DE 3346814 and US 4661630 disclose carboxylic acid amides. These compounds are useful for diseases attended with cerebral dysfunction and also have anti-ulcer, anti-asthma, anti-inflammatory and hypo-cholesterol activities.

In EP 0097056, JP 55157547, DE 2851379 and DE 2921002 tetrahydrophthalamic acid derivatives are described.

It is an object of the present invention to provide alternative effective agents, specifically in the form of their calcium salts, which can be used for the treatment of diseases which require the inhibition of DHODH.

Particularly, it has previously been found that compounds of the general formula (I) shown herein below, such as 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-cyclopent-1-enecarboxylic acid (INN Vidofludimus), exhibit good anti-inflammatory activity and their usability in the oral therapy for the treatment of autoimmune diseases such as for example rheumatoid arthritis or inflammatory bowel diseases had been adressed. However, the solubility of the aforementioned compounds in aqueous media is less than 1 mg/ml at neutral pH.

The solubility of a compound is an important characteristic in drug discovery, as it serves as a starting point for formulation development. Furthermore, after oral administration, the resorption of a drug from the intestines into the circulation is at least in part dependent on its solubility. Only dissolved substances can be resorbed, so that an increase in solubility can be expected to result in a better uptake of a compound in the gastrointestinal tract, i.e. a better oral bioavailability and hence improved pharmacokinetic properties. It is desirable to provide compounds having enhanced bioavailability in order to improve their use as pharmaceutical compound for oral application.

Summary

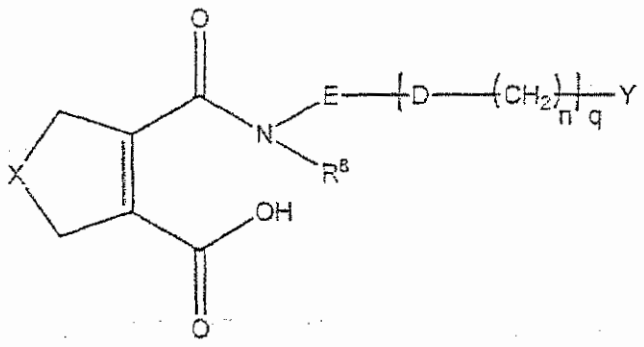
Therefore, the present inventors have undertaken efforts to increase the solubility of the compounds in aqueous media and consequently their bioavailability. With this motivation, a study to develop a novel salt form of the compounds was performed, resulting in salts which unexpectedly exhibit significantly improved physicochemical properties.

It has been found that the calcium salts of compounds of formula (I) as described herein below, such as the calcium salt of 2-(3-Fluoro-3'-methoxy-biphenyl-4-ylcarbamoyl)-

cyclopent-1-enecarboxylic acid, exhibit favorable physicochemical properties such as improved aqueous solubility while maintaining good long-term stability. Furthermore, it was found that not all salts of the compound generally increase aqueous solubility to the same extent; in fact, although the solubilities of the tested salts are all higher than for the free acid, they significantly differ from each other. More importantly, the calcium salt surprisingly exhibits a markedly increased bioavailability, compared with other salts or the free acid.

Accordingly, a novel class of calcium salts of compounds with an inhibitory effect on DHODH, in particular human DHODH, was found.

In one aspect, there is provided the calcium salt of a compound of the general formula (I)



(I),

wherein

X is selected from the group consisting of CH_2, S, or O;

D is O or S;

R^8 is hydrogen or alkyl;

E is an optionally substituted phenylene group;

Y is a monocyclic or bicyclic substituted or unsubstituted 6-9 membered ring system which may contain one or more heteroatoms selected from N or S and which contains at least one aromatic ring;

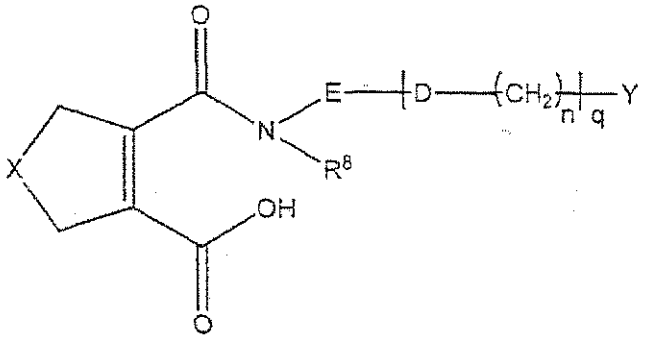
n is 0 or 1; and

q is 0 or 1;

with the proviso that the calcium salts of compounds wherein X = CH_2, q =0 , Y= unsubstituted phenyl and E = unsubstituted phenylene are excluded,

or a hydrate thereof.

The present ~~invention~~disclosure is ~~therefore~~ directed to the calcium salts of compounds of the general formula (I)



(I)

, wherein

X is selected from the group consisting of CH_2, S, or O;

D is O or S;

R^8 is hydrogen or alkyl, preferably hydrogen or methyl;

E is an optionally substituted phenylene group;

Y is a monocyclic or bicyclic substituted or unsubstituted 6-9 membered ring system which may contain one or more heteroatoms selected from N or S and which contains at least one aromatic ring; preferably, Y is substituted or unsubstituted phenyl;

A haloalkyl group denotes an alkyl group which is substituted by one or more halogen atoms, the alkyl group being as defined above; a trifluoromethyl being preferred.

A haloalkyloxy group denotes an alkoxy group which is substituted by one or halogen atoms, the alkoxy group being as defined above; a OCF_3 being preferred.

Halogen is preferably chlorine, bromine, fluorine or iodine, fluorine, chlorine or bromine being preferred, fluorine being more preferred.

The ~~invention~~present disclosure also provides in another aspect a pharmaceutical composition comprising the calcium salts of the compounds of formula (I) as described above ~~or~~ , together with ~~a~~ pharmaceutically acceptable diluents or carriers ~~therefore~~.

In another ~~aspect~~embodiment, the present ~~invention~~disclosure also provides a method for the treatment or prophylaxis of a condition where there is an advantage in inhibiting dihydroorotate dehydrogenase (DHODH) which comprises the administration of an effective amount of a calcium salt of the compounds of formula (I) as described above.

In another aspect, the present disclosure provides a calcium salt or hydrate thereof as defined above for the use as a medicament.

The ~~invention~~present disclosure is also directed to the use of a calcium salt of the compounds of formula (I) as described above for the production of a medicament for the prevention and treatment of diseases, where inhibition of the pyrimidine biosynthesis is of benefit.

In an aspect, the present disclosure provides the use of a calcium salt or hydrate thereof as defined above in the manufacture of a medicament for use in treatment of a disease or a therapeutic indication selected from the group comprising rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma or athropathy.

The present ~~invention~~disclosure also encompasses hydrates of the salts according to the present ~~invention~~disclosure, which specifies that crystals obtainable from said salts contain water in specific stoichiometric or substoichiometric amounts, such as for example 0.5, 1 or 2 water molecules per molecule of the compound of formula (I) or formula (Ia) as described herein,

Further preferred ~~aspects~~embodiments of the present ~~invention~~disclosure are summarized in the following items [1] to [8]:

[1] A salt of the compound of the formula (Ia)

[8] The use of the compound of the formula (Ia) as defined in any of items [1] to [2] in the manufacture of a medicament for use in treatment of any forms of neoplasms.

In addition, the present ~~invention~~disclosure provides methods for preparing the compounds of the ~~invention~~present disclosure such as desired amides of the formula(I), as well as for the calcium salts thereof as described above.

In an aspect, the present disclosure provides a process for the preparation of a calcium salt or hydrate thereof as defined above which comprises the steps of

a) adding a suspension of calcium hydroxide in an organic solvent to a solution of the free acid of a compound of formula (I) as defined above,

b) stirring the suspension obtained in step a),

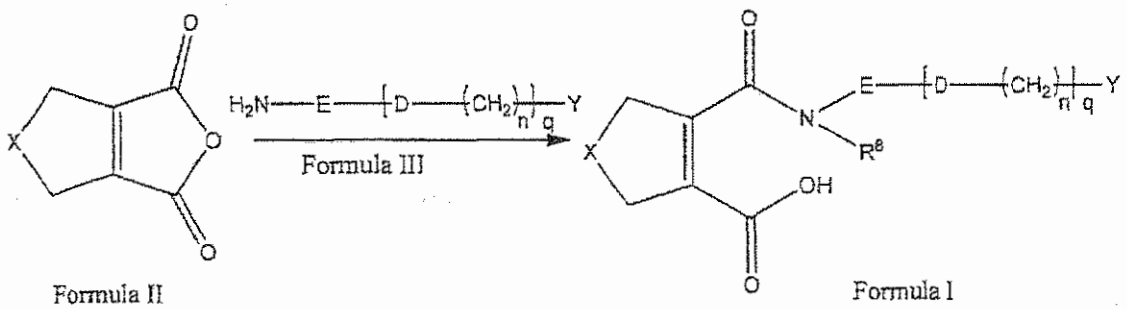
c) at least partially evaporating said organic solvent to obtain a suspension of the calcium salt of said compound of formula (I),

d) recovering the calcium salt of said compound of formula (I) from the mixture obtained in step c), and

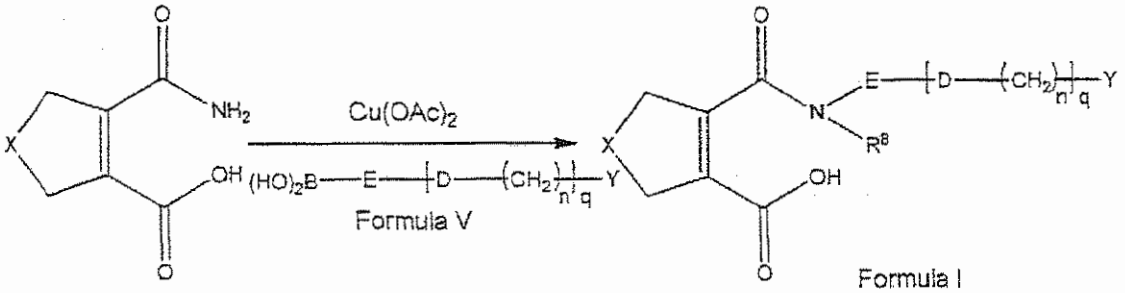
e) washing the calcium salt of said compound of formula (I) obtained in step d), with said organic solvent.

Detailed Description

A first method for synthesis of amides of formula (I) comprises the step of reacting an acid anhydride of formula (II) with an amine of the formula (III).



A second method of the invention for preparing the compounds of formula (I) comprises the step of reacting an amine of the formula (IV) with an aryl-boronic acid of the general formula (V) $(HO)_2B$-E-[D-$(CHR^3)_n]_q$-Y [M. P. Winters, Tetrahedron Lett, 39, (1998), 2933-2936].



A third method of the invention for preparing the compounds of formula (I) comprises the step of reacting an halogen derivative of the formula (VI) with an arylboronic acid of the general formula (VII) [N. E. Leadbeater, S. M. Resouly, Tetrahedron, 55, 1999, 11889-11894]. Q is a halogen group such as chlorine, bromine, fluorine or iodine, bromine being preferred.