminomethylpyrido[1,2-a]pyrimidin-4-one,

2-(2-Hydroxyethyl)amino-3-(2-hydroxyethyl)iminomethyl-pyrido[1,2-a]pyrimidin-4-one,
2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]-iminomethyl-pyrido[1,2-a]pyrimidin-4-one,
2-[2-(Thiophen-2-yl)-ethyl]amino-3-[2-(thiophen-2-yl)-ethyl]iminomethyl-pyrido[1,2-a]pyrimidin-4-one,
2-Cyclopropylamino-3-cyclopropyliminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclopropylmethylamino-3-cyclopropylmethyl-iminomethylpyrido[1,2-a]pyrimidin-4-one,
2-[2-(Pyrrolidin-1-yl)ethyl]amino-3-[2-(pyrrolidin-1-yl)ethyl]-iminomethylpyrido[1,2-a]pyrimidin-4-one,
2-[2-(Tetrahydropyran-4-yl)ethylamino]-3-[2-(tetrahydropyran-4-yl)ethyliminomethyl]pyrido[1,2-a]pyrimidin-4-one,
2-(2-Dimethylaminoethylamino)-3-(2-dimethylaminoethyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one,
2-Phenylamino-3-phenyliminomethylpyrido[1,2-a]pyrimidin-4-one,
2-(2-Bromophenylamino)-3-(2-bromophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Morpholin-4-yl-phenylamino)-3-(4-morpholin-4-yl-phenyliminomethyl)-pyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Acetylaminophenyl)amino-3-(4-acetylaminophenyl)-iminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-(4-Trifluoromethylphenylamino)-3-(4-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(2-Trifluoromethylphenylamino)-3-(2-trifluoromethylphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(4-Fluorophenylamino)-3-(4-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,

2-(2-Fluorophenylamino)-3-(2-fluorophenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-(4-Methoxyphenylamino)-3-(4-methoxyphenylimino)-methylpirimido[1,2-a]pyrimidin-4-one,
2-(2-Methoxyphenylamino)-3-(2-methoxyphenylimino)-methylpyrido[1,2-a]pyrimidin-4-one,
2-Allylamino-3-allylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Propylamino-3-propylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclopropylamino-3-cyclopropylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclopropylmethylamino-3-cyclopropylmethylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Cyclohexylamino-3-cyclohexylaminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Tetrahydropyran-4-yl)-ethyl]-amino-3-[2-(tetrahydropyran-4-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Morpholin-4-yl)-ethyl]amino-3-[2-(morpholin-4-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one trihydrochloride,
2-[2-(Thiophen-2-yl)-ethyl]-amino-3-[2-(thiophen-2-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-[2-(Pyrrolidin-1-yl)-ethyl]-amino-3-[2-(pyrrolidin-1-yl)-ethyl]-aminomethylpyrido[1,2-a]pyrimidin-4-one trihydrochloride,
2-Cyclopentylamino-3-cyclopentylaminomethylpyrido[1,2-a]pyrimidin-4-one hydrochloride,
2-phenylamino-3-phenylaminomethylpyrido[1,2-a]pyrimidin-4-one,
2-Dimethylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(Allylmethylamino)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,

4-Oxo-2-(pyrrolidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
4-Oxo-2-(piperidin-1-yl)-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(Morpholin-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-(2-Hydroxymethylpiperidin-1-yl)-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-Allylamino-4-oxopyrido[1,2-a]pyrimidine-3-carbaldehyde-hydrate,
4-Oxo-2-propylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
2-tertiary butoxycarbonylmethylamino-4-oxopyrido[1,2-a]-pyrimidine-3-carbaldehyde,
4-Oxo-2-phenylaminopyrido[1,2-a]pyrimidine-3-carbaldehyde hydrate,
4-Oxo-2-phenylamino-pyrido[1,2-a]pyrimidine-3-carbaldehyde,
and the pharmaceutically applicable organic or inorganic salts of these compounds.

3. Use of the compounds according to Claim 1 possessing the general formula (I) and their pharmaceutically applicable organic or inorganic salts for preventing and/or treatment of diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

4. Pharmaceutical preparation **characterized by that** it contains as active ingredient one or more compounds of the general formula (I) and/or their pharmaceutically applicable organic or inorganic salts according to Claims 1 or 2, in

therapeutically effective amounts, in addition to one or more pharmaceutically applicable diluent, excipient and/or inert carrier.

5. Use of pharmaceutical preparation according to Claim 4 for preventing and/or treatment of diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

6. Process for manufacture of a pharmaceutical preparation to prevent and/or treat diseases caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria **characterized in that** it contains as active ingredient one or more compounds according to Claims 1 or 2, possessing the general formula (I) and/or their pharmaceutically applicable organic or inorganic salts.

7. Pharmaceutical treatment protocol **characterized in** administration of a non-toxic dose of one or more compounds according to Claims 1 or 2, possessing the general formula (I) and/or their pharmaceutically applicable salts to patients suffering from disease caused by the bacterium *Mycobacterium tuberculosis* or any other Mycobacteria.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 2011/000009

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04 *(2006.01)*
A61K 31/519 *(2006.01)*
A61K 31/5377 *(2006.01)*
A61P 31/06 *(2006.01)*

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 471/04, A61K 31/519, 31/5377, A61P 31/06

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN, RUPAT, EAPO, Esp@cenet, PAJ, USPTO, CIPO, DEPATIS, PCT Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/003533 A2 (INSTITUT PASTEUR KOREA) 14.01.2010, claims 1-14, compounds on pp. 71-98, p. 85, compound H4, p. 205, table 1 (2-nd compound), p. 302-303 & compounds with RN 300377-09-7P, 302936-53-4P, 1204419-55-5P, 1204419-62-4P retrived from STN	1-7
X	WO 2002/087589 A1 (DAIICHI SEIYAKU et al.) 07.11.2002, compounds with RN 475057-74-0P, 475058-12-9P retrived from STN & EP 1389463 A1, p. 10, p. 24, lines 47, p. 33, lines 2, 15, 47, claim 1	1-7
X	US 2007/0027164 A1 (BRENT R. STOCKWELL et al.) 01.02.2007, fig. 19, compound 180-42	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is nit considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2011 (13.05.2011)	02 June 2011 (02.06.2011)

Name and mailing address of the ISA/RU FGU FIPS	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 2011/000009

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HORVATH, Agnes et al. "Nitrogen bridgehead compounds. Part 65. Vilsmeier-Haack formylation of 4H-pyrido [1, 2-a] pyrimidin-4-ones. Part 6". Journal of Heterocyclic Chemistry, 1986, 23 (5), 1295-8 (abstract) [online] Retrived from STN, CA:107:58966, compounds with RN 109274-76-2P, 17481-62-8P, 33345-96-9P, 109274-78-4P, 109274-80-8P, 109274-81-9P, 109274-82-0P	1, 2
X	SUN, BIN et al. "Intramolecular 1, 3-polar cycloaddition at the periphery of heterocyclic systems. Part 4. A facile cyclopropane ring-formation by the thermal reaction of 2-(alk-2-enylamino)-4-oxo-4H-pyrido[1, 2-a]pyrimidine-3-carboxaldehydes with tosylhydrazine". Synthesis, 1997, 1, 53-56 (abstract) [online] Retrived from STN, CA: 126:144246, compound with RN 186646-36-6	1
X	GEORGE, Thomas et al. "Synthesis of pyrido[1, 2-a]pyrimido[4, 5-b]pyridine and related tricyclic systems". Journal of Organic Chemistry, 1971, 36 (15), 2192-4 (abstract) [online] Retrived from STN, CA: 75:88564, compound with RN 29494-75-5P	1
X	SHIRAI, Masashi et al. Reaction of 2-substituted-4-oxo-4H-pyrido [1, 2-a] pyrimidine-3-carbaldehyde oximes with electron-deficient olefins and acetylenes. Tetrahedron, 2003, v. 59, 4113-4121, sheme 3, compounds 1 a-d, sheme 5, compound 13, sheme 6, starting compound on the second line	1, 2
X	GURNOS, Johnes et al. "The Vilsmeier reaction of fully conjugated carbocycles and heterocycles". Organic Reactions, 1997, 49 [online] Retrived from STN, CA: 149:575981, compound with RN 109274-79-5P, 17481-62-8P, 33345-96-9P, 109274-76-2P, 109274-78-4P, 109274-81-9P, 111680-71-8P, 111680-72-9P, 111680-73-0P, 111680-78-5P	1
X	NOGUCHI, MICHIHIKO et al. "Competitive thermal ene reaction and Deils-Alder reactions of 2-[N-(alk-2-enyl)benzylamino]-3-vinylpyrido[1, 2-a]pyrimidin-4 (4H)-ones". Tetrahedron, 2007, 63 (21), 4548-4557 (abstract) [online] Retrived from STN, CA: 147:95617, compounds with RN 174317-33-0, 174317-35-2, 174317-36-3	1
X	ZHANG, YUCHI et al. "A convenient synthesis of 2-functionalized pyrrolo[2, 3-d]-pyrido[1, 2-a]pyrimidines". Heterocycles, 2006, 70, 181-184 (abstract) [online] Retrived from STN, CA: 146:401932, compounds with RN 597558-89-9, 597558-90-2, 597558-93-5, 933984-40-8, 933984-42-0, 933984-44-2, 933984-46-4, 933984-47-5, 933984-48-6	1
X	YOSHIDA, KEN-ICHI et al. "MexAB-OprM specific efflux pump inhibitors in Pseudomonas aeruginosa. Part 5: Carbon-substituted analogues at the C-2 position". Bioorganic & Medicinal Chemistry, 2006, 14 (6), 1993-2004 (abstract) [online] Retrived from STN, CA: 144:366386, compound with RN 881997-02-0P	1
X	NAKAYAMA, KIYOSHI et al. "MexAB-OprM specific efflux pump inhibitors in Pseudomonas aeruginosa. Part 4: Addressing the problem of poor stability due to photoisomerization of an acrylic acid moiety". Bioorganic & Medicinal Chemistry Letters, 2004, 14 (10), 2493-2497 (abstract) [online] Retrived from STN, CA: 141:71507, compound with RN 475060-27-6P	1

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROMAI, G et al. "Synthesis, antiplatelet activity and comparative molecular field analysis of substituted 2-amino-4H-pyrido[1, 2-a]pyrimidin-4-ones, their congeners and isosteric analogues". Bioorganic & Medicinal Chemistry, 2000, 8 (4), 751-768 (abstract) [online] Retrived from STN, CA: 133:68351, compounds with RN 111680-72-9, 154816-49-6	1
X	NOGUCHI, MICHIHIKO et al. " Acid-catalyzed [4 + 2] cycloaddition reaction of 2-(alk-2-enyl) amino-3-(N-arylimino) methyl-4-oxo-4H-pyrido [1, 2-a] pyrimidines". Bulletin of the Chemical Society of Japan, 1997, 70 (9), 2201-2207 (abstract) [online] Retrived from STN, CA: 127:278180, Original Reference No. 127:54333a, 54336a, compounds with RN 174317-33-0, 174317-35-2, 174317-36-3, 186646-36-6 186646-37-7	1
X	NOGUCHI, MICHIHIKO et al. "Mechanistic considerations on the azepine-ring formation through the ene reactions at the periphery of heterocyclic systems". Tetrahedron, 1996, 52 (41), 13097-13110 (abstract) [online] Retrived from STN, CA: 126:144245, Correction of 126:8061, compounds with RN 183969-01-9, 183969-02-0, 174317-33-0, 174317-35-2, 174317-36-3, 183969-95-8P	1
X	NOGUCHI, MICHIHIKO et al. "An asymmetry induced azepine-ring formation through the ene reactions at the periphery of heterocyclic systems". Tetrahedron, 1996, 52 (41), 13111-13120 (abstract) [online] Retrived from STN, CA: 126:8062, Original Reference No. 126:1794h, 1795a, compounds RN 17481-62-8, 147317-35-2, 183901-06-6, 183661-52-1P	1
X	GOTOH, MITSUHIRO et al. "Inramolecular 1, 3-dipolar cycloaddition at the periphery of heterocyclic systems. Part 2. A mechanistic proposal for the facile oxime-nitrone isomerization at the periphery of pyridine and pyrido[1, 2-a]-pyrimidine systems". Tetrahedron, 1996, 52 (3), 887-900 (abstract) [online] Retrived from STN, CA: 124:202156, Original Reference No. 124:37373a, 37376a, compounds with RN 174317-33-0, 174317-35-2, 174317-36-3, 174317-56-7, 174317-57-8	1
X	NOGUCHI, MICHIHIKO et al. " A facile and stereoselective azepine-ring formation at the periphery of pyridone and pyrido[1, 2-a pyrimidone systems via intramolecular imine and carbonyl ene reactions". Tetrahedron, 1996, 52 (41), 13081-13096 (abstract) [online] Retrived from STN, CA: 126:8060, Original Reference No. 126:1791a, 1794a compounds with RN 174317-33-0P, 174317-35-2P, 174317-36-3P, 174317-56-7P, 174317-57-8P, 174317-58-9P, 183863-80-1P, 183863-83-4P	1, 2
X	MAGYAR, KALMAN et al. "Monamine oxidase-inhibitory activity of new homopyrimidazole derivatives". Orvostudomany, 1974, 25 (2), 143-50 (abstract) [online] Retrived from STN, CA: 82:120801, Original Reference No. 82:19299a, 19302a, compound with RN 54978-26-6	1

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAUL, C.L. et al. "Antihypertensive and monoamine oxidase inhibitory activity of 3-amino-2-oxazolidinone (3AO) and its condensation product with 2-substituted-3-formyl-4-oxo-(4H)-pyrido[1, 2-a]pyrimidines". Biochemical Pharmacology, 1972, 21 (3), 303-16 (abstract) [online] Retrived from STN, CA: 76:135864, Original Reference No. 76:21991a, 21994a, compounds with RN 34484-91-8, 35877-25-9, 36146-44-8	1