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(54) Title: Pharmaceutical compositions for the regeneration of leukocytes and their use in the treatment of acquired immuno-deficiency syndrome.

(57) Abstract:

This invention relates to novel pharmaceutical compositions, to new products and to method for regenerating or improving the level of T_4 lymphocytes in patients suffering from immuno-deficiency syndrome.

The new pharmaceutical compositions according to this invention contain as active ingredient at least one compound selected from the group consisting of 9-amino 1,2,3,4-Tetrahydroacridine, in the free base form or as an acid addition salt, and its biological precursors, in admixture or conjunction with an inert non toxic pharmaceutically-acceptable carrier or vehicle.

This invention also extends to a method for regenerating or improving the count of T_4 lymphocytes in patients suffering from said symptoms alone or in addition with a therapy with an antiviral drug selected from the group consisting of derivatives of Thymidine, Uracil and Uridine.

These new drugs may be given to children as well as to adults for an extended period of time with significant evidence of recovery.

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(56) Documents cited: EP 0 319 429

A B S T R A C T

This invention relates to the field of medicinal chemistry.

It has as the subject matter, pharmaceutical compositions allowing the regeneration of lymphocytes T_4 or the increase thereof in patients, showing an immuno-deficitary syndrom, which contain as active ingredient 9-amino 1,2,3,4-Tetrahydroacrine, a salt thereof or a biological precursor thereof.

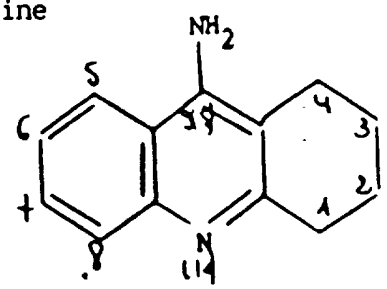
This invention also relates as novel compounds to the biological precursors of 9-amino 1,2,3,4-Tetrahydroacridine.

NEW PHARMACEUTICAL COMPOSITIONS AND NEW PHARMACEUTICAL PRODUCTS ALLOWING THE REGENERATION OF LEUKOCYTES AND THEIR USE IN THE TREATMENT IMMUNO-DEFICIENT SYNDROM

This invention relates to the field of medicinal therapy and more particularly to the field of immunological therapy.

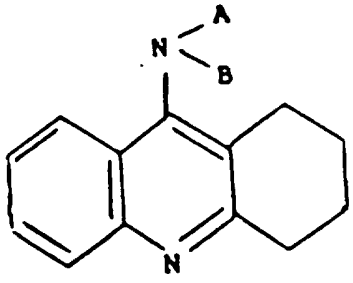
It has more precisely as subject matter some products and some pharmaceutical compositions which allow to obtain alone or in combination with another active ingredient the treatment of acquired or non-acquired immuno deficitary syndroms.

Specifically it provides pharmaceutical compositions intended for the regeneration of lymphocytes T_4 or the increase of the number of lymphocytes T_4 in patients showing an immuno-deficitary syndrom which contain as active ingredient the 9-(or 5)amino 1,2,3,4-Tetrahydroacridine



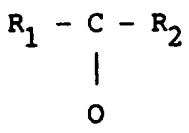
as a free base or in the form of a salt
or a biological precursor thereof
in admixture or conjunction with an inert non-toxic pharmaceutically-acceptable carrier or vehicle.

This invention also relates as new compounds to the biological precursors of 9-amino 1,2,3,4-Tetrahydroacridine having the formula

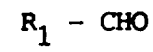


In which A and B are labile functional groupings which are easily split in the body and namely in the digestive tract.

Among the labile groupings A and B, it may be cited the acyl residues of an organic aliphatic or aromatic, carboxylic acid, lower alkyl radicals or the alkoylidene or arylidene moiety of a Schiff's Base deriving from a ketone of the formula



or from an aldehyde of the formula

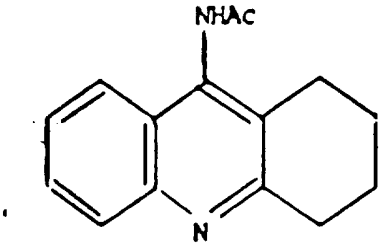


wherein R_1 is a lower alkyl radical, a monocyclic aryl radical which is unsubstituted or substituted by one, two or three substituents, a monocyclic heterocyclic radical
and R_2, is a hydrogen or a R_1 radical

In the foregoing, the acid addition salt of 9-amino tetrahydro acridine or of the derivatives thereof are those obtained by adding a mineral or organic therapeutically-compatible acid such as a hydrochloride, a hydrobromide, a sulphate, a nitrate, a phosphate, a sulphite, a thiosulphate, an acetate, a butyrate, a caproate, a suberate, a succinate, a tartarate, a citrate, an ascorbate, a gluconate, a cetoglutarate, a glutamate, an aspartate, a benzoate, a gentisate, a salicylate, a trimethoxybenzoate, a vanillinate, an eugenate, a nicotinate, a naphtoate, a benzene sulfonate, a methane sulfonate, an isethionate, an ethane sulfonate, a p.toluene sulfonate, a camphosulfonate, a naphtalene sulfonate, a glucose 1-phosphate and a glucose 1,6-diphosphate.

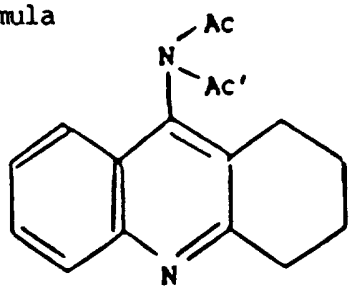
The biological precursors of 9-amino 1,2,3,4-Tetrahydroacridine are namely the mono- and di-acyl amines such as for example :

- the compounds of formula



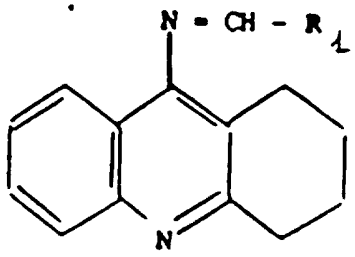
in which Ac is the acyl residue such as acetyl, propionyl, benzoyl,

- the compounds of formula



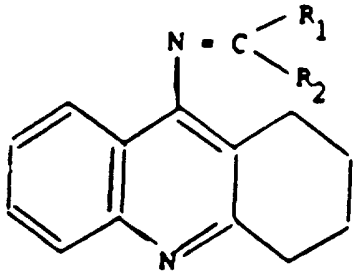
wherein Ac and Ac' the same or different are selected from the group consisting of alkanoyl radicals with 1 to 6 carbon atoms and mono- cyclic aroyl radicals which are unsubstituted or substituted with from 1 to 3 usual substituent

- the compounds of formula



wherein R_1 is a lower alkyl radical, a phenyl or a substitued phenyl

- the compounds of formula



wherein R_1 and R_2 the same or different are selected from the group consisting of a lower alkyl radical, a phenyl radical, and a monocyclic heterocyclic radical.

9-amino 1,2,3,4-Tetrahydroacridine is a known therapeutic agent already used under the Trade Name Tacrine for many years as an antidote of the curarizing agents and the cholines terasic agents. Its use has also been proposed in the treatment of Alzeimer's disease as anticholinesterasic agent and cerebral stimulant but its efficiency can not yet be judged lacking the necessary background. The mode of action of this active ingredient is still not determined with certainty due to the high number of pharmacological studies performed thereon.

Now it has been found that 9-amino 1,2,3,4-Tetrahydroacridine and the acid addition salts thereof as well as their biological precursors (pro-drugs) are efficient drugs for allowing the regeneration of lymphocytes T_4 and more particularly lymphocytes T_4 the number of which significantly and dangerously, decreases during and in the cases of immuno-deficitary syndrom.

It has been evidenced in patients the number of lymphocytes T_4 of which was deeply decreased, that it was possible after few weeks of treatment to obtain a very marked increase of the levels of lymphocytes in the blood and that in patient where the count of lymphocytes T_4 has fallen to a level close of the disappearance, it was possible to get under the same conditions a recovery to subnormal levels of lymphocytes T_4. At the same time the clinical cases stated a significant regression of the opportunistic infections symptoms and/or the disappearance of the seropositivity.

9-amino 1,2,3,4-Tetrahdroacridine appears to act mainly as an inhibitor of the RNA polymerase of the viruses and more precisely of the HIV Viruses which are involved in the origin of AIDS.

The biological precursors of 9-amino tetrahydroacridine behalve in about the same manner and lead to the formation of 9-amino tetrahydroacridine in the stomach. It has been shown that in an artificial gastric juice, at pH 1, methylene 9-imino tetrahydroacridine, isopropylidene 9-imino tetrahydroacridine or benzylidene 9-imino tetrahydroacridine are split into the 9-amino derivative in about quantitative manner in less than 15 mn.

9-amino tetrahydroacridine and its biological precursors are also endowed with the ability to strenghten the action of antiviral drugs such as the thymidine, Uracile or uridine derivatives (AZT, DDI namely) and thus to allow a very marked decrease of the doses of antiviral drug to be efficient.

It is now known that the treatment of AIDS using Azathymidine (AZT) progressively losses its efficacy and let an only very limited chance of life to the patients affected with AIDS. The mixed treatment of AIDS with an antiviral drug and with 9-amino tetrahydroacridine or a salt thereof or one of its biological precursors have shown a significant presumption of life. It appears as very significative the clinical case of a patient treated for 15 months with AZT for which the number of lymphocytes T_4 was about zero and after treatment with 9-amino 1,2,3,4-Tetrahydroacridine was still alive. It exists accordingly two possible therapeutic schemes :

- administration of 9-amino tetrahydroacridine alone

- or administration of 9-amino tetrahydroacridine in admixture or in support of a treatment with an antiviral drug.

In the case of antiviral drugs such as AZT or HPAZI, it has been shown a synergistic action which allows a decrease in the dosology of the antiviral drug of a factor of 10 while preserving the efficacy of the antiviral drug.

The pharmaceutical compositions according to this invention contain from 40 to 300 mg of 9-amino 1,2,3,4-tétrahydroacridine or an addition salt thereof or one of its biological precursors in admixture or conjunction with an inert non-toxic pharmaceutically-acceptable diluent or carrier and preferably from 50 to 200 mg of active ingredient.

As preferred diluent it may be cited a lecithin such as soja lecithin, or a phospholipid such as a ganglioside or a cerebroside, or a chemically-modified cellulose such as hydroxypropyl methylcellulose.

Among the pharmaceutical compositions according to this invention which contain as active ingredient either 9-amino tetrahydroacridine or a salt thereof or a biological precursor, it may be cited those which are suitable for the administration through the digestive route such as tablets, coated tablets, microgranules with protracted release, dragees, the soft gelatine capsules, the capsules, the hard shell capsules, the lozenges, the solutions or suspensions to be drunk, the jellies and the emulsions (O/W).

For the parenteral administration it will be preferably used a solution or suspension of active ingredient divided in ampuls, in multidoses flasks, or auto-injectible syringes ; they are preferably utilized in the form of an acid addition salt.

For the rectal way they will be preferably be given in the form of rectal suppositories or capsules.

These pharmaceutical compositions are manufactured in accordance with the usual methods of pharmacotechnology. The following examples are intended to illustrate the invention without limiting it in any manner.

EXAMPLE I

Tablets with 100 g of 9-amino 1,2,3,4-tetrahydroacridine

. 9-amino 1,2,3,4-tetrahydroacridine as the hydrated hydrochloride	117 g
. Lactose	220 g
. microcristalline cellulose	15 g
. Calcium Carbonate	20 g
. Calcium Phosphate $(PO_4)_2$ Ca_3	35 g
. Copolymer of ethylene oxyde and propylene oxyde sold under the Trade Name PLURONIC F18 .	13 g
. Magnesium stearate	15 g
for 1000 tablets finished at the mean weight of	.43 g

EXAMPLE II

Clinical Trial with 9-amino 1,2,3,4-tetrahydroacridine in patients suffering from immuno-deficitary syndrom

PATIENTS	DOSIS	CONCENTRATION LYMPHOCYTES T4 BEFORE per mm3	CONCENTRATION LYMPHOCYTES T4 AFTER per mm3	SYMPTOMS OF CLINICAL IMPROVEMENT
1	100 mg/day 5 months	0	600	Becomes sero-negative
2	100 mg/day 3 months	80	250	Decrease of the infectious symptoms
3	100 mg/day 2 months	80	210	No marked symptom of infection
4	100 mg/day 2 months	100	270	-d°-
5	200 mg/day 2 months	80	200	Regression of the opportunist infections

Normal level in T4 is 600-800 per mm3

EXAMPLE III

Determination of the inhibitory action of 9-amino 1,2,3,4-Tetrahydroacridine (THA) against RNA polymerase of HIV Viruses.

In vitro THA inhibits RNA polymerase of HIV Viruses with a close window of efficiency

at 0,1 µmol/l ——→ 0% inhibition
1 µmol/l ——→ 100 % inhibition

EXAMPLE IV

Methodology of the clinical trials

a) in the adults

. 1st week : 50 mg/day + 1200 mg soja lecithin

. 2nd week : 100 mg/day + 1200 mg soja lecithin

. 3rd week : 150 mg/day if necessary + soja lecithin

. 4th week : 200 mg/day if necessary + soja lecithin

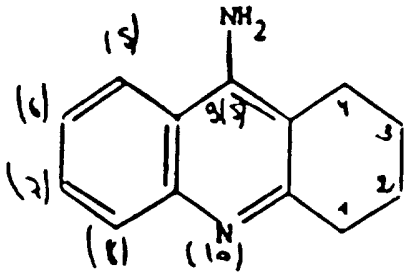
b) in the children

The treatement is started at 10 up to 25 mg/day.

An adult patient formerly treated with AZT after what, his blood level in T_4 was about zero, has been given 9-amino 1,2,3,4-Tetrahydroacridine up to 100 mg/day. After 5 months of this treatment, the lymphocytes T_4 have been increased and the patient was still alive, whilst under treatment with AZT alone, the presumption of his survival was minimal.

WHAT IS CLAIMED IS

1°- A process for producing pharmaceutical compositions intended to allow the regeneration of lymphocytes t_4 or the increase of their number in patients suffering from an immuno-deficitary syndrom which comprises mixing a compound selected from the group consisting of 9(or 5) amino 1,2,3,4-tetrahydroacridine of the formula

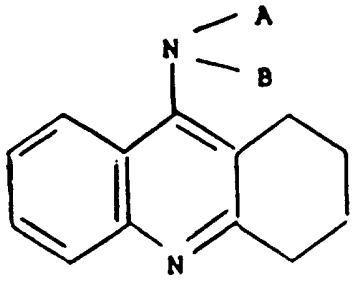


as the free base or as an acid addition salt thereof
and one of its biological precursors
with an inert non-toxic pharmaceutically-acceptable carrier or vehicle

2°- A pharmaceutical composition according to claim 1 wherein the content in active ingredient ranges from 10to 300 mg per unit dosage.

3°- A pharmaceutical composition according to claim 1° which further contains an antiviral drug selected from the group consisting of derivatives of Thymidine, Uracile and Uridine.

4°- As new compounds the biological precursors of 9-amino 1,2,3,4-Tetrahydroacridine having the formula



wherein A and B are labile fonctional groupings selected from the group consisting of acyl residues from aliphatic or

aromatic organic carboxylic acids, lower alkyl radicals, an alkoylidene group and a arylidene groupe

5°- A compound according to claim 4° which is 9-methylene imino 1,2,3,4-Tetrahydroacrdine.

6°- A compound according to claim 4° which is 9-isopropylidene imino 1,2,3,4-Tetrahydroacridine.

7°- A compound according to claim 4° which is 9-benzylidene imino 1,2,3,4-Tetrahydroacridine.

8°- A pharmaceutical composition according to claim 1° in which the inert carrier is one of those suitable for administration through the parenteral, oral, rectal, percutaneous or permucous routes of administration.

9°- The pharmaceutical compositions according to claim 8° wherein the amount of active ingredient ranges from 10 to 200 mg per unit dosage.

10°- The pharmaceutical composition according to any of claims 8 to 9° in which the inert non-toxic carrier is lecithin.