1,180,202

PATENT SPECIFICATION

NO DRAWINGS

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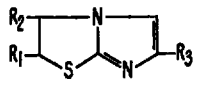
COMPLETE SPECIFICATION

Imidazo[2,1-b]Thiazole Derivatives

We, RHONE-POULENC S.A., a French Body Corporate of 22, Avenue Montaigne, Paris 8e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

THIS INVENTION relates to new therapeutically useful imidazo[2,1 - b]thiazole derivatives and acid addition salts thereof, to a process for their preparation and pharmaceutical compositions containing them.

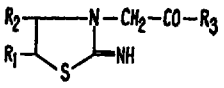
The imidazo[2,1 - b]thiazole derivatives of the present invention are those of the general formula:



I

wherein R_1 represents a hydrogen atom or a phenyl group, R_2 represents a hydrogen atom or a methyl group, and R_3 represents a hydrogen atom, or a phenyl or hydroxyphenyl group, and their acid addition salts.

According to a feature of the invention, the aforesaid imidazo[2,1 - b]thiazole derivatives are prepared by the process which comprises the cyclisation by heating of a thiazolidine of the general formula:

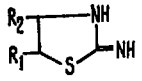


II

wherein R_1, R_2 and R_3 are as hereinbefore defined, or an acid addition salt thereof. The cyclisation is generally effected by heating the thiazolidine, optionally prepared in situ, in aqueous or organic solution, and preferably in the presence of a concentrated inorganic acid at a temperature between 40° and 120°C. Preferably it is carried out in concentrated aqueous hydrochloric acid at or near the boiling temperature of the reaction mixture.

When R_3 represents a hydroxyphenyl group, it is advantageous to protect the hydroxy radical beforehand by the formation of an ester group, which will be hydrolysed during the cyclisation reaction.

The thiazolidines of formula II can be obtained by reacting a thiazolidine of the general formula:



III

with a compound of the general formula:

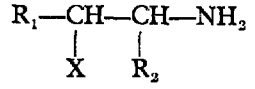
$$Z—CH_2—CO—R_3$$

IV

wherein Z represents the acid residue of a reactive ester such as a halogen atom or a sulphuric or sulphonic ester residue, for example a methoxysulphonyloxy, methanesulphonyloxy or toluene - p - sulphonyloxy group. It is advantageous to carry out the reaction in an inert organic solvent, for example acetone or ethanol, at about 20°C.

[*Price 5s. 0d.*]

The thiazolidines of formula III can be prepared by condensing a halogenated ester of the general formula:

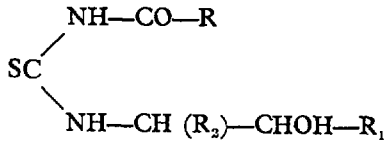


V

wherein X represents a halogen (preferably chlorine) atom, with thiourea in an anhydrous inert organic solvent, for example ethanol, or with an alkali metal salt of thiocyanic acid in an aqueous or aqueous-organic solution and at the boiling point of the solvent.

The products of general formula V are prepared by halogenation of the corresponding amino-alcohol R_1—CHOH—CHR_2—NH_2 according to methods known per se.

The thiazolidines of formula III can also be obtained by cyclising an acylthiourea of the general formula:



VI

wherein R is an aliphatic or aromatic radical, preferably methyl or phenyl, in an acid medium. It is advantageous to carry out the process by heating the suspension of the acylthiourea in an aqueous solution of an inorganic acid under reflux.

The acylthioureas of general formula VI are obtained from aminoalcohols of the general formula R_1—CHOH—CHR_2—NH_2 by condensation wih an acylisothiacyanate of the general formula:

R—CO—N=C=S

VII

wherein R is as hereinbefore defined. It is advantageous to carry out this operation in an inert organic solvent at the boiling point of the latter.

The products of formula I may optionally be purified by physical methods such as crystallisation of chromatography.

The new imidiazo[2,1 - b]thiazole derivatives prepared according to the invention can optionally be converted into acid addition salts by methods known per se, e.g. by reacting the bases with acids in appropriate solvents, for example alcohols, ethers, ketones or chlorinated hydrocarbons. The salt formed precipitates, if necessary after concentrating its solution, and is separated off by filtration or decantation.

The imidazo[2,1 - b]thiazole derivatives of formula I and their acid addition salts posses useful chemotherapeutic properties; they possess a valuable anti-viral activity, particularly against viruses of the rhinovirus group.

For therapeutic purposes, the compounds of formula I are employed as such or in the form of non-toxic acid addition salts, i.e. salts containing anions which are relatively innocuous to the animal organism in therapeutic doses of the salts (such as the hydrochlorides and other hydrohalides, phosphates, nitrates, sulphates, acetates, propionates, succinates, benzoates, picrates, fumarates, maleates, citrates, tartrates, salicylates, methanesulphonates, ethanedisulphonates, benzenesulphonates and toluene-p-sulphonates) so that the beneficial physiological properties inherent in the bases are not vitiated by side-effects ascribable to the anions.

The following Examples illustate the present invention.

EXAMPLE 1

A suspension of 2 - amino - 3 - benzoyl - methyl - 4 - methyl - 5 - phenylthiazolidine hydrobromide (31.3 g.) in 12N hydrochloric acid (160 cc.) is heated with stirring for 2 hours at 105°C. After cooling, the insoluble matter is filtered off and washed with water (4×50 cc.). This insoluble matter is thereafter taken up in water (200 cc.) and methylene chloride (300 cc.), and the solution rendered alkaline by the addition of 4N sodium hydroxide solution so as to maintain a pH of about 7. The organic layer is decanted and the aqueous layer is re-extracted with further methylene chloride (100 cc.). The combined organic phases are washed with water (100 cc.) and then dried over sodium sulphate. The solvent is evaporated under reduced pressure (30 mm.Hg). The crystalline product (24 g.) thus obtained, melting at 122—125°C., is recrystallised from acetonitrile (50 cc.) after treatment with decolourising charcoal. 2,6 - Diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole (19 g.), melting at 125—126°C. (it re-solidifies and then melts at 134°C.), is obtained.

2 - Imino - 3 - benzoylmethyl - 4 - methyl - 5 - phenylthiazolidine hydrobromide is obtained by adding a solution of 2 - imino - 4 - methyl - 5 - phenylthiazolidine (34.7 g.) in ethanol (280 cc.) to a solution of phenacyl bromide (36 g.) in ethanol (280 cc.). The temperature slowly changes from 22° to 34°C. and a precipitate appears after about 25 minutes; the mixture is left for 16 hours at ambient temperature. The product which has crystallised is filtered off and washed with ethanol (4×20 cc.) to yield 2 - imino - 3 - benzoylmethyl - 4 - methyl - 5 - phenylthiazolidine hydrobromide (37.2 g.) decomposing at about 230°C.

The 2 - imino - 4 - methyl - 5 - phenyl -

thiazolidine is prepared by one of the following methods:

a) 1 - Methyl - 2 - chloro - 2 - phenyl - ethylamine hydrochloride (70.2 g.) is added over the course of 5 minutes to a solution of sodium ethoxide (23 g.) in ethanol (700 cc.); thiourea (26 g.) is then added and the mixture is heated at 75°C. for 7 hours. The ethanol is evaporated under reduced pressure (30 mm. Hg) and the residue is taken up in water (1000 cc.), 4N hydrochloric acid (150 cc.) and methylene chloride (250 cc.). The organic phase is separated off and the aqueous phase is re-extracted with further methylene chloride (150 cc.). The combined organic solutions are washed with water (100 cc.). The aqueous phases are then combined and rendered alkaline with 10N sodium hydroxide solution (100 cc.). A solid separates out and this is filtered off and washed with water (4×100 cc.). After drying, a product (49.7 g.) melting at 138—140°C. is obtained. This is recrystallised from acetonitrile (150 cc.) after treatment with decolourising charcoal to yield 2 - amino - 4 - methyl - 5 - phenylthiazolidine (34.8 g), melting at 143°C.

The 1 - methyl - 2 - chloro - 2 - phenyl - ethylamine hydrochloride may be prepared according to H. Pfanz and H. Wiedurwilt, Arch, Pharm., 288, 563 (1955).

b) A suspension of 1 - benzyl - 3 - (1 - methyl - 2 - hydroxy - 2 - phenylethyl) - thiourea (11.7 g.) in 48% hydrobromic acid (50 cc.) is heated under reflux for 2 hours. The solution is diluted with water (200 cc.) and a precipitate separates out; the mixture is rendered alkaline with 10N sodium hydroxide solution (70 cc.) and is extracted with chloroform (150 cc. followed by 100 cc.). The combined organic layers are washed with water (100 cc.) and then dried over sodium sulphate. The solvent is evaporated under reduced pressure (30 mm.Hg) to give 2 - imino - 4 - methyl - 5 - phenylthiazolidine (7.1 g.) melting at 142°C.

1 - Benzoyl - 3 - (1 - methyl - 2 - hydroxy - 2 - phenylethyl)thiourea is prepared in the following manner:

Norephedrine hydrochloride (71.5 g.) is added to a solution of sodium ethoxide (27.2 g.) in ethanol (250 cc.). Decolourising charcoal (5 g.) is added and the suspension is filtered. The filtrate is evaporated under reduced pressure (30 mm.Hg). The oily residue is dissolved in acetone (120 cc.) and heated under reflux, and a solution of benzoyl isothiocyanate (61.8 g.) in acetone (120 cc.) is then added over the course of 10 minutes. The mixture is left for 16 hours at 25°C. and the volatile products are then evaporated under reduced pressure (30 mm.Hg). An oily residue (143 g.) is obtained which is taken up in diisopropyl ether (300 cc.). The crystals which form are separated off and washed with diisopropyl ether (2×20 cc.) to yield 1 - benzoyl - 3 - (1 - methyl - 2 - hydroxy - 2 - phenyl - ethyl)thiourea (39.5 g.) melting at 138—141°C.

Benzoyl isothiocyanate can be prepared according to I.B. Douglas and F.B. Dains. J. Amer. Chem. Soc., 56, 719 (1934).

Example 2

A mixture of 2 - imino - 3 - benzoylmethyl - 5 - phenylthiazolidine hydrobromide (30.5 g.) and 12N hydrochloric acid (150 g.) is heated under reflux for 2 hours. After cooling, water (400 cc.) is added and the insoluble matter is filtered off. This insoluble matter is suspended in a mixture of water (200 cc.) and methylene chloride (250 cc.) and 4N sodium hydoxide solution (20 cc.) is added with stirring. The organic layer is decanted and the aqueous layer is extracted with further methylene chloride (150 cc.). The combined organic phases are washed with water (100 cc.) and then dried over anhydrous sodium sulphate. The solvent is evaporated under reduced pressure (30 mm.Hg). A crystalline product (19.5 g.) melting at 153—154°C. is obtained and this is successively recrystallised from acetonitrile (120 cc.) and then from ethanol (205 cc.). 2,6 - Diphenyl - 2,3 - dihydro - imidazo [2,1 - b]thiazole (10.9 g.), melting at 155°C., is thus obtained.

The 2 - imino - 3 - benzoylmethyl - 5 - phenylthiazolidine hydrobromide is obtained by adding a solution of 2 - imino - 5 - phenylthiazolidine (14.4 g.) in acetone (155 cc.) to a solution of phenacyl bromide (16 g.) in acetone (100 cc.), whilst keeping the temperature at about 10°C. The mixture is thereafter left at 20°C. for 16 hours. The product which has crystallised is filtered off and washed with acetone (4×25 cc.) to yield 2 - imino - 3 - benzoylmethyl - 5 - phenylthiazolidine hydrobromide (31 g.) melting at about 208—210°C.

2 - Imino - 5 - phenylthiazolidine can be prepared according to F. Wolfheim, Ber. 47, 1440 (1914).

Example 3

A solution of 2 - imino - 4 - methyl - 5 - phenylthiazolidine (14.7 g.) and of chloracetaldehyde hydrate (14.8 g.) in acetone (150 cc.) is heated under reflux for 4 hours. The acetone is evaporated under reduced pressure (30 mm.Hg), the residue is taken up in water (200 cc.) and methylene chloride (100 cc.) and a few drops of 12N hydrochloric acid are added so as to bring the pH to about 2. The organic phase is separated and the aqueous phase is extracted with further methylene chloride (150 cc.). The aqueous phase is rendered alkaline with 10N sodium hydroxide solution (8.5 cc.); a yellow oil separates out and this is extracted with methylene chloride (100 cc.). The organic phase is separated and the aqueous phase is extracted with further methylene chloride (100 cc.). The combined organic

phases are washed with water (100 cc.) and then dried over anhydrous sodium sulphate. The solvent is evaporated under reduced pressure (30 mm.Hg), and the oily residue (12.3 g.) is taken up in 36N sulphuric acid (10 cc.) at 50°C. The solution thus obtained is left at 20°C. for 15 hours and then poured into water (150 cc.). A brown precipitate forms and this is filtered off.

The aqueous phase is rendered alkaline with 10N sodium hydroxide solution (37 cc.) and extracted with methylene chloride (2×100 cc.). The combined organic phases are washed with water (100 cc.) and then dried over anhydrous sodium sulphate. The solvent is evaporated under reduced pressure (30 mm.Hg) and a brown non-crystalline residue (8.6 g.) is obtained. This residue (6.7 g.) is dissolved in a mixture of carbon tetrachloride (40 cc.) and methylene chloride (10 cc.) and the solution is filtered through a column of alumina (130 g.). Elution is carried out successively with a mixture of carbon tetrachloride (800 cc.) and methylene chloride (200 cc.), and then with a mixture of methylene chloride (1000 cc.) and carbon tetrachloride (700 cc.). The eluted organic fractions are combined and then evaporated under reduced pressure (30 mm.Hg) and crystals (3.2 g.) melting at 93°C. are obtained, which are recrystallised from cyclohexane (50 cc.) after treatment with decolourising charcoal. 2 - Phenyl - 3 - methyl-2,3 - dihydroimidazo[2,1 - b] - thiazole (2.6 g.), melting at 95°C., is thus obtained.

Example 4

A suspension of 2 - imino - 3 - [(4 - acetoxybenzyl)methyl] - 4 - methyl - 5 - phenylthiazolidine hydrobromide (8.6 g.) in 12N hydrochloric acid (80 cc.) is heated with stirring for 1 hour at 105°C. After cooling, the insoluble matter is filtered off and washed with water (3×20 cc.) and ethanol (3×20 cc.). This insoluble matter is dissolved with boiling in ethanol containing 20% of water (280 cc.) and the resulting solution is poured with stirring into 2N ammonia (100 cc.); the white product which precipitates is filtered off and washed with water (5×10 cc.). The product thus obtained is recrystallised from dimethylformamide containing 20% of water (90 cc.) to yield 2 - phenyl - 3 - methyl - 6 - (4 - hydroxyphenyl) - 2,3 - dihydro - imidazo[2,1 - b]thiazole (4.3 g.) melting at 278°C.

The 2 - imino - 3 - [(4 - acetoxybenzoyl) methyl] - 4 - methyl - 5 - phenylthiazolidine hydrobromide is obtained by adding 4 - acetoxyphenacyl bromide (31.3 g.) all at once to a solution of 2 - imino - 4 - methyl - 5 - phenylthiazolidine (23.4 g.) in methyl ethyl ketone (610 cc.) at 30°C. The mixture is left at 5°C. for 18 hours. The product which has crystallised is filtered off and washed with methyl ethyl ketone (50 cc.) to yield 2 - imino - 3 - [(4 - acetoxybenzoyl)methyl] - 4 - methyl - 5 - phenylthiazolidine hydrobromide (11.1 g.) melting at about 195°C. (with decomposition).

The 4 - acetoxyphenacyl bromide can be prepared according to K. W. Rosenmund and K. Pfroepffer Ber. 90, 1922 (1957).

Example 5

A solution of 2 - imino - 4 - methyl - thiazolidine hydrochloride (6.9 g.) in water (110 cc.) is added to a solution of phenacyl bromide (9 g.) in methylene chloride (110 cc.). 2N Sodium hydroxide solution (45 cc.) is added slowly to this mixture over the course of 2 hours whilst stirring slowly, and the mixture is then vigorously stirred for 1 hour. 12N hydrochloric acid (50 cc.) is added and the mixture is heated on a water-bath so as to distil the methylene chloride and attain a temperature of 90°C., which is maintained for 30 minutes. A beige crystalline precipitate forms. The mixture is cooled to about 0°C. and the crystals are filtered off and dried in air. A product (11 g.) of melting at about 100°C. is obtained which re-crystallises and again melts at about 190°C.

This product (15 g.) is suspended in water (100 cc.) and ethyl acetate (200 cc.) and treated with 4N sodium hydroxide solution (30 cc.). The organic phase is decanted and washed with distilled water (2×50 cc.), dried over potassium carbonate, and the solvent is then evaporated. The crystalline residue (11.2 g.) melts at 103—105°C. It is dissolved in ethyl acetate (100 cc.) and 4N hydrochloric acid (15 cc.) is added. A hydrated hydrochloride crystallises. The crystals are filtered off and washed with diethyl ether to yield 3 - methyl - 6 - phenyl - 2,3 - dihydro - imidazo - [2,1 - b]thiazole (8.5 g.) in the form of a hydrated hydrochloride melting at 100°C. and then at 190°C.

The preparation of the 2 - imino - 4 - methyl - thiazolidine has been described by S. Gabriel and H. Ohle, Ber. 50 813 (1917).

The present invention includes within its scope pharmaceutical compositions which comprise at least one imidazo[2,1 - b]thiazole of general formula I, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier or coating. In clinical practice the compounds of the present invention will normally be administered intranasally, orally or rectally.

Solid compositions for oral administration include tablets, pills, powders and granules. In such solid compositions the active compound is mixed with at least one inert diluent such as sucrose, lactose or starch. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. Liquid compositions for oral administration include pharmaceutically ac-

ceptable emulsions, solutions, suspension syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. These liquid compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening and flavouring agents.

The compositions according to the invention for intranasal administration may be sterile aqueous or non-aqueous solutions, suspensions or emulsions. As the solvent or vehicle, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, and organic esters, for example ethyl oleate, may be used. These compositions may also contain adjuvants, in particular wetting, emulsifying and dispersing agents.

The compositions may be sterilised by, for example, filtration through a bacteria-retaining filter, by incoporation in the compositions of sterilising agents, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile medium immediately before use.

Compositions for rectal administration are suppositories which contain, in addition to the active substance, excipients such as cacao butter or a suitable wax base or solidified glycerin.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage will depend on the therapeutic effect sought, the route of administration and on the duration of the treatment. In human therapy, the compositions should generally be administered so as to give, in the case of oral administration, between 100 and 1000 mg. of active substance per day for an adult.

The imidazo[2,1 - b]thiazole derivatives of the present invention have been tested in cultures of human KB cells against human rhinovirus strains 2060 (JH) and HGP (type 2). Complete inhibition of the cytopathogenic effect and of the multiplication of the viruses manifests itself at concentrations between 60 μg./cc. (maximum non-cytotoxic concentration) and 2 μg./cc. (minimum inhibitory concentration), corresponding to a chemotherapeutic index of 30. Furthermore, at the concentrations indicated above, the products remain active when added to the cultures two hours after the inoculation of the virus.

In a culture of human HeLa cells and against human rhinovirus strains HGP (type 2), DC (type 9) and GT (type 43), the maximum non-cytotoxic concentration is 20 μg./cc. and complete inhibition of the cytopathogenic effect of these three viruses manifests itself at a concentration of 10 μg./cc. (minimum tested concentration).

In the case of strain DC (type 9) at a concentration of 10 μg./cc. in cultures of human HeLa cells the products cause a reduction of 4.5 log of the infectious strength of the virus in relation to comparison cultures (strengths measured 5 days after inoculation of the virus); in the case of strain GT (type 43), under the same experimental conditions, the reduction in strength caused by the presence of the products is 1 log.

EXAMPLE 6

A 1% strength solution of 2,6 - diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole for intranasal administration is prepared by dissolving 2,6 - diphenyl - 3 - methyl - 2,3 - dihydro - imidazol[2,1-b]thiazole (1 g.) in propylene glycol (90 cc.) and making up to 100 cc. with distilled water. The solution is sterilised by passing it through a millipore filter. In use, the solution obtained is applied to the nasal mucous membranes by means of a dropper.

EXAMPLE 7

A 1% strength oily solution for intranasal administration is obtained by dissolving 2,6 - diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b] - thiazole (1 g.) in olive oil (100 cc.) at 40—50°C. and filtering the greenish-yellow solution obtained through a millipore filter. In use, the solution is applied to the nasal mucous membrane by means of a dropper.

EXAMPLE 8

The following ingredients are dissolved by mixing them at 40—50°C:

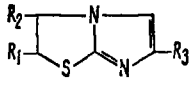
2,6 - diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole	1 g.
olive oil	5 cc.
mixture of polyhydroxyethers of fatty alcohols of high molecular weight	3 g.
mixture of monooleic esters of polyhydroxyethylated sorbitan	1 g.

The solution thus obtained is thereafter sterilised by filtration and then dispersed in a sterile isotonic solution of sodium chloride sufficient to make 100 cc. An oily emulsion containing 1% of 2,6 - diphenyl - 3 - methyl-2,3 - dihydro - imidazo[2,1 - b]thiazole is thus obtained.

For application to the nasal mucous membrane the emulsion is divided into fine droplets by means of a pressure-type nebulizer.

WHAT WE CLAIM IS:—

1. Imidazo[2,1 - b]thiazole derivatives of the general formula:



ceptable emulsions, solutions, suspension syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. These liquid compositions may also comprise adjuvants, such as wetting and suspending agents, and sweetening and flavouring agents.

The compositions according to the invention for intranasal administration may be sterile aqueous or non-aqueous solutions, suspensions or emulsions. As the solvent or vehicle, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, and organic esters, for example ethyl oleate, may be used. These compositions may also contain adjuvants, in particular wetting, emulsifying and dispersing agents.

The compositions may be sterilised by, for example, filtration through a bacteria-retaining filter, by incoporation in the compositions of sterilising agents, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile medium immediately before use.

Compositions for rectal administration are suppositories which contain, in addition to the active substance, excipients such as cacao butter or a suitable wax base or solidified glycerin.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. The dosage will depend on the therapeutic effect sought, the route of administration and on the duration of the treatment. In human therapy, the compositions should generally be administered so as to give, in the case of oral administration, between 100 and 1000 mg. of active substance per day for an adult.

The imidazo[2,1 - b]thiazole derivatives of the present invention have been tested in cultures of human KB cells against human rhinovirus strains 2060 (JH) and HGP (type 2). Complete inhibition of the cytopathogenic effect and of the multiplication of the viruses manifests itself at concentrations between 60 μg./cc. (maximum non-cytotoxic concentration) and 2 μg./cc. (minimum inhibitory concentration), corresponding to a chemotherapeutic index of 30. Furthermore, at the concentrations indicated above, the products remain active when added to the cultures two hours after the inoculation of the virus.

In a culture of human HeLa cells and against human rhinovirus strains HGP (type 2), DC (type 9) and GT (type 43), the maximum non-cytotoxic concentration is 20 μg./cc. and complete inhibition of the cytopathogenic effect of these three viruses manifests itself at a concentration of 10 μg./cc. (minimum tested concentration).

In the case of strain DC (type 9) at a concentration of 10 μg./cc. in cultures of human HeLa cells the products cause a reduction of 4.5 log of the infectious strength of the virus in relation to comparison cultures (strengths measured 5 days after inoculation of the virus); in the case of strain GT (type 43), under the same experimental conditions, the reduction in strength caused by the presence of the products is 1 log.

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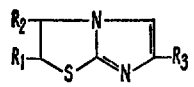
2,6 - diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole	1 g.
olive oil	5 cc.
mixture of polyhydroxyethers of fatty alcohols of high molecular weight	3 g.
mixture of monooleic esters of polyhydroxyethylated sorbitan	1 g.

The solution thus obtained is thereafter sterilised by filtration and then dispersed in a sterile isotonic solution of sodium chloride sufficient to make 100 cc. An oily emulsion containing 1% of 2,6 - diphenyl - 3 - methyl-2,3 - dihydro - imidazo[2,1 - b]thiazole is thus obtained.

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WHAT WE CLAIM IS:—

1. Imidazo[2,1 - b]thiazole derivatives of the general formula:



wherein R_1 represents a hydrogen atom or a phenyl group, R_2 represents a hydrogen atom or a methyl group, and R_3 represents a hydrogen atom or a phenyl or hydroxyphenyl group, and acid addition salts thereof.

2. 2,6 - Diphenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole and acid addition salts thereof.

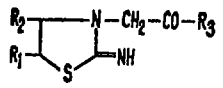
3. 2,6 - Diphenyl - 2,3 - dihydro - imidazo [2,1 - b]thiazole and acid addition salts thereof.

4. 2 - Phenyl - 3 - methyl - 2,3 - dihydro - imidazo[2,1 - b]thiazole and acid addition salts thereof.

5. 2 - Phenyl - 3 - methyl - 6 - (4 - hydroxyphenyl) - 2,3 - dihydro - imidazo [2,1 - b]thiazole and acid addition salts thereof.

6. 3 - Methyl - 6 - phenyl - 2,3 - dihydro-imidazo[2,1 - b]thiazole and acid addition salts thereof.

7. Process for the preparation of imidazo [2,1 - b]thiazole derivatives as claimed in claim 1 which comprises the cyclisation by heating of a thiazolidine of the general formula:



wherein R_1, R_2 and R_3 are as defined in claim 1, or an acid addition salt thereof.

8. A process according to claim 7 in which the cyclisation is effected by heating the thiazolidine in aqueous or organic solution at a temperature between 40° and 120°C.

9. Process according to claim 7 or 8 in which the cyclisation is carried out in the presence of a concentrated inorganic acid.

10. Process according to claim 9 in which the inorganic acid is hydrochloric acid.

11. Process according to any one of claims 7 to 10 followed by the step of converting an imidazo[2,1 - b]thiazole base obtained into an acid addition salt.

12. Process for the preparation of imidazo [2,1 - b]thiazole derivatives of the formula specified in claim 1 substantially as described in Example 1.

13. Process for the preparation of imidazo [2,1 - b]thiazole derivatives of the formula specified in claim 1 and acid addition salts thereof substantially as described in any one of Examples 2 to 5.

14. Imidazo[2,1 - b]thiazole derivatives of the formula specified in claim 1, and acid addition salts thereof, when prepared by the process claimed in any one of claims 7 to 13.

15. Pharmaceutical compositions which comprise, as active ingredient, at least one imidazo [2,1 - b]thiazole derivative as claimed in any one of claims 1 to 6, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier or coating.

16. Pharmaceutical compositions according to claim 15 substantially as hereinbefore described with especial reference to Example 6, 7 or 8.

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