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SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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Evento : 379
Actuación: 538

Referencia : Expediente No. 03.108.302

Asunto : Solicitud de patente para DERIVADOS
DE IMIDAZOTRIACINONAS Y SU USO
CONTRA PROCESOS INFLAMATORIOS Y/
ENFERMEDADES INMUNITARIAS

Solicitante : BAYER HEALTHCARE AG

Fecha de solicitud : 10 de Diciembre 2003

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 05-87.541 por valor de \$186.000.00, que corresponde a la tasa fijada según lo dispuesto en la Resolución No. 31980 del 24 de diciembre de 2004.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 23 NOV. 2005
Señora Jefe,



EMILIO FERRERO
T.P.A. No. 31.929

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FCC/FCC/ID-000164/WPC14033

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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Ob 14033-841-001-6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	27496710	15/11/2005	56,100,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	186,000.00
		TOTAL :	\$ 186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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United States Patent [19]

Hartley et al.

(10)

[11]

4,278,673

[49]

Jul. 14, 1981

[34] PHARMACOLOGICALLY ACTIVE COMPOUNDS

[75] Inventors: David Hartley, Ware; Alexander W. Oxford, Royston, both of England

[73] Assignee: Allen & Hanbury Limited, London, England

[21] Appl. No.: 72,898

[22] Filed: Sep. 4, 1979

Related U.S. Application Data

[63] Continuation of Ser. No. 888,522, Mar. 21, 1979, abandoned.

[30] Foreign Application Priority Data

Mar. 25, 1977 [GB] United Kingdom 12598/77

Nov. 14, 1977 [GB] United Kingdom 47230/77

[51] Int. Cl.³ C07D 487/04; A61K 31/415

[52] U.S. Cl. 434/249; 544/184

[56] Field of Search 544/184; 434/249

[36] References Cited

U.S. PATENT DOCUMENTS

3,941,785 3/1976 Clark et al. 544/184

FOREIGN PATENT DOCUMENTS

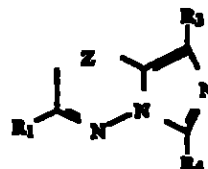
1400999 7/1975 United Kingdom 544/184

Primary Examiner—John M. Ford

Attorney, Agent, or Firm—Bacon & Thomas

[37] ABSTRACT

There are provided compounds of the general formula (I):



and physiologically acceptable salts thereof in which Z represents a group



wherein R3 represents a hydrogen atom or a straight or branched chain alkyl radical, or Z can additionally represent a group



and R1, R3 and R4, which may be the same or different, each represent a hydrogen atom, a cycloalkyl group, an aryl group which may optionally be substituted by one or more hydroxy, alkoxy, or halogen radicals, or a straight or branched alkyl or alkenyl group, which alkyl or alkenyl group may be substituted with an aryl group, which aryl group may optionally be substituted by one or more hydroxy, alkoxy or halogen radicals. The compounds possess spasmolytic and cAMP phosphodiesterase inhibitory activity.

14 Claims, No Drawings

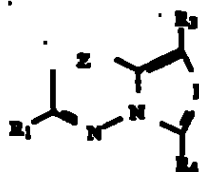
PHARMACOLOGICALLY ACTIVE COMPOUNDS

This is a continuation, of application Ser. No. 888,522, filed Mar. 21, 1978, now abandoned.

This invention relates to certain heterocyclic compounds having pharmacological activity, and to processes for the preparation thereof, as well as to pharmaceutical compositions containing them, and their use in medical treatment.

We have found that certain imidazo [5,1-f]-1,2,4-triazines and derivatives thereof possess spasmolytic and cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitory activity. They are therefore particularly useful as bronchodilators in the treatment of diseases involving constriction of bronchial muscle, for example, asthma and bronchitis. The compounds may also be useful for the treatment of pulmonary oedema and congestive heart failure, and for topical application as in the treatment of skin disorders, for example psoriasis.

The present invention therefore provides compounds of the general formula I:



and physiologically acceptable salts thereof in which Z represents a group



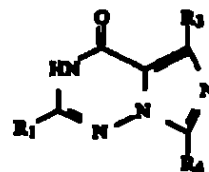
wherein R3 represents a hydrogen atom or a straight or branched chain alkyl radical, or Z can additionally represent a group



and R1, R3 and R4, which may be the same or different, each represent a hydrogen atom, a cycloalkyl group, an aryl group which may optionally be substituted by one or more hydroxy, alkoxy or halogen radicals, or a straight or branched alkyl or alkenyl group, which alkyl or alkenyl group may be substituted with an aryl group, which aryl group may in turn optionally be substituted by one or more hydroxy, alkoxy or halogen radicals. When Z represents the group



the compound may exist in its tautomeric form as a lactam (II) and such tautomeric forms are within the scope of the invention



(II)

The term alkyl preferably refers to a group containing 1 to 6 carbon atoms, in particular 1 to 4 carbon atoms; and the term alkenyl a group containing 2 to 6, in particular 3 to 5 carbon atoms. The term aryl preferably indicates phenyl. Cycloalkyl preferably means a group which contains 3 to 7 carbon atoms. The term alkoxy preferably refers to a group containing 1 to 4 carbon atoms and the term halogen radicals preferably refers to fluorine or chlorine groups.

Particularly preferred meanings for the groups R1-R4 are as follows:

R1 is hydrogen; alkyl, preferably methyl, ethyl or isopropyl; aryl, preferably phenyl; or aralkyl, preferably benzyl or phenethyl;

R2 is hydrogen or alkyl, preferably methyl;

R3 is alkyl, preferably methyl; or aryl, preferably phenyl; and

R4 is alkyl, preferably methyl, propyl or isobutyl; or cycloalkyl, preferably cyclopentyl.

Particularly preferred compounds are:

2,5-dimethyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine-4(3H)-one, 3,4-dihydro-2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine and 3,4-dihydro-7-(2-methylpropyl)-2,4,5-trimethylimidazo[5,1-f]-1,2,4-triazine, and physiologically acceptable salts thereof.

The spasmolytic activity of the compounds of the invention was demonstrated by their abilities in the isolated guinea-pig tracheal strip preparation to relax spontaneous tone and to reverse the spasmogenic action of methacholine (R. F. Coburn and T. Tomita. Am. J. Physiol., 1973, 224, 1072-1080). In the anaesthetised guinea-pig the compounds reduce intratracheal pressure (G. W. Lynn-James, J. Pharm. Pharmacol., 1969, 21, 379-386).

The ability of compounds according to the invention to inhibit the cAMP phosphodiesterase was demonstrated on an enzyme preparation from human lung on the basis of the method described by T. R. Russell, W. L. Teranski and M. M. Appleman (1973) J. Biol. Chem. 248, 1334-1340.

In addition compounds in which Z is

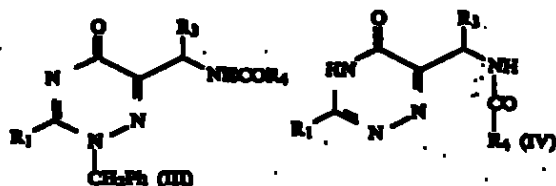


have the advantage that they selectively reduce intratracheal pressure without increasing heart rate in the anaesthetised guinea-pig. They also exhibit an interesting profile of action in that at low concentrations they cause a spasmolytic effect resulting from enhanced intracellular levels of cAMP but this effect is due neither to stimulation of β -adrenoceptors nor to inhibition of cAMP phosphodiesterase. Inhibition of cAMP phosphodiesterase occurs at much higher concentrations than those required to cause a spasmolytic action. Thus, the ratio of spasmolytic activity to cAMP phosphodiesterase inhibitory activity is high.

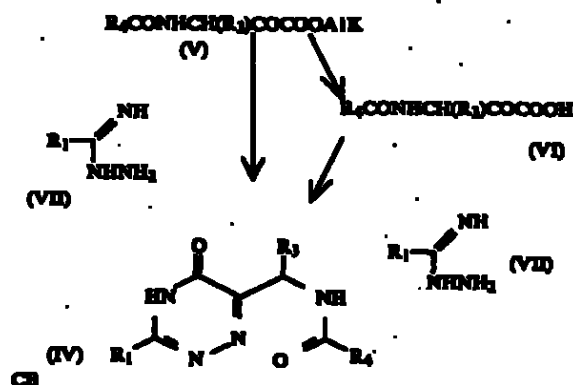
Intracellular levels of cAMP were measured on the basis of the procedure described by B. L. Brown, J. D. M. Albano, R. P. Elms and A. M. Scherri (Biochem. J. 1971, 121, 561-2).

The compounds according to the invention may conveniently be prepared by methods analogous to those described in U.K. Patent Specification Nos. 1,400,999 and 1,457,873.

Thus a compound of the invention as represented by formula II may be prepared by treating a compound of formula III, wherein R_1 , R_3 and R_4 have the meanings given above, with a suitable cyclodehydrating agent capable of concomitant N-debenzylation under the conditions of the reaction, such as phosphorus oxychloride, optionally in the presence of a solvent such as a halogenated hydrocarbon, for example dichloroethane. Alternatively the compound III may be converted into compound IV by removal of the benzyl group by for example hydrogenolysis in the presence of a noble metal catalyst. The reaction of IV with a suitable cyclodehydrating reagent such as polyphosphoric acid or phosphorus oxychloride or polyphosphoric ester then gives the required compound II. Again this reaction may optionally be carried out in the presence of a solvent, for example dichloroethane.



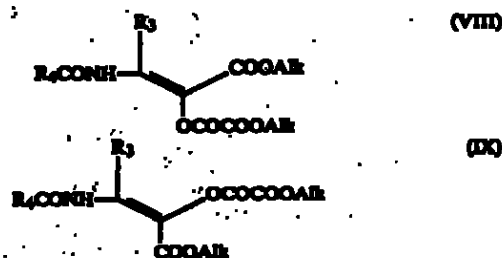
In addition to the routes described in U.K. Patent Specification No. 1,400,999 the compound IV may be prepared by the novel route which is described below with reference to the reaction scheme given.



In this process an α -ketoester (V) is subjected to reaction with an appropriate amidrazone (VII) in a suitable solvent such as ethanol. The amidrazone (VII) is conveniently generated in situ by treatment of the corresponding amidine hydrochloride with hydrazine. Alternatively the triazolinone (IV) may be prepared by treatment of the α -ketoester (V) with an appropriate amidrazone hydrochloride, again suitably in a solvent such as ethanol. In a further alternative process the α -ketoester may first be converted into the corresponding keto acid (VI) which is then transformed into the triazolinone (IV). This novel route has the advantage that

it involves less steps than the previously described routes.

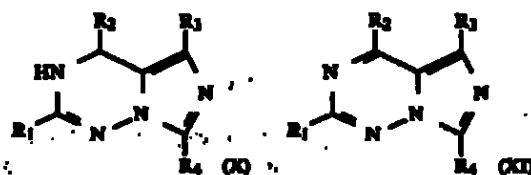
The keto ester (V) may be prepared from an N-acyl amino acid of the formula $R_2\text{CONHCH}(R_3)\text{COOH}$. This is reacted with a suitable acid chloride conveniently an alkyl oxalyl chloride in the presence of a suitable base such as pyridine, 4-dimethylaminopyridine or piperidine, according to the conditions of the Dakin-West reaction but with isolation of the intermediate isomeric enol esters of the formulae (VIII) and (IX):



These esters may then be hydrolysed, for example, with a mild acid or base to the α -ketoester of formula (V).

The compounds of the invention as represented by formula (X) below, in which R_2 represents a hydrogen atom may be prepared by reduction of the compounds of formula (II). Suitable reducing agents include diborane or complex metal hydrides such as lithium aluminium hydride and sodium dihydro-bis(2-methoxyethoxy) aluminium. The reaction is carried out in an aprotic solvent, for example tetrahydrofuran, ether, dimethoxyethane or diglyme, and if desired with heating.

The compounds of the invention, as represented by formula (XI) below, in which R_2 represents a hydrogen atom may be prepared by dehydrogenation of the compound (X) in which R_2 represents hydrogen. The dehydrogenation may be carried out using an oxidising agent for example potassium ferrioxalate or by heating with palladium oxide on charcoal in an inert solvent, preferably a high boiling inert solvent such as p-cymene or decalin.



Compounds of formula (X) in which R_2 represents an alkyl group may conveniently be prepared by reacting a compound of formula (XI) in which R_2 represents hydrogen with a metal alkyl such as a lithium alkyl or a Grignard reagent, conveniently in a solvent such as diethyl ether or tetrahydrofuran. Dehydrogenation of the compounds (X) in which R_2 represents alkyl using the conditions referred to above gives the corresponding compound (XI) in which R_2 represents alkyl.

The compounds according to the invention may be formulated for use in human and veterinary medicines for therapeutic and prophylactic purposes. They may be used in the form of their physiologically acceptable salts, in particular acid addition salts, if desired. Preferred salts include the hydrochloride, sulphate, male-

ate, tartrate etc. Such compounds may be presented for use in the conventional manner with the aid of carriers or excipients and formulating agents as required, and with or without supplementary medicinal agents. The compositions may include solid and liquid preparations for oral use, suppositories or injections, or forms suitable for administration by inhalation. Convenient oral presentations are in the form of tablets. Injections may be formulated with the aid of physiologically acceptable carriers and agents as solutions, suspensions or as dry products for reconstitution before use. For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, or as a cartridge from which the powdered composition may be inhaled with the aid of a suitable device. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. A typical dose for treating asthma in humans is from 1-1200 mg. depending on the age, weight and condition of the patient and the route of administration.

The compounds according to the invention may be formulated in combination with compounds that have stimulant activity at the β -adrenoceptors such as a salbutamol, isoprenaline, clenbuterol, procaterol and terbutaline etc. The provision of therapeutic compositions comprising as active ingredients, a compound according to the invention and a β -adrenoceptor stimulant, in particular salbutamol, represents an important aspect of the invention.

The following Examples illustrate the invention. Examples 1, 2 and 3 describe the production of intermediates and illustrate the novel route herein referred to.

EXAMPLE 1

Ethyl 3-isovaleramido-2-oxo-butyrates

Ethyl oxalyl chloride (212 g) was added dropwise with stirring to a solution of isovalerylalanine (136 g) and pyridine (186.5 g) in anhydrous tetrahydrofuran (300 ml) at a rate sufficient to initiate refluxing. The reaction mixture was stirred and heated at reflux for 5 hours. The cooled reaction mixture was treated with water (1000 ml) and extracted with ethyl acetate (4x400 ml). The combined organic extracts were washed with water (3x200 ml) and dried (anhydrous sodium sulphate). Removal of solvent provided a yellow syrup which was evaporated with benzene (2x200 ml) to yield the isomeric enol esters of the title compound.

These were dissolved in absolute ethanol (400 ml) and heated at reflux in the presence of sodium bicarbonate (70 g) for 3 hours. After cooling, the sodium bicarbonate was filtered off and the filtrate was evaporated in vacuo. The resultant residue was taken up in ethyl acetate (300 ml) and washed with water (4x100 ml). The dried (anhydrous sodium sulphate) ethyl acetate phase was evaporated in vacuo to provide crude α -ketoester as a golden syrup, 147 g.

(i) In a similar manner was prepared ethyl 3-cyclopentanecarbonamido-2-oxobutyrate as an oil from N-(cyclopentylcarbonyl)-alanine (5.55 g), the oil was used directly in the next stage.

(ii) In a similar manner was prepared ethyl 3-butyramido-2-oxo-3-phenylpropionate (7.6 g) as an oil, from butyryl α -phenylglycine (22.1 g).

EXAMPLE 2

(i) 6-(1-isovaleramidoethyl)-3-(1-methylethyl)-1,2,4-triazin-5(4H)-one

Isobutyrylamidine hydrochloride (4.5 g) was dissolved in absolute ethanol (25 ml) and the solution cooled in ice. Hydrazine hydrate (1.84 g) in absolute ethanol (5 ml) was added dropwise (25 min) with stirring. After completion of the addition stirring was continued at room temperature for 10 minutes. A solution of ethyl 3-isovaleramido-2-oxobutyrate (8.45 g) in absolute ethanol (20 ml) was added and the mixture heated at 50°-60° C. for 26 hours. The reaction mixture was concentrated in vacuo, triturated with ethyl acetate and the resultant crystalline triazinone collected by filtration, washed thoroughly with water and dried. The ethyl acetate solution was concentrated and applied to a column of silica gel. Elution with ethyl acetate containing 2-5% ethanol provided a further quantity of the triazinone. The product was recrystallised from ethyl acetate, 1.72 g, m.p. 203°-265°.

(ii) In a similar manner was prepared 3-benzyl-6-(1-isovaleramidoethyl)-1,2,4-triazin-5(4H)-one, 10 g, m.p. 190°-193° (from ethanol-ethyl acetate) from phenylacetamidine hydrochloride (29.5 g) and ethyl 3-isovaleramido-2-oxobutyrate (42.1 g).

(iii) In a similar manner was prepared 6-(1-cyclopentanecarbonamidoethyl)-3-methyl-1,2,4-triazin-5(4H)-one, 1.02 g, m.p. 211°-214° (from ethyl acetate) from acetamidine hydrochloride (1.89 g) and ethyl 3-cyclopentanecarbonamido-2-oxobutyrate.

(iv) In a similar manner was prepared 6-(1-isovaleramidoethyl)-1,2,4-triazin-5(4H)-one (12.0 g) [the hydrochloride had m.p. 167°-169° (from ethanol-ethyl acetate)], from formamidine acetate (41.75 g) and ethyl 3-isovaleramido-2-oxobutyrate (127.4 g).

(v) In a similar manner was prepared 6-(1-butyramidoethyl)-3-ethyl-1,2,4-triazin-5(4H)-one, 13.4 g, m.p. 174°-177° (from ethanol) from propionamidine hydrochloride (48.8 g) and ethyl 3-butyramido-2-oxobutyrate (96.8 g).

(vi) In a similar manner was prepared 3-benzyl-6-(1-butyramidoethyl)-1,2,4-triazin-5(4H)-one, 7.81 g, m.p. 173.5°-177° (from ethanol) from phenacetamidine hydrochloride (40.26 g) and ethyl 3-butyramido-2-oxobutyrate (89.5 g).

(vii) In a similar manner was prepared 6-(1-butyramidoethyl)-3-(2-phenylethyl)-1,2,4-triazin-5(4H)-one, 5.56 g, m.p. 201°-201.5° (from ethanol) from 3-phenylpropionamidine hydrochloride (12.27 g) and ethyl 3-butyramido-2-oxobutyrate (25 g).

(viii) In a similar manner was prepared 6-butyramido-benzyl-3-methyl-1,2,4-triazin-5(4H)-one (1.36 g), m.p. 210°-212° (from ethyl acetate), from acetamidine hydrochloride (2.66 g) and ethyl 3-butyramido-2-oxo-3-phenylpropionate (7.8 g).

EXAMPLE 3

(i) 6-(1-Butyramidoethyl)-3-methyl-1,2,4-triazin-5(4H)-one

Acetamidrazone hydroiodide (6.63 g) was heated with ethyl 3-butyramido-2-oxobutyrate (7.01 g) in absolute ethanol (40 ml) at 80° for 50 minutes. The dark red solution was concentrated to a viscous oil which was triturated with ethyl acetate to give the triazinone as a yellow solid (1.65 g). The filtrate was concentrated and chromatographed on silica gel. Fractions eluted with ethyl acetate-ethanol (4:1) afforded a second crop (0.31

g). The two crops were combined and recrystallized from ethanol to give material, m.p. 235°-237.5°, 1.69 g.

(h) In a similar manner was prepared 6-(1-isovaleramidoethoxy)-3-phenyl-1,2,4-triazin-5(4H)-one, 6.2 g, m.p. 236°-238°, from benzamidine hydrochloride (26.4 g) and ethyl 3-isovaleramido-2-oxobutyrate (22.9 g).

EXAMPLE 4

(i) 2-(1-Methylethoxy)-5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one, hydrochloride 6-(1-isovaleramidoethoxy)-3-(1-methylethoxy)-1,2,4-triazin-5(4H)-one (1.55 g) was added with stirring to polyphosphoric acid (15 g) at 150°. After complete dissolution of the added triazinone derivative the reaction mixture was maintained at 150° with occasional stirring for 1 hour. The cooled reaction mixture was then added to ice-water and the solution adjusted to pH 7.5 by addition of 8% aqueous sodium bicarbonate solution. The precipitated product was collected by filtration and recrystallized from ether to give 0.81 g of the product, m.p. 135°-137°. This was converted into a hydrochloride salt, m.p. 208°-211° (from ethanol-ethyl acetate).

(ii) In a similar manner was prepared 5-methyl-2-phenyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one, 0.4 g, m.p. 253°-255° (from ethyl acetate) from 6-(1-isovaleramido)ethyl-3-phenyl-1,2,4-triazin-5(4H)-one (0.7 g).

(iii) In a similar manner was prepared 2-methyl-5-phenyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one (0.26 g) m.p. 190°-191° (from ethyl acetate) from 6-butyramidobenzyl-3-methyl-1,2,4-triazin-5(4H)-one (0.70 g).

(iv) In a similar manner was prepared 2-benzyl-5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one (1.26 g), m.p. 164°-165° (from ethyl acetate) (the hydrochloride had m.p. 236.5°-240° from ethanol-ethyl acetate), from 3-benzyl-6-(1-isovaleramidoethoxy)-1,2,4-triazin-5(4H)-one (2.0 g).

(v) In a similar manner was prepared 7-cyclopentyl-2,5-dimethylimidazo[5,1-f]triazin-4(3H)-one, 0.4 g, m.p. 208°-210° (from ethyl acetate) (the hydrochloride salt had m.p. 272°-274°, from ethanol), from 6-(1-cyclopentylcarbamidoethoxy)-3-methyltriazin-5(4H)-one (0.7 g).

(vi) In a similar manner was prepared 5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one, 0.12 g, m.p. 227°-229° (from ether), (the hydrochloride salt had m.p. 184°-186° from ethanol-ethyl acetate) from 6-(1-isovaleramidoethoxy)-1,2,4-triazin-5(4H)-one (0.4 g).

(vii) In a similar manner was prepared 2-ethyl-5-methyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one, 4.6 g, m.p. 215°-217° (from ethyl acetate) (the hydrochloride had m.p. 212°-213°, from ethanol-ethyl acetate) from 6-(1-butyramidoethoxy)-3-ethyl-1,2,4-triazin-5(4H)-one (11.9 g).

(viii) In a similar manner was prepared 2-benzyl-5-methyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one, 5.14 g, m.p. 156°-157° (from ethyl acetate) (the hydrochloride salt had m.p. 247.5°-249.5° from ethanol-ethyl acetate), from 2-benzyl-6-(1-butyramidoethoxy)-1,2,4-triazin-5(4H)-one (6.45 g).

(ix) In a similar manner was prepared 2-(2-phenylethyl)-5-methyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one, 8.78 g, m.p. 156°-159.5° (from ethyl acetate) (the hydrochloride salt had m.p. 198.5°-200.5° from

ethanol-ethyl acetate) from 6-(1-butyramidoethoxy)-3-(2-phenylethoxy)-1,2,4-triazin-5(4H)-one (13.22 g).

EXAMPLE 5

2,5-Dimethyl-7-isobutylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one

(a) 6-(1-isovaleramidoethoxy)-3-methyl-1,2,4-triazin-5(4H)-one

Hydrazine hydrate (100%, 78 ml; 80 g) in absolute ethanol (40 ml) was added with stirring over a period of 15 minutes to a solution of acetamidine hydrochloride (151 g) in absolute ethanol (1200 ml) cooled to 5°. The mixture was stirred for a further 10 minutes, then ethyl-3-isovaleramido-2-oxobutyrate [prepared by hydrolysis of the enol esters (335 g) as in Example 1(i)] in absolute ethanol (200 ml) was added and heated at 70°-80° with stirring for 20 hours. After cooling the mixture to room temperature, ammonium chloride was removed by filtration and the filtrate concentrated and diluted with ethyl acetate (250 ml) to precipitate the triazinone (94.0 g). The filtrate on standing deposited a second crop (6.7 g). Two recrystallizations from ethanol gave a sample of m.p. 224°-226°.

(b) 2,5-Dimethyl-7-isobutylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one

6-(1-isovaleramidoethoxy)-3-methyl-1,2,4-triazin-5(4H)-one (91.6 g) was added portionwise with stirring to polyphosphoric acid (800 g), heated to 150°. All the solid dissolved in about 15 minutes, and the mixture was then cooled to 100° and poured onto ice water (3 liters). The solution was brought to pH 7 by addition of sodium carbonate and the imidazotriazinone precipitated and was collected. The filtrate was extracted with ethyl acetate (3 liters) to give a second crop which was combined with the first and recrystallized from ethyl acetate to give white needles m.p. 186°-188°, 53.1 g.

The hydrochloride salt had m.p. 227°-229° from ethyl acetate-ethanol.

EXAMPLE 6

2,5-Dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one

A mixture of 6-(1-butyramido)ethyl-3-methyl-1,2,4-triazin-5(4H)-one (1.47 g) and phosphorus oxychloride (5 ml) in 1,2-dichloroethane (40 ml) was heated under reflux for 2 hours. The solvent was removed in vacuo and to the residue was added 2 N sodium carbonate (50 ml) and ethyl acetate (30 ml) and the mixture vigorously stirred until all the solid dissolved. The organic layer was separated and the aqueous solution extracted further with ethyl acetate (2×30 ml). The extracts were then combined and dried. Removal of the solvent gave the imidazotriazinone as an off-white solid (1.30 g). Recrystallization from ethyl acetate gave a sample m.p. 229.5°-234°, 1.03 g.

EXAMPLE 7

(i) 2,5,7-Trimethylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one

(a) 2,5-Dihydro-3,α-dimethyl-5-oxo-1,2,4-triazine-6-acetic acid, ethyl ester

Hydrazine hydrate (100%, 78 ml) was added dropwise with stirring to a solution of acetamidine hydrochloride (151 g) in absolute ethanol (1.2 liters) keeping the temperature at 0° to -2°. The addition was complete after 15 minutes. The mixture was stirred for a further 15 minutes and then the cooling bath was removed. Diethyl oxalopropionate (322.5 g) was added

and the temperature rose to 30°. The mixture was heated at this temperature for 30 minutes, then at 80° for 3½ hours. The dark yellow solution was cooled, filtered to remove ammonium chloride and concentrated to an oil. This was taken up into cold water (1 liter) and the yellow solid that separated was removed by filtration and discarded. The filtrate was extracted with cyclohexane to remove unchanged diethyl oxalopropionate and then with ethyl acetate (7×200 ml) and continuously for 46 hours to give an oil which on trituration with ether gave the triazinone as a pale yellow solid, 118.4 g, m.p. 127.5°–129° (from ethyl acetate-cyclohexane).

(b) 2-Benzyl-2,5-dihydro-3,α-dimethyl-1,5-oxo-1,2,4-triazine-6-acetic acid, ethyl ester

Benzyl chloride (4.0 g), sodium iodide (4.73 g), 2,5-dihydro-3,α-dimethyl-5-oxo-1,2,4-triazine-6-acetic acid, ethyl ester (6.3 g) and finely powdered anhydrous potassium carbonate (4.34 g) were stirred together in ethyl methyl ketone (300 ml) heated under reflux for 2½ hours. The solution was filtered to remove inorganic material and concentrated to an oil. This was taken up into ethyl acetate (400 ml) and the solution was washed with water (2×100 ml) and dried. Removal of the solvent gave an oil which solidified on trituration with ether and cyclohexane. Recrystallization from ethyl acetate-ether gave the benzylated triazinone as prisms, 4.74 g, m.p. 94.5°–98°.

(c) 2-Benzyl-2,5-dihydro-3,α-dimethyl-5-oxo-1,2,4-triazine-6-acetic acid, hydrazide

2-Benzyl-2,5-dihydro-3,α-dimethyl-5-oxo-1,2,4-triazine-6-acetic acid, ethyl ester (60.0 g) was taken up in methanol (600 ml) and the solution, chilled in ice, was treated with hydrazine hydrate (200 ml), added dropwise with stirring over a period of 10 minutes. The solution was kept at room temperature for 16 hours and then concentrated to a yellow crystalline mass. Azeotropic distillation with toluene removed residual traces of hydrazine. Recrystallization from isopropanol afforded the hydrazide as needles, 19.79 g, m.p. 171°–174°.

(d) 6-(1-Aminomethyl)-2-benzyl-3-methyl-1,2,4-triazin-5(4H)-one

Sodium nitrite (1.29 g) in water (25 ml) was added to a stirred solution of 2-benzyl-2,5-dihydro-3,α-dimethyl-5-oxo-1,2,4-triazine-6-acetic acid, hydrazide (5.0 g) in conc. hydrochloric acid (3.3 ml) and water (75 ml) keeping the temperature at –1° to –2°. The azide separated as a white solid which rapidly became a thick gum. Conc. hydrochloric acid (5 ml) was added and the mixture was raised to 65° over 30 minutes and left at this temperature for 2 hours. During this period the gum gradually dissolved to give a clear yellow solution. This was cooled and brought to pH 8 by the addition of sodium bicarbonate. Water was removed by rotary evaporation and the residual solid was extracted with boiling isopropanol (6×100 ml). The extract was filtered and concentrated to give the amine as a gum (4.37 g) which failed to crystallize.

(e) (i) 6-(1-Acetamidomethyl)-2-benzyl-3-methyl-1,2,4-triazin-5(4H)-one

Dry dioxan (80 ml) was added to 6-(1-aminomethyl)-2-benzyl-3-methyl-1,2,4-triazin-5(4H)-one (4.34 g) and the cloudy suspension stirred at room temperature was treated with acetic anhydride (1.9 ml). The mixture was stirred for 2 hours then concentrated to a brown solid. Recrystallization from ethanol-ether afforded the acetamide, 3.1 g, m.p. 196°–203°.

(ii) In a similar manner was prepared 2-benzyl-6-(1-butyramidomethyl)-3-methyl-1,2,4-triazin-5(4H)-one, 6.55 g, m.p. 168°–169° (from ethyl acetate) by acylation of 6-(1-aminomethyl)-2-benzyl-3-methyl-1,2,4-triazin-5(4H)-one (8.66 g) with butyric anhydride.

(f) (i) 2,5,7-Trimethylimidazo[3,1-f]-1,2,4-triazin-4(3H)-one

Phosphorus oxychloride (5 ml) was added to a cloudy solution of 6-(1-acetamidomethyl)-2-benzyl-3-methyl-1,2,4-triazin-5(4H)-one (1.5 g) in 1,2-dichloroethane (25 ml). There was a slight exothermic reaction, the solution darkened and a dark yellow gum separated. The mixture was heated to boiling over 10 minutes then refluxed for 10 minutes. During this period the gum dissolved to give a dark yellow solution which was cooled and poured onto ice water (50 ml). The aqueous layer was basified with sodium bicarbonate and the mixture was extracted with ethyl acetate (2×100 ml, 8×50 ml). The extracts were dried and removal of the solvent gave the imidazotriazinone as a buff solid, 0.57 g, m.p. 322°–323° (from ethanol).

(ii) In a similar manner was prepared 2,5-dimethyl-7-propylimidazo[3,1-f]-1,2,4-triazin-4(3H)-one, 0.43 g, m.p. 232°–236° (from ethyl acetate) from 2-benzyl-6-(1-butyramidomethyl)-3-methyl-1,2,4-triazin-5(4H)-one (1.5 g).

EXAMPLE 8

(i) 3,4-Dihydro-2,5-dimethyl-7-isobutylimidazo[3,1-f]-1,2,4-triazine, maleate

Lithium aluminum hydride (2.3 g) was added in portions with stirring to anhydrous tetrahydrofuran (200 ml) under nitrogen. A solution of 2,5-dimethyl-7-isobutylimidazo[3,1-f]-1,2,4-triazin-4(3H)-one (3.0 g) in anhydrous tetrahydrofuran (150 ml) was added dropwise and the mixture stirred and heated gently under reflux for 16 hours.

After cooling to room temperature the excess of lithium aluminum hydride was destroyed by the sequential addition of water (2.3 ml), 15% sodium hydroxide solution (2.3 ml) and finally water (6.9 ml).

The resultant suspension was filtered through a diatomaceous earth and the filtrate concentrated under reduced pressure to an oil which crystallized on standing. The white crystals were filtered, recrystallized from ethyl acetate and dried in vacuo to give 3.9 g, m.p. 165°–168°.

This base was dissolved in a mixture of dry ether/ethyl acetate/trace ethanol (ca. 50 ml total volume) and added to a warm solution of maleic acid (1.2 g) in dry ether/ethyl acetate (50 ml). The suspension formed was concentrated to ca. 70 ml and cooled to room temperature. The white crystals were filtered off and recrystallized from isopropanol/dry ether to give 2.0 g, m.p. 145°–148°.

(ii) In a similar manner was prepared 3,4-dihydro-5-methyl-7-(2-methylpropyl)imidazo[3,1-f]-1,2,4-triazine, 0.22 g, m.p. 146.5°–149° (from ether) from 5-methyl-7-(2-methylpropyl)imidazo[3,1-f]-1,2,4-triazin-4(3H)-one (1.3 g) in 1,2-dimethoxyethane.

(iii) In a similar manner was prepared 3,4-dihydro-2-ethyl-5-methyl-7-propylimidazo[3,1-f]-1,2,4-triazine, 1.03 g, m.p. 115°–117° (from ethyl acetate) (the hydrochloride salt had m.p. 234°–235° from ethanol-ethyl acetate) from 2-ethyl-5-methyl-7-propylimidazo[3,1-f]-1,2,4-triazin-4(3H)-one (3.49 g) in 1,2-dimethoxyethane.

(iv) In a similar manner was prepared 3,4-dihydro-5-methyl-2-(2-phenylethyl)-7-propylimidazo[3,1-f]-1,2,4-

triazine, 1.81 g, m.p. 115°-116.5° (from ether) (the hydrochloride salt had m.p. 171°-171.5° from ethanol-ethyl acetate) from 5-methyl-2-(2-phenylethyl)-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one (2.0 g) in 1,2-dimethoxyethane.

(v) In a similar manner was prepared 3,4-dihydro-2,5,7-trimethylimidazo[5,1-f]-1,2,4-triazine, 0.89 g, m.p. 250°-252° (from ethyl acetate) (the maleate salt had m.p. 178°-180° from ethanol-ethyl acetate) from 2,5,7-trimethylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one (1.07 g) in 1,2-dimethoxyethane.

EXAMPLE 9

(i) 2,5-Dimethyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine, maleate

3,4-Dihydro-2,5-dimethyl-7-isobutylimidazo[5,1-f]-1,2,4-triazine (1.5 g) was heated under reflux in p-cymene (100 ml) with 10% palladium oxide on charcoal (2.85 g) for 4 hours. After cooling to room temperature the mixture was filtered through a diatomaceous earth and the catalyst washed with ethyl acetate. The filtrate and washings were extracted with 2 N hydrochloric acid (3×75 ml) and the extract washed with ethyl acetate (3×75 ml) and basified with solid sodium carbonate. The oily layer which separated was extracted into ethyl acetate (3×75 ml) and dried over magnesium sulphate. Removal of the solvent gave an orange oil (1.8 g). This material was absorbed on to silica gel (29 g) and eluted with ethyl acetate to give the product as a gum (1.0 g).

This material was taken up in anhydrous ether (20 ml) and added dropwise with stirring to a solution of maleic acid (0.7 g) in anhydrous ether (50 ml). The orange oil which separated slowly crystallised. Two recrystallisations from dry ether/ethyl acetate gave the monophosphate maleate salt (0.68 g) m.p. 100°-103°.

(ii) In a similar manner was prepared 2-benzyl-5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine, 0.2 g, m.p. 72.5°-74° (sublimed) from 2-benzyl-3,4-dihydro-5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine (0.95 g).

(iii) In a similar manner was prepared 5-methyl-7-(2-methylpropyl)-2-(1-methylethyl)imidazo[5,1-f]-1,2,4-triazine as an oil, 0.68 g [the hydrochloride salt had m.p. 144°-146° (dec.) from ethanol-ethyl acetate] from 3,4-dihydro-5-methyl-2-(1-methylethyl)-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine (1.5 g).

EXAMPLE 10

3,4-Dihydro-2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine, hydrochloride

(a) Ethyl-3-butyramido-2-oxo-butyrate

Ethyl oxalyl chloride (409.5 g) was added dropwise with stirring to a solution of butyrylalanine (238.5 g), anhydrous pyridine (355.5 g) and 4-dimethylaminopyridine (6 g) in anhydrous tetrahydrofuran (1 liter) at a rate sufficient to initiate refluxing. The mixture was heated to maintain a gentle reflux for 1½ hours, then cooled, diluted with water (1 liter) and extracted with ethyl acetate (3×500 ml). The extract was washed with water (2×250 ml) and dried (anhydrous sodium sulphate). Removal of the solvent gave a mixture of enol esters as an orange syrup. This material contained polar impurities which were removed by column chromatography in two batches. The crude product was absorbed onto silica gel (2×700 g) and eluted with cyclohexane-ethyl acetate (3:1) to give the purified enol esters (293 g).

This material was dissolved in absolute ethanol (270 ml) and heated at reflux in the presence of sodium bicarbonate (66 g) for 2½ hours. The mixture was cooled and sodium bicarbonate removed by filtration. The filtrate was concentrated to give the α-ketoester as a golden-yellow syrup which was used directly in the next stage.

(b) 6-(1-Butyramido)ethyl-3-methyl-1,2,4-triazin-5(4H)-one

To an ice-cold solution of acetamidine hydrochloride (66.2 g) in absolute ethanol (600 ml) was slowly added a solution of hydrazine hydrate (35 g) in absolute ethanol (20 ml) over 20 minutes. After completion of the addition stirring was continued at room temperature for 10 minutes. A solution of ethyl 3-butyramido-2-oxo-butyrate (151 g) in absolute ethanol (100 ml) was then added and the mixture heated at 65°-70° with stirring for 20 hours. The precipitated ammonium chloride was removed by filtration and the filtrate concentrated in vacuo whereupon the triazones separated. Ethyl acetate (ca. 300 ml) was added to aid the precipitation and the solid was collected. The filtrate was concentrated to give a second crop which was combined with the first and recrystallised from ethanol, 28.6 g. A further recrystallisation from ethanol afforded an analytical sample, m.p. 235°-237°.

(c) 2,5-Dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one

6-(1-Butyramido)ethyl-3-methyl-1,2,4-triazin-5(4H)-one (21.8 g) was added portionwise to polyphosphoric acid (220 g) at 160°. When all the solid had dissolved the mixture was heated for 1 hour with occasional stirring at 100°, then cooled and poured onto ice-water (ca. 1 liter). The pH was adjusted to ca. 7.5 by the addition of 8% sodium bicarbonate and the precipitated imidazotriazinone collected, dried and recrystallised from ethyl acetate. Extraction of the filtrate with ethyl acetate gave a second crop which was also recrystallised from ethyl acetate. Total yield: 16.2 g, m.p. 228°-231°.

The base (1.33 g) was dissolved in a minimum amount of absolute ethanol and ethereal hydrogen chloride added until the pH was 1-2. Dry ether was then added until precipitation ceased. The hydrochloride was collected and twice recrystallised from ethanol-ethyl acetate, m.p. 254°-258°, 0.79 g.

(d) 3,4-Dihydro-2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine, hydrochloride

Lithium aluminium hydride (5.5 g) was added portionwise under nitrogen to a suspension of 2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazin-4(3H)-one (16.6 g) in dry dimethoxyethane (450 ml). The addition was complete after 20 minutes. The mixture was heated at reflux for 2 hours, then cooled and treated sequentially with water (10 ml), 2 N sodium hydroxide (15 ml) and water (10 ml). The granular precipitate of aluminium salts was filtered off and the filtrate concentrated in vacuo. The partially crystalline residue was dissolved in ethyl acetate (200 ml) and the solution washed with water (25 ml) and dried (sodium sulphate). Removal of the solvent gave the dihydroimidazotriazinone. Recrystallisation twice from ethyl acetate gave white crystals m.p. 143°-149° (dec.), 11.4 g.

Part of the base (11.1 g) was dissolved in absolute ethanol (ca. 25 ml) and treated with ethereal hydrogen chloride until the solution was pH 2. Dry ether (ca. 100 ml) was added until precipitation ceased. The solid was collected and recrystallised from ethanol-ethyl acetate to give the hydrochloride salt, m.p. 251°-255°, 9.7 g.

EXAMPLE 11

3,4-Dihydro-7-(2-methylpropyl)-2,4,5-trimethylimidazo[5,1-f]-1,2,4-triazine

An ethereal solution (89 ml) of methyl magnesium iodide [prepared from methyl iodide (3.56 g) and magnesium turnings (0.6 g)] was added under nitrogen to a stirred solution of 2,5-dimethyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazine (2.5 g) in anhydrous ether (20 ml). The mixture was stirred at room temperature overnight and then aqueous ammonium chloride was added until all the solid dissolved. The ethereal layer was separated and the aqueous layer extracted further with ethyl acetate. The organic layers were combined and dried (anhydrous sodium sulphate). Removal of the solvent gave an orange solid. Recrystallisation from ethyl acetate-ether gave the adduct as a cream solid m.p. 164°-167°, 1.63 g.

The base (1.63 g) was dissolved in anhydrous ether (200 ml) and the solution cooled in an ice-bath and treated with ethereal hydrogen chloride, dropwise with stirring, until precipitation ceased. The hydrochloride was collected and recrystallised from ethanol-ethyl acetate to give material m.p. 198°-201.5°. A second recrystallisation gave m.p. 199°-206° (dec.), 1.47 g.

(II) In a similar manner was prepared 3,4-dihydro-2,4,5-trimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine, 1.31 g, m.p. 175°-179° (from ethyl acetate) (the hydrochloride salt had m.p. 224°-227° from ethanol-ethyl acetate) from 2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine (1.90 g).

EXAMPLE 12

2,5-Dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine

10% Palladium oxide on charcoal (2.2 g) was suspended in a solution of 3,4-dihydro-2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine (1.00 g) in p-cymene (100 ml) and the mixture was heated at reflux under nitrogen for 6 hours. The mixture was cooled and the catalyst removed by filtration through diatomaceous earth and washed thoroughly with hot ethanol. The filtrate and washings were combined and extracted with 2 N hydrochloric acid (2×75 ml). The extract was brought to pH 8 by the addition of aqueous sodium carbonate and extracted with ether (3×50 ml). The ethereal extract was dried (sodium sulphate) and concentrated and the residue absorbed onto silica gel. Elution with ethyl acetate afforded the imidazotriazine as a solid (0.56 g), which was sublimed at 50°-52°/0.02 mm Hg to give lemon yellow crystals m.p. 54°-56°.

Pharmaceutical Compositions

EXAMPLE 13

To prepare 10,000 capsules each containing 5 mg of active ingredient

Mix together 50 g powdered active ingredient with a sufficient quantity of microcrystalline cellulose BPC and fill into No. 3 hard gelatin capsules so that each capsule contains about 120 mg of the mixture.

Capsules may be similarly prepared each containing 10 mg active ingredient.

EXAMPLE 14

To prepare 5,000 tablets each containing 2 mg active ingredient

Mix together 10 g active ingredient, 585 g microcrystalline cellulose BPC, 5 g magnesium stearate and 5 g stearic acid. Compress the powders on a suitable tablet-

ting press to produce tablets each 6 mm in diameter and weighing about 120 mg.

Tablets of other strengths may be prepared similarly.

Tablets may also be prepared by a wet granulation process as follows:

To prepare 5,000 tablets each containing 2 mg active ingredient, mix together 10 g active ingredient, 498 g lactose BP, 60 g Maize starch BP and 30 g Prugelatinized maize starch BP. Add sufficient cold water to produce a damp cohesive mass and pass the mass through a No. 14 mesh BSS sieve and dry the resulting granules in an oven or fluid bed dryer at 60° C. Pass the dried granules through a No. 22 BSS sieve and mix with 2 g magnesium stearate BP. Compress the granules on a suitable tabletting press to produce tablets 6 mm in diameter weighing about 120 mg.

Tablets of other strengths may be prepared similarly. The tablets may be film coated with suitable film forming materials such as methyl cellulose, hydroxypropylmethyl cellulose or mixtures of the materials using standard techniques.

The tablets may also be sugar coated by the standard sugar coating techniques.

EXAMPLE 15

To prepare 10 liters of flavoured syrup containing 2 mg active ingredient in each 5 ml

Dissolve 5.5 kg sucrose BP in sufficient distilled water to produce 9 l. of syrup. Mix into the syrup 1 l. of glycerin and dissolve 4 g active ingredient, sufficient preservative, colour and flavour and filter through a suitable filter pad and distribute into bottles.

EXAMPLE 16

To prepare an injection containing 2 mg active ingredient in 5 ml

Dissolve 2 g active ingredient and 8.5 g sodium chloride in 950 ml water for injections. When solution is complete make up to 1 l. with more water for injection. Purge the solution with nitrogen and fill, under nitrogen, into suitable size ampoules (1 ml, 5 ml or 10 ml) seal and sterilise by heating in an autoclave.

EXAMPLE 17

To prepare suppositories each containing 2 mg active ingredient

Melt 4 kg of a suitable fatty suppository base and stir in 2 g active ingredient. Keeping the active ingredient suspended through the base by stirring, pour the mixture into suitable 4 g suppository moulds.

EXAMPLE 18

To prepare 1,000 pressurised aerosol cans each containing about 200 doses of 500 µg active ingredient per 85 mg shot

Micronise the active ingredient so that the majority of the crystals are between 1 and 5 µm in longest dimension and none are greater than 10 µm. Disperse 120 g of the micronised active ingredient in 5.7 kg of a 0.21% w/w solution of Oleic Acid BP in Propellant 11 BPC. Make this suspension up to 20.4 kg with Propellant 12 BPC and fill into suitable sized aerosol cans by standard techniques. Seal the cans with a suitable metering valve capable of delivering 85 mg of suspension with each actuation.

EXAMPLE 19

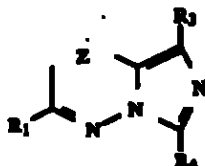
To prepare 10,000 cartridges for inhalation each containing 1 mg active ingredient

Micronize the active ingredient so that the majority of the crystals are between 1 μ m and 5 μ m in longest dimension and none are greater than 10 μ m. Disperse 10 g of the micronized active ingredient in 240 g lactose BP. Fill about 25 mg of the powder into No. 3 hard gelatin capsules.

In all the above examples of pharmaceutical compositions, the active ingredient is a compound according to the invention.

We claim:

1. A compound which is a imidazo[5,1-f]-1,2,4-triazine or a derivative thereof of the formula (I):



and physiologically acceptable salts thereof in which



wherein R₂ represents a hydrogen atom or a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms, or Z can additionally represent a group



and R₁, R₃ and R₄, which may be the same or different, each represent a hydrogen atom; a cycloalkyl group, said cycloalkyl group containing from 3 to 7 carbon atoms; a phenyl group which may optionally be substituted by one or more hydroxy, alkoxy or halogen radicals, said alkoxy radical containing from 1 to 4 carbon atoms; or straight or branched alkyl or alkenyl group, said alkyl group containing from 1 to 6 carbon atoms, said alkenyl group containing 2 to 6 carbon atoms, which alkyl or alkenyl group may be substituted with a phenyl group, which phenyl group may optionally be substituted by one or more hydroxy, alkoxy or halogen radicals, said alkoxy radical containing from 1 to 4 carbon atoms.

2. A compound as claimed in claim 1 in which Z represents a group of the formula:



in which R₁ represents methyl, R₂ represents hydrogen or methyl, R₃ represents methyl, and R₄ represents n-propyl or isobutyl, except that R₄ does not represent isobutyl when R₂ represents hydrogen.

3. A compound as claimed in claim 1 in which:

R₁ is hydrogen, alkyl or phenyl or phenylalkyl;

R₂ is hydrogen or alkyl;

R₃ is alkyl or phenyl;

R₄ is alkyl or cycloalkyl.

4. A compound as claimed in claim 3 in which:

R₁ is hydrogen, methyl, ethyl or isopropyl, phenyl, benzyl or phenethyl;

R₂ is hydrogen or methyl;

R₃ is methyl or phenyl;

R₄ is methyl, propyl or isobutyl, or cyclopentyl.

5. A compound as claimed in claim 1 selected from 2,5-dimethyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one and physiologically acceptable salts thereof.

6. A compound as claimed in claim 1 selected from 3,4-dihydro-2,5-dimethyl-7-propylimidazo[5,1-f]-1,2,4-triazine and physiologically acceptable salts thereof.

7. A compound as claimed in claim 1 selected from 3,4-dihydro-7-(2-methylpropyl)-2,4,5-trimethylimidazo[5,1-f]-1,2,4-triazine and physiologically acceptable salts thereof.

8. A compound as claimed in claim 1 selected from 2-(1-methylethyl)-5-methyl-7-(2-methylpropyl)imidazo[5,1-f]-1,2,4-triazin-4(3H)-one, and physiologically acceptable salts thereof.

9. A pharmaceutical composition comprising at least one compound as claimed in claim 1 in association with a physiologically acceptable carrier.

10. A composition as claimed in claim 9 including supplementary medicinal agents.

11. A composition as claimed in claim 9 in the form of solid or liquid preparations for oral use, as suppositories or injections or forms suitable for inhalation.

12. A composition as claimed in claim 11 in the form of a powder which may be inhaled.

13. A composition as claimed in claim 9 in dosage unit form.

14. A method for the treatment of a patient suffering from a condition involving constriction of the bronchial muscle which comprises administering an effective amount of a compound as claimed in claim 1.

[54] IMIDAZO [5,1-F]-AS-TRIAZINES

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[73] Assignee: Allen & Hanbury Limited, London, England

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[58] Field of Search..... 260/249.5

[56] References Cited

UNITED STATES PATENTS

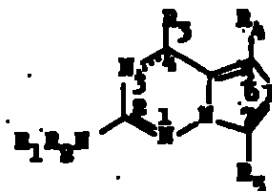
3,840,537 10/1974 Garalde et al..... 260/249.5

Primary Examiner—John M. Ford

Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

Compounds of the general formula:



in which:

R₁ and R₂ which may be the same or different, represent a hydrogen atom or an alkyl group which may optionally be substituted by an aryl group, or represents an alkanyoyl, aroyl or alkanesulphonyl group;

R₃ represents a hydrogen atom, or an alkyl group which may optionally be substituted by an aryl group, or represents an alkenyl, aryl or alkylthio group;

R₄ represents a hydrogen atom or an alkyl group; and

R₅ represents a hydrogen atom or an aryl or alkyl group, which alkyl group may optionally be substituted by a cycloalkyl group;

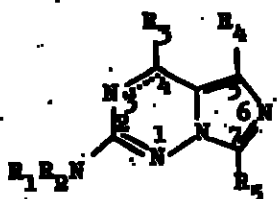
and physiologically acceptable salts and derivatives thereof and addition products formed by nucleophilic addition.

These compounds act as spasmolytics and phosphodiesterase inhibitors and have cardiotonic and diuretic properties. They are also of use in the treatment of skin disorders and gout.

64 Claims, No Drawings

RELATED APPLICATION

The present invention therefore provides compounds of the general formula I:



The invention includes physiologically acceptable salts and derivatives thereof. Suitable salts include acid

The compounds according to the invention may be formulated for use in human and veterinary medicine for therapeutic and prophylactic purposes. They may be used in the form of their physiologically acceptable salts if desired. Preferred salts include the hydrochloride, sulphate, maleate, tartrate, etc. Such compounds may be presented for use in the conventional manner with the aid of carriers or excipients and formulating agents as required, and with or without supplementary medicinal agents. The compositions may include solid and liquid preparations for oral use, suppositories or injections, or forms suitable for administration by inhalation. Oral administration is most convenient in the form of tablets. Injections may be formulated with the

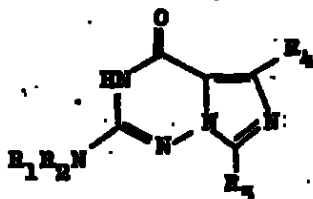
aid of physiologically acceptable carriers and agents as solutions, suspensions or as dry products for reconstitution before use. For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. A typical dose for treating asthma in humans is from 1-1200 mg. depending on the age, weight and condition of the patient and the route of administration.

The compounds according to the invention may be formulated in combination with compounds such as salbutamol and isoprenaline that have stimulant activity at β -adrenoreceptors. The provision of therapeutic compositions comprising as active ingredients, a compound according to the invention and a β -adrenoreceptor stimulant, in particular salbutamol, represents an important aspect of the invention. In some such mixtures a degree of synergism is seen between the active constituents.

As indicated above certain of the compounds show an action which may be advantageous in the treatment of gout. Particular compounds showing this activity are those of Examples 14a and 14b herein.

The compounds according to the invention may be prepared in principle by one main process.

In this process the compounds according to the invention in which there is a single bond in the 3,4 position are prepared from compounds of general formula II below such as by reduction. The compounds of formula II are described in copending application Ser. No. 300,749 filed Oct. 25, 1972 and now U.S. Pat. No. 3,840,537 or may be prepared in a manner similar to that described therein. The compounds according to the invention in which there is a double bond in the 3,4 position may be prepared by dehydrogenation of those compounds of the invention in which there is a single bond in that position. The compounds of formula II are represented below:



II

In these compounds the groups R_1 , R_2 , R_3 and R_4 have the meanings given above.

In addition R_1 and R_2 may represent groups which are converted on reduction to groups R_1 and R_2 within the meanings given and/or may represent groups which are convertible in a subsequent conversion to groups R_1 and R_2 within the meanings given. Another possibility consists in that the groups R_1 and R_2 may be converted from a group within the meaning given above in a subsequent conversion. Also in the reduction step the groups R_1 and R_2 within the above meaning may be formed in the reduction.

The conversion of the imidazotriazinone II into the compounds of the invention with a single bond in the 3,4 position may be carried out by reduction with a metal hydride such as lithium aluminium hydride, diborane or sodium dihydro-bis(2-methoxyethoxy) alumi-

nate. The reaction may be carried out by heating in an aprotic solvent such as tetrahydrofuran, diglyme and diethyl digol. A suitable reaction temperature is from 80°-130°C preferably 100°-110°C. In an alternative conversion the imidazotriazinone II may be converted to a compound according to the invention in which there is a single bond in the 3,4 position via the alkylthio compound as described later.

The dehydrogenation of the compounds according to the invention in which there is a single bond in the 3,4 position may be carried out by heating with a noble metal catalyst, such as palladium oxide on charcoal, preferably in the presence of a high boiling solvent e.g., cymene or decalin.

Thus compounds according to the invention in which R_1 or R_2 represents an alkanoyl, aroyl or alkanesulphonyl group may be prepared from those compounds in which R_1 represents hydrogen and R_2 represents hydrogen or alkyl or aralkyl group by conventional acylation procedures. Preferred methods include the reaction with an alkanoyl halide e.g. acetyl or butyryl chloride in the corresponding alkanotic acid, or the reaction with an alkanotic or aromatic acid e.g. isovaleric or benzoic acid in methanesulphonyl chloride. The alkanesulphonyl derivative e.g. methanesulphonyl is most conveniently prepared from the reaction with the corresponding alkanesulphonic anhydride. These acylation reactions may be carried out with heating if desired. Those compounds of general formula I in which R_1 and/or R_2 are alkyl or aralkyl may be conveniently prepared from the corresponding compound in which R_1 or R_2 is alkanoyl or aroyl by reduction with a complex metal hydride e.g. lithium aluminium hydride. Alternatively these compounds may be prepared by the direct reduction of the imidazotriazinone II, in which R_1 or R_2 is an alkanoyl, aralkenoyl or aroyl group with a complex metal hydride as described above.

The imidazotriazinones I in which R_1 represents an alkyl, alkanoyl or aroyl group and R_2 represents a hydrogen atom or an alkyl or aralkyl group may advantageously be prepared by dehydrogenation of the corresponding dihydroimidazotriazine I using the reaction conditions previously described.

Compounds according to the invention wherein R_4 is other than hydrogen may be conveniently compounds of the invention where R_4 is hydrogen and there is a double bond in the 3,4 position. Thus reaction with organometallic derivatives, e.g. R_4 MgHal or R_4 Li in which R_4 is other than hydrogen, in an aprotic solvent such as diethyl ether or tetrahydrofuran gives the compounds of the invention in which there is a single bond in the 3,4 position. This reaction is particularly advantageous for preparing compounds in which R_4 is an alkyl, aralkyl, aroyl or alkenyl group. The compounds in which there is a double bond in the 3,4 position may be obtained by dehydrogenation of the dihydro derivative as described above.

Addition products of compounds of the invention in which there is a double bond in the 3,4 position may be obtained by reaction with compounds containing an activated methylene group e.g. with barbituric acid or dimedone in water or aqueous alcohol. In the presence of a strong mineral acid such as hydrochloric acid, acetophenones also add across the 3,4 double bond to give corresponding dihydroimidazotriazines in which R_4 represents a phenacyl group.

Other classes of compounds also add across the 3,4 double bond, for example the addition of sodium meta-

bisulphite gives an additional product in which there is a sulphonic acid group in the R_2 position.

Compounds of the general formula I in which R_2 is alkylthio group may be made by treating the corresponding imidazotriazinone II with phosphorus pentasulphide, followed by alkylation of the thione thus formed. The resulting alkylthio imidazotriazine I may be reduced to the corresponding dihydroimidazotriazine I $R_2 = H$. For example by reaction with sodium borohydride in a dipolar aprotic solvent such as N-methylpyrrolidone preferably with heating.

The procedure thus provides as indicated earlier an alternative method for the preparation of dihydroimidazotriazines I; $R_2 = H$ from the imidazotriazinone II.

The following examples illustrate the invention. Examples 1 to 23 describe the production of compounds of the invention. Example 24 describes the production of starting materials for Example 12. Example 25 describes the production of starting materials for Example 1.

EXAMPLE 1

a. 2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4(3H)-one, hydrochloride (5 g.) (prepared according to Example 8 of application Ser. No. 300,749 and lithium aluminium hydride (2.9 g.) in tetrahydrofuran were heated under reflux for 78 hours, and cooled. Water (11.6 ml.) was added cautiously, followed by aqueous sodium hydroxide (2.9 ml., 15%). The solid was filtered off, the filtrate was evaporated and the residue was triturated with ethyl acetate. The product was crystallised from ethyl acetate and had m.p. 242°-246°.

b. 2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (2 g.) in ethanol was treated with a solution of hydrogen chloride in ether. The solid was collected and crystallised from a mixture of ethanol and ether to give a white solid m.p. 263° (decomp.).

The following compounds were prepared by a similar procedure:

c. 2-Amino-3,4-dihydro-7-isopropyl-5-methylimidazo[5,1-f]-as-triazine, m.p. 284°-286° (recrystallised from a mixture of ethanol and ethyl acetate) and its hydrochloride m.p. 210°-12° were obtained from 2-amino-7-isopropyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one (Example 25).

d. 2-Amino-3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine, m.p. 258°-263° (crystallised from aqueous methanol) and its hydrochloride m.p. 225°-228° were obtained from 2-amino-7-isobutyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one (Example 25).

e. 2-Amino-3,4-dihydro-5-methyl-7-phenylimidazo[5,1-f]-as-triazine, m.p. 262°-264° (recrystallised from a mixture of methanol and ethyl acetate) and its hydrochloride m.p. 328°-331° were obtained from 2-amino-5-methyl-7-phenylimidazo[5,1-f]-as-triazin-4(3H)-one.

f. 2-Amino-7-cyclohexylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine, m.p. 228°-230° (crystallised from a mixture of ethyl acetate and ether) was obtained from 2-amino-7-cyclohexylmethyl-5-

methylimidazo[5,1-f]-as-triazin-4(3H)-one (Example 25).

g. 2-Amino-7-cyclohexylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine, hydrogen maleate

2-Amino-7-cyclohexylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine, (0.7 g.) in ethanol (50 ml.) was treated with maleic acid (0.4 g.) in ether (50 ml.) and the solid was collected and crystallised from a mixture of methanol and ethyl acetate to give a white solid, m.p. 130°-133°.

EXAMPLE 2

a. 2-Amino-3,4-dihydro-5-methyl-7(2-methylbutyl)imidazo[5,1-f]-as-triazine

2-Amino-5-methyl-7(2-methylbutyl)imidazo[5,1-f]-as-triazin-4(3H)-one (1.7 g.) and lithium aluminium hydride (0.9 g.) in diglyme (50 ml., freshly redistilled) were stirred and heated to 100° for 4.5 hours and cooled. Water (1 ml.) was added dropwise, followed by 2N sodium hydroxide (2 ml.) and water (1 ml.). The solid was filtered off, the filtrate was evaporated and the residue was crystallised from isopropanol. The product had m.p. 207°-213° (63%). It was converted to its hydrochloride, m.p. 203°-205.5° by treating a solution in ethanol with hydrogen chloride in ether.

In a similar way:

b. 2-Amino-7-cyclopentylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine, m.p. 194°-198° (49%) was obtained from 2-amino-7-cyclopentylmethyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one (AH 12963). It was converted to its hydrochloride, m.p. 255°-257°.

c. 2-Amino-3,4-dihydro-7(3-methylbutyl)imidazo[5,1-f]-as-triazine, hydrochloride, m.p. 167°-172° (crystallised from a mixture of ethanol and ethyl acetate) was obtained from 2-amino-5-methyl-7(3-methylbutyl)imidazo[5,1-f]-as-triazine-4(3H)-one (Example 25).

d. 2-Amino-3,4-dihydro-5-methyl-7(1-methylpropyl)imidazo[5,1-f]-as-triazine, m.p. 275°-290° and its dihydrochloride m.p. 270°-187° were prepared from 2-amino-5-methyl-7(1-methylpropyl)imidazo[5,1-f]-as-triazine-4(3H)-one (AH 13014A).

EXAMPLE 3

a. 5-Methyl-7-propyl-2-propylaminimidazo[5,1-f]-as-triazine, hydrochloride

3,4-Dihydro-5-methyl-7-propyl-2-propylaminimidazo[5,1-f]-as-triazine (Example 12a) (1.44 g.) and palladium on charcoal catalyst (2.8 g., 10%) in p-cymene (100 ml.) were heated under reflux in p-cymene for 3 hours. The catalyst was filtered off and the filtrate was extracted with 2N hydrochloric acid (3 x 100 ml.). The extracts were neutralised with potassium carbonate and the mixture was extracted with ethyl acetate. The ethyl acetate solution was dried over magnesium sulphate, filtered and evaporated. The oil in ethyl acetate was treated with a solution of hydrogen chloride in ether. The solid was collected and had m.p. 201°-206°.

In a similar way, the following compounds were prepared:

b. 2-Benzylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine was prepared from 2-benzylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 12b). It was converted into its hydrogen maleate which had m.p. 141°-142°.

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c. 5-Methyl-2(2-phenethylamino)-7-propylimidazo[5,1-f]-as-triazine m.p. 124°-128° was prepared from 3,4-dihydro-5-methyl-2(2-phenethylamino)-7-propylimidazo[5,1-f]-as-triazine (Example 12c). It was converted to its hydrochloride m.p. 205°-206°.

d. 2-Isobutylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine, m.p. 87°-88°, was prepared from 2-isobutylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 12f). It was converted to its hydrochloride, m.p. 201°-213°.

e. 2-(3,4-Dimethoxybenzylamino)-5-methyl-7-propylimidazo[5,1-f]-as-triazine, m.p. 158°-160° was prepared from 2-(3,4-dimethoxybenzylamino)-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 12d). It was converted to its hydrogen maleate salt, m.p. 118°-121°.

f. 2-Amino-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine, m.p. 84°-86°, was prepared (72%) from 2-amino-3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine (Example 1d). It was converted to its hydrogen maleate which was crystallized from a mixture of methanol and ether and had m.p. 178°-180°.

g. 2-Amino-4(p-methoxyphenyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine was prepared from 2-amino-3,4-dihydro-4(p-methoxyphenyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 14b). It was converted to its hydrochloride, which was crystallized from a mixture of ethanol and ether and had m.p. 224°-226° (21%).

h. 2-Amino-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazine, was prepared from 2-amino-3,4-dihydro-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazine (Example 16c). It was converted into its hydrogen maleate which had m.p. 155°-156°.

EXAMPLE 4

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 1a) (2 g.) and palladium on charcoal catalyst (3 g.) in decalin (100 ml.) were heated under reflux for 6 hours. The mixture was filtered and cooled and extracted with 2N hydrochloric acid (2 x 100 ml.). The extracts were made alkaline with 2N sodium hydroxide and extracted with ethyl acetate. The ethyl acetate solution was dried over magnesium sulphate, filtered and evaporated and the residue was chromatographed on silica (50 ml.) to give a yellow solid (0.32 g.), 5N sodium hydroxide (2.5 ml) and water (7.5 ml.). The solid was filtered off and extracted with ethyl acetate (3 x 100 ml.). The extracts were dried and evaporated and the solid was crystallized from ethyl acetate and had m.p. 157°-167°, 1.74 g. (The hydrochloride had m.p. 271°-276°, and was prepared in ethyl acetate by addition HCl/Et₂O).

EXAMPLE 5

N-(5-Methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-methanesulphonamide

N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-methanesulphonamide, methanesulphonate (Example 8) in water was treated with sodium bicarbonate. The solution was evaporated and the residue was extracted with hot isopropanol. The extract was evaporated to give N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-methane sul-

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phonamide. This sulphonamide (1.5 g.) and 10% palladium on charcoal catalyst (3g, 10%) in p-cymene (100 ml) were heated under reflux for 2.5 hours and cooled. The catalyst was filtered off and the filtrate was evaporated. The residue was triturated with ethyl acetate to give a yellow solid, m.p. 191°-195°. It was converted into its hydrogen maleate salt m.p. 165°-168°.

EXAMPLE 6

a. N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)benzamide, hydrogen maleate

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 1a) (1.5 g.) and benzoic acid (2.46 g.) in methanesulphonyl chloride (10 ml.) were heated to 140° to 4 hours and cooled. The mixture was shaken several times with ether and poured into aqueous sodium carbonate. The mixture was extracted with ethyl acetate, the extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residual solution was dissolved in ethyl acetate and maleic acid (1 g.) in ethyl acetate (40 ml.) was added followed by ether (50 ml.). The solid was collected and crystallized from a mixture of isopropanol and ether and had m.p. 183°-185°.

In a similar way:

b. N-(3,4-Dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazin-2-yl)-p-chlorobenzamide, m.p. 236°-239° was prepared from 2-amino-3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazine (Example 1d) and p-chlorobenzoic acid. It was converted into its hydrochloride salt m.p. 240°-247°.

c. N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl) isovaleramide hydrochloride m.p. 233°-235° (crystallized from a mixture of isopropanol and ether) was prepared using isovaleric acid in place of benzoic acid.

EXAMPLE 7

N-Ethyl-N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride

2-Ethylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 12e) (1.1 g.) and acetyl chloride (1.65 ml.) in glacial acetic acid (10 ml.) were heated on a steam bath for 16 hours. The acetic acid was distilled off and the residue was crystallized from a mixture of isopropanol and ether to give a solid, m.p. 190°-192° (73%).

EXAMPLE 8

N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-methanesulphonamide, methanesulphonate

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride (Example 1b) (2.5 g.) in methanesulphonic anhydride (12 g.) was heated at 140° for 2 hours and cooled. The mixture was triturated several times with ether and the solid was crystallized from ethanol to give the product, m.p. 209°-222° (68%).

EXAMPLE 9

a. N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 1a) (1.9 g.) and acetyl chloride (1.8 g.) in acetic acid (20 ml.,

glacial) were heated at 100° for 3 hours. The solution was evaporated under reduced pressure and the residue was crystallized from a mixture of ethanol and ethyl acetate to give a white solid m.p. 302°.

The following compounds were prepared in a similar way:

b. N-(3,4-Dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazin-2-yl)acetamide, m.p. 269°-271° (crystallized from a mixture of ethanol and ether) (Starting material Example 1d).

c. N-(3,4-Dihydro-7-isopropyl-5-methylimidazo[5,1-f]-as-triazin-2-yl)acetamide, m.p. 319°-321° (crystallized from a mixture of ethanol and ethyl acetate) (Starting material Example 1e).

d. N-(3,4-Dihydro-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide hydrochloride m.p. 272°-274° (crystallized from a mixture of ethanol and ethyl acetate) (Starting material Example 16c).

EXAMPLE 10

a. N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)formamide

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 1a) (2.2 g.) in formic acid (50 ml., 99°) was heated under reflux for 24 hours and evaporated under reduced pressure. The residue was stirred with 2N sodium carbonate and the solid was collected and dried and had m.p. 188.5°-190.5°. Its hydrogen maleate salt had m.p. 159°-161° (crystallized from a mixture of methanol and ether).

b. In a similar manner N-(3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazin-2-yl)formamide m.p. 209°-211° (crystallized from ethyl acetate) and its hydrochloride m.p. 257°-258° (crystallized from a mixture of ethanol and ethyl acetate).

EXAMPLE 11

N-(3,4-Dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)butyramide, hydrochloride

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 1a) (2 g.) and butyric chloride (11 ml.) in butyric acid (50 ml.) were heated under reflux for 5.5 hours and cooled with ice. 5N sodium hydroxide was added slowly and until the mixture was alkaline and the solid was filtered off. The filtrate was evaporated under reduced pressure and the residue was stirred with aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate and the extract was dried over magnesium sulphate, filtered and evaporated. The residue was crystallized from methanol to give a white solid, m.p. 161°-162°.

EXAMPLE 12

a. 3,4-Dihydro-5-methyl-7-propyl-2-propylaminimidazo[5,1-f]-as-triazine, hydrochloride

N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl) propionamide, hydrochloride (5.08 g.) and lithium aluminium hydride (5 g.) in dry tetrahydrofuran (300 ml.) were stirred and heated under reflux for 60 hours and cooled. Water (5 ml.) was added dropwise followed by 5N sodium hydroxide (5 ml.) and water (15 ml.). The solid was filtered off and the filtrate was evaporated. The residue was dissolved in ethanol and hydrogen chloride in ether was added to give a solid that was crystallized from a

mixture of ethanol and ethyl acetate and had m.p. 264°-272°.

In a similar manner:

b. 2-Benzylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride was prepared from N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)benzamide and had m.p. 235°-240°.

c. 3,4-Dihydro-5-methyl-2-(2-phenylethylamino)-7-propylimidazo[5,1-f]-as-triazine, hydrochloride, m.p. 195°-200°, was obtained from N-(3,4-dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)phenylacetamide, methanesulphonate.

d. 3,4-Dihydro-2-(3,4-dimethoxybenzylamino)-5-methyl-7-propylimidazo[5,1-f]-as-triazine m.p. 120°-123° (66%) was prepared from N-(3,4-dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-3,4-dimethoxybenzamide, methanesulphonate.

e. 2-Ethylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrogen maleate m.p. 129°-130.5° was obtained from N-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide hydrochloride.

f. 3,4-Dihydro-2-iso-aminylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine m.p. 157°-167° and its hydrochloride m.p. 271°-276° are prepared from N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)isobutyramide hydrochloride.

EXAMPLE 13

2-Methylamino-3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazine, hydrochloride

N-(3,4-Dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazin-2-yl)formamide (Example 10b) (1 g.) and lithium aluminium hydride (0.9 g.) in dry tetrahydrofuran (60 ml.) were heated under reflux for 4.5 hours, and cooled. Water (1 ml.) was added dropwise followed by 5N sodium hydroxide (1 ml.) and water (3 ml.). The mixture was filtered and the filtrate was evaporated. The residue in ethanol was treated with hydrogen chloride in ether and the solid was crystallized from a mixture of ethanol and ethyl acetate and had m.p. 290°-293°(d).

EXAMPLE 14

2-Amino-3,4-dihydro-5-methyl-4-phenyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1.9 g.) in dry tetrahydrofuran (75 ml) was added to phenyl magnesium bromide (from bromobenzene (7.85 g.) and magnesium (1.2 g.) in ether (60 ml.) and the mixture stirred for 5 hours. Saturated aqueous ammonium sulphate (50 ml.) was added and the organic layer was separated, dried over magnesium sulphate and filtered and concentrated. The solid was crystallized from aqueous ethanol and dried and had m.p. 278°-279°. The solid in ethanol was treated with hydrogen chloride in ether and the solid was collected and crystallized from a mixture of ethanol and ether and had m.p. 179°-181°.

b. In a similar way, 2-amino-3,4-dihydro-4-(p-methoxyphenyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride was prepared from p-methoxyphenyl magnesium bromide and 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) and had m.p. 178°-181°.

EXAMPLE 15

4-Allyl-2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrogen maleate

Allyl chloride (9.9 ml) in anhydrous tetrahydrofuran (75 ml) was added to magnesium turnings (2.9 g.) in anhydrous tetrahydrofuran (30 ml.). When the reaction was complete, 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1.93 g.) in anhydrous tetrahydrofuran (20 ml.) was added and the mixture was stirred for 30 minutes. Ammonium chloride (6.5 g.) in water (25 ml.) was added and the organic layer was separated, dried over magnesium sulphate, filtered and evaporated. The solid in ethyl acetate (100 ml.) was treated with maleic acid (1.7 g.) in ethyl acetate (100 ml.) and the solid was collected and crystallized from a mixture of isopropanol and ether and had m.p. 229°-231°.

EXAMPLE 16

a. 2-Amino-3,4-dihydro-4,5-dimethyl-7-isobutylimidazo[5,1-f]-as-triazine, hydrochloride

2-Amino-3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine (Example 3f) (2 g.) in dry ether (50 ml) was added to methyl magnesium iodide (prepared from magnesium (1.17 g.) and methyl iodide (2.56 ml.)) in ether (50 ml.). The mixture was heated under reflux for 2 hours and kept overnight. Aqueous ammonium chloride (100 ml., 1%) was added and the ether layer was separated. The aqueous layer was kept for 4 days and the solid that crystallized was collected and crystallized from a mixture of ethanol and ethyl acetate and had m.p. 265°-267°. (The hydrochloride had m.p. 142°-143°).

b. In a similar manner, 2-amino-3,4-dihydro-4-ethyl-5-methyl-7-propylimidazo[5,1-f]-as-triazine was prepared from 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) and ethylmagnesium bromide. It was isolated as its hydrochloride salt which was crystallized from a mixture of isopropanol and ether and had m.p. 170°-172°.

c. 2-Amino-3,4-dihydro-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazine m.p. 268°-271° (crystallized from ethyl acetate) and its hydrochloride m.p. 252°-254° (crystallized from a mixture of ethanol and ether) were prepared from 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) and methyl magnesium iodide.

EXAMPLE 17

N-(4-Benzyl-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1.9 g.) was added to benzyl magnesium chloride (prepared from benzyl chloride (6.3 g.) and magnesium (1.2 g.)) in ether (400 ml.), and the mixture was stirred for 4 hours at room temperature. Aqueous ammonium chloride (50 ml., 20%) was added and the aqueous layer was separated and extracted with ethyl acetate. The extracts were dried over magnesium sulphate, filtered and evaporated and the residue was chromatographed on silica gel (100 g.). Fractions eluted with ethyl acetate were discarded. The fractions eluted with a mixture of ethyl acetate and methanol (4:1) were evaporated to give 2-amino-4-benzyl-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine

as a gum (0.83 g.). This gum (0.7 g.) and acetyl chloride (0.3 ml.) in glacial acetic acid (10 ml.) were heated at 100° for 2.5 hours. Acetic acid was distilled off and the residue was crystallized from a mixture of ethanol and ethyl acetate to give a white solid, m.p. 240°-241°.

EXAMPLE 18

a. 5-(2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4-yl)-barbituric acid

Barbituric acid (1.36 g.) and 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (2 g.) in water (60 ml.) were stirred for 1.75 hours. The solid was collected and crystallized from water to give a solid m.p. 256°-258°.

b. 5-(2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4-yl)barbituric acid, hydrochloride

5-(2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4-yl)barbituric acid (0.5 g.) in ethanol (10 ml.) was treated with a solution of hydrogen chloride in ether. The solid was collected and crystallized from a mixture of methanol and ether and had m.p. 200°-205°.

EXAMPLE 19

2-Amino-3,4-dihydro-4-(4,4-dimethyl-2,6-dioxocyclohexyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1 g.) in aqueous ethanol (20 ml., 1:1) and 5,5-dimethylcyclohexane-1,3-dione (1 g.) in aqueous ethanol (20 ml., 1:1) were mixed. The solid was collected and dried and had m.p. 243°.

EXAMPLE 20

2-Amino-3,4-dihydro-4-(p-methoxyphenacyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

2-Amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1.9 g.), p-methoxyacetophenone (1.65 g.) and concentrated hydrochloric acid (2 ml.) in ethanol (50 ml.) were heated under reflux for 1.5 hours. The solvent was distilled off and the residue was treated with 2N sodium carbonate. The mixture was extracted with ethyl acetate and the extract was dried over magnesium sulphate, filtered and evaporated. The residue was crystallized from a mixture of ethyl acetate and light petroleum and had m.p. 193°-195°. The solid in ethanol (20 ml.) was treated with hydrogen chloride in ether. The mixture was further diluted with ether and the solid that crystallized from a mixture of isopropanol and ether and had m.p. 122°.

EXAMPLE 21

2-Amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine-4-sulphonic acid

Sodium metabisulphite (1.5 g.) in water (45 ml.) was added to 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine (Example 4) (1.9 g.) in ethanol (20 ml.). The solid was collected and dried and had m.p. 232°-234°.

EXAMPLE 22

2-Diethylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

N-Ethyl-N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride (Example 7) (4.1 g.) and lithium aluminum hydride (3.3

g.) in a mixture of dimethyl digol (130 ml.) and diethyl digol (150 ml.) were heated under reflux for 24 hours and cooled. Water (3.37 ml.) was added followed by aqueous sodium hydroxide (3.3 ml.) and water (9.8 ml.). The solid was filtered off and the filtrate was evaporated. The residue was chromatographed on active alumina (300 g.) using ethyl acetate as eluent. The first 400 ml. of eluate was discarded and a fraction (900 ml.) then collected was evaporated to give an oil. This oil (1.1 g.) and palladium on charcoal catalyst (1 g., 10%) in p-cymene (60 ml.) were heated under reflux for 30 minutes, cooled and filtered. The filtrate was shaken with 2N hydrochloric acid (3 x 25 ml.) and the aqueous acid solution was separated and neutralized by addition of potassium carbonate. The mixture was extracted with ethyl acetate and the extracts were dried over magnesium sulphate, filtered and evaporated. The residue in ether was treated with a solution of hydrogen chloride in anhydrous ether. The solid crystallized from a mixture of ethyl acetate and ether to give the product, m.p. 83°-84°.

EXAMPLE 23

2-Amino-5-methyl-4-methylthio-7-propylimidazo[5,1-f]-as-triazine, hydrochloride

a. 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine-4(3H)-thione, hydrochloride.

2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine-4(3H)-one hydrochloride (10 g.) and phosphorus pentasulphide (14 g.) in pyridine (150 ml.) were heated under reflux for 18 hours. The pyridine was distilled off and the residue was dissolved in 2N sodium hydroxide. Glacial acetic acid was added and the solid was collected and dissolved in ethanol. A solution of hydrogen chloride in ether was added and the solid was collected and crystallized from a mixture of ethanol and ether. It had m.p. 290°-292°.

b. 2-amino-5-methyl-4-methylthio-7-propylimidazo[5,1-f]-as-triazine

2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine-4(3H)-thione, hydrochloride (0.65 g.) in a slight excess of 2N sodium hydroxide was treated with iodomethane (0.4 g.) and the mixture was stirred 2 hours at room temperature. The solid was collected and crystallized from aqueous ethanol and had m.p. 139°-140°. Its hydrochloride melted at 207°-208°.

c. 2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

2-amino-5-methyl-4-methylthio-7-propylimidazo[5,1-f]-as-triazine (1 g.) and sodium borohydride (0.5 g.) in N-methylpyrrolidone (25 ml.) were heated on a steam bath for 7 hours. Water (150 ml.) was added and the mixture was extracted continuously with ethyl acetate for 3 hours. The extract was dried over magnesium sulphate, filtered and evaporated and the residue was purified by chromatography on silica gel using a mixture of ethyl acetate and ethanol as eluent. The eluate was evaporated and the residue in ethanol was treated with a solution of hydrogen chloride in ether. The solid was crystallized from a mixture of ethanol and ether and had m.p. 251°.

EXAMPLE 24

N-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl)-2-phenylacetamide, methanesulphonate

A mixture of 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4(3H)-one hydrochloride (3.0 g.), methanesulphonyl chloride (1.6 ml, 2.36 g.) and phenylacetic acid (15 g.) was stirred and heated at 140° for 3½ hours. The mixture was allowed to cool then diluted with ether (75 ml). An oil separated which changed to a buff solid. This was collected, washed with ether, and recrystallized from ethanol-ethyl acetate to give the methanesulphonate salt of the phenylacetamide as white needles, m.p. 214°-219°.

By a similar procedure was prepared:

N-(3,4-Dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-f]-as-triazin-2-yl) propionamide, hydrochloride, m.p. 252°-257° (sinters at 248°) (from ethanol-ethyl acetate).

N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl) isobutyramide, hydrochloride, m.p. 248°-255° (from ethanol).

N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl) benzamide, methanesulphonate, m.p. 198°-200.5° (from ethyl acetate).

N-(3,4-Dihydro-4-oxo-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)-3,4-dimethoxybenzamide, methanesulphonate, m.p. 211°-213.5° (from ethanol).

In these reactions toluene was used as a co-solvent.

EXAMPLE 25

2-Amino-7-isopropyl-5-methylimidazo[5,1-f]-as-triazin-4-one

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]isobutyramide

3-Amino-1-benzyl-6(1-aminoethyl)-as-triazin-5-one (1 g.) and isobutyric anhydride (0.75 ml.) in 1,4-dioxan (20 ml.) were stirred for some hours at room temperature. Ether was added and the solid was collected and crystallized from ethyl acetate. It had m.p. 226°-228°.

In a similar way N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]isovaleramide m.p. 149.5° was prepared from 3-amino-1-benzyl-6(1-aminoethyl)-as-triazin-5-one and isovaleric anhydride.

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-cyclohexylacetamide, m.p. 200°-202° (recrystallized from methanol) was obtained from 3-amino-1-benzyl-6(1-aminoethyl)-as-triazin-5-one and cyclohexyl-acetic anhydride.

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)-ethyl]-4-methyl valeramide

4-Methylvaleric acid (0.5 g.) and methylamine (0.44 g.) in dioxan (25 ml.) was treated with phosgene (0.5 g.) in dioxan (25 ml.) and the mixture was stirred 1 hour at room temperature. The solid was filtered off and 3-amino-1-benzyl-6(1-aminoethyl)-as-triazin-5-one (1 g.) was added. The mixture was stirred for 24 hours at room temperature and ether (300 ml.) was added. The solid was collected and crystallized from ethanol. The product had m.p. 188°-190°.

In a similar way the following compounds were prepared from 3-amino-1-benzyl-6-(1-aminoethyl)-as-triazin-5-one and the appropriate acid.

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-3-methyl valeramide, m.p. 212°-215° (from ethanol).

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-2-methyl butyramide, m.p. 233°-235° (from ethanol).

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-cyclopentylacetamide, m.p. 195°-196.5° (from a mixture of ethanol and ether).

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-isobutyramide, hydrochloride

N-[1-(3-Amino-2-benzyl-2,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-isobutyramide (14.2 g.) 2N hydrochloric acid (50 ml.) and palladium oxide on charcoal catalyst (2 g.) and ethanol (250 ml.) was shaken with hydrogen at atmosphere pressure and room temperature. The catalyst was filtered off and the filtrate was evaporated to give the product, m.p. 310°-314°.

In a similar way the following compounds were prepared:

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]isovaleramide, m.p. 281°.

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]cyclohexylacetamide, m.p. 200°-202°.

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl] 4-methylvaleramide, m.p. 280°-283°.

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-3-methylvaleramide, 298°-300°.

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]-2-methylbutyramide, m.p. 268°-270°.

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]cyclopentylacetamide, m.p. 313°-315°.

2-Amino-7-isopropyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one

N-[1-(3-Amino-4,5-dihydro-5-oxo-as-triazin-6-yl)ethyl]isobutyramide (1 g.) in polyphosphoric acid (10 g.) was heated at 150° for 1 hour, cooled and poured onto ice. The solution was neutralized by the addition of sodium carbonate and extracted with ethyl acetate. The extract was dried over magnesium sulphate filtered and evaporated to give the product, m.p. 310°-314°.

In a similar way, the following compounds were prepared:

2-Amino-7-isobutyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one, m.p. 251°.

2-Amino-7-cyclohexylmethyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one m.p. 278°-283°.

2-Amino-5-methyl-7-(3-methylbutyl)imidazo[5,1-f]-as-triazin-4(3H)-one m.p. 251°-255°.

2-Amino-5-7-(2-methylbutyl)imidazo[5,1-f]-as-triazin-4(3H)-one m.p. 220°-232°.

2-Amino-5-methyl-7-(1-methylbutyl)imidazo[5,1-f]-as-triazin-4(3H)-one, m.p. 262°-268°.

2-Amino-7-cyclopentylmethyl-5-methylimidazo[5,1-f]-as-triazin-4(3H)-one, m.p. 159°-160°.

EXAMPLE 26

This Example gives representative formulations containing as active ingredient 2-amino-3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine referred in the Examples as AH 11554. This compound is used in the form of the hydrochloride which is referred to as AH 11554A.

Injection — containing 10 mg AH 11554 per ml

Formula	per ml	
AH 11554	11.76	mg (equivalent to 10 mg AH 11554 base)
Sodium chloride	6.1	mg
Water for injections to	1.0	ml

Method of manufacture

Dissolve the AH 11554 and the sodium chloride in 90% of the water for injections. When solution is complete make up to volume with further water for injections. Filter through a suitable clarifying filter.

The solution can then either be packed into 1 ml neutral glass snap-ring ampoules and sterilised by heating in an autoclave or by filtration or may be prepared aseptically.

Tablets

Formula	mg/tablet	mg/tablet
AH 11554 (equivalent to AH 11554 base)	29.4 mg	11.8 mg
Lactose B.P.	146.6	120.2
Maize starch B.P.	20.0	15.0
Maize starch as 5% paste	2.0	1.5
Magnesium stearate B.P.	2.0	1.5
Final Tablet Weight	200	190

Method of Manufacture

Blend together the milled AH 11554 and Lactose. Prepare the requisite quantity of 5% Starch Paste and add to the mixed powder and mix until a uniform damp cohesive mass is formed. Granulate this mass by passing through a suitable mill or sieve to produce discrete granulates. Dry the granules in either a fluid bed drier or on trays in a hot air oven at a temperature of about 50°C. After drying pass the granules through a 30 mesh B.S. sieve to break up aggregates.

Mix together the dried granules, the Maize Starch and the Magnesium Stearate and compress on a suitable tablet press. The tablets containing 30 mg AH 11554 each weigh about 200 mg and are 8.0 mm in diameter, those containing 10 mg AH 11554 each weigh about 156 mg and are 7.0 mm in diameter.

Inhalation Aerosol

Formulation	mg/measured dose
1. AH 11554 base (micronized)	0.5
2. Sorbitan trioleate	0.5
3. Trichlorofluoromethane B.P.	25
4. Dichlorodifluoromethane B.P.	85 mg

Method of Manufacture

Disperse the micronized AH 11554 base in the trichlorofluoromethane with the Sorbitan trioleate. Fill the requisite volume of this dispersion into suitable aerosol cans and seal by means of a suitable metering valve. Pressurise the containers by injecting the dichlorodifluoromethane through the valve.

In an alternative formula components 1, 3 and 4 are identical to 1, 3 and 4 identified above but 2 is replaced by Emulsifier YN 0.01 mg.

Topical Preparation

Formula	% w/v
AH 11554 base	1.0
Cetomacrogol cream B.P.C. to	100.0

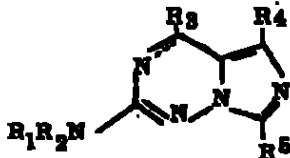
Method of Manufacture

Prepare the cetomacrogol cream as directed in the B.P.C. 1968. Disperse the finely divided AH 11554 in a proportion of the cream and carefully incorporate this concentrated mixture into the remainder of the cream base. Subdivide into suitable lacquered aluminium tubes.

In an alternative formulation salbutamol sulphate is used as additional active ingredient in an amount up to 1.0% w/v. This is incorporated at the same stage as the AH 11554.

We claim:

1. A compound of the formula:



in which

- R_1 and R_2 may be the same or different, represent a hydrogen atom, or a C_{1-6} alkyl group which may optionally be substituted by a phenyl group, or represent a C_{1-6} alkanoyl group of C_{1-6} alkane sulphonyl group;
- R_3 represents a hydrogen atom, or a C_{1-6} alkyl group which may optionally be substituted by a phenyl group, or represents a C_{2-6} alkanoyl group, phenyl, methoxyphenyl, or C_{1-6} alkylthio group;
- R_4 represents a hydrogen atom or C_{1-6} alkyl group; and
- R_5 represents a hydrogen atom, a C_{1-6} alkyl group, which alkyl group may optionally be substituted by a C_{2-6} cycloalkyl group, or a phenyl group, and physiologically acceptable salts and addition products formed by nucleophilic addition.
2. Compounds as claimed in claim 1 in which R_1 represents a hydrogen atom or a methyl, ethyl, propyl, isobutyl, 3-methylbutyl group, or a 3,4-dimethoxybenzyl, phenethyl, formyl, acetyl, butyryl, isovaleryl, benzoyl, 4-chlorobenzoyl or methanesulphonyl group.
3. Compounds as claimed in claim 1 in which R_2 represents an ethyl radical.
4. Compounds as claimed in claim 1 in which R_3 represents hydrogen, methyl, ethyl, benzyl, phenethyl, phenyl, 4-methoxyphenyl, allyl or methylthio.
5. Compounds as claimed in claim 1 in which R_4 represents hydrogen or methyl.
6. Compounds as claimed in claim 1 in which R_5 represents propyl, isopropyl, isobutyl, secbutyl, 2-methylbutyl, 3-methylbutyl, cyclopentylmethyl, cyclohexylmethyl or phenyl.
7. Compounds as claimed in claim 1 in the form of physiologically acceptable salts with inorganic or organic acids.
8. Compounds as claimed in claim 1 in the form of addition production formed by nucleophilic addition across the 3,4 bond when this is a double bond, with sodium bisulphite.

9. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine.
10. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.
11. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-7-isopropyl-5-methylimidazo[5,1-f]-as-triazine and its hydrochloride.
12. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine and its hydrochloride.
13. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-phenylimidazo[5,1-f]-as-triazine and its hydrochloride.
14. A compound as claimed in claim 1 which is 2-amino-7-cyclohexylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine.
15. A compound as claimed in claim 1 which is 2-amino-7-cyclohexylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine, hydrogen maleate.
16. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-(2-methylbutyl)imidazo[5,1-f]-as-triazine and its hydrochloride.
17. A compound as claimed in claim 1 which is 2-amino-7-cyclopentylmethyl-3,4-dihydro-5-methylimidazo[5,1-f]-as-triazine.
18. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-7-(3-methylbutyl)imidazo[5,1-f]-as-triazine, hydrochloride.
19. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-(1-methylpropyl)imidazo[5,1-f]-as-triazine and its dihydrochloride.
20. A compound as claimed in claim 1 which is 5-methyl-7-propyl-2-propylaminimidazo[5,1-f]-as-triazine, hydrochloride.
21. A compound as claimed in claim 1 which is 2-benzylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine.
22. A compound as claimed in claim 1 which is 5-methyl-2-(2-phenethylamino)-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.
23. A compound as claimed in claim 1 which is 2-isobutylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.
24. A compound as claimed in claim 1 which is 2-(3,4-dimethoxybenzylamino)-5-methyl-7-propylimidazo[5,1-f]-as-triazine.
25. A compound as claimed in claim 1 which is 2-amino-7-isobutyl-5-methylimidazo[5,1-f]-as-triazine.
26. A compound as claimed in claim 1 which is 2-amino-4-(p-methoxyphenyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.
27. A compound as claimed in claim 1 which is 2-amino-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazine.
28. A compound as claimed in claim 1 which is 2-amino-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.
29. A compound as claimed in claim 1 which is N-(5-methyl-7-propylimidazo[5,1-f]-as-triazine-2-yl) methanesulphonamide.
30. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)benzamide, hydrogen maleate.
31. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazin-2-yl)-p-chlorobenzamide and its hydrochloride.

32. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)isovaleramide hydrochloride.

33. A compound as claimed in claim 1 which is N-Ethyl-N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride.

34. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)methanesulphonamide, methanesulphonate.

35. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride.

36. A compound as claimed in claim 1 which is N-(3,4-dihydro-7-isobutyl-5-methylimidazo[5,1-f]-as-triazin-2-yl)acetamide.

37. A compound as claimed in claim 1 which is N-(3,4-dihydro-7-isopropyl-5-methylimidazo[5,1-f]-as-triazin-2-yl)acetamide.

38. A compound as claimed in claim 1 which is N-(3,4-dihydro-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide hydrochloride.

39. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)formamide.

40. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazin-2-yl)formamide and its hydrochloride.

41. A compound as claimed in claim 1 which is N-(3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)butyramide, hydrochloride.

42. A compound as claimed in claim 1 which is 3,4-dihydro-5-methyl-7-propyl-2-propylaminoimidazo[5,1-f]-as-triazine, hydrochloride.

43. A compound as claimed in claim 1 which is 2-benzylamino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

44. A compound as claimed in claim 1 which is 3,4-dihydro-5-methyl-2-(2-phenylethylamino)-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

45. A compound as claimed in claim 1 which is 3,4-dihydro-2-(3,4-dimethoxybenzylamino)-5-methyl-7-propylimidazo[5,1-f]-as-triazine.

46. A compound as claimed in claim 1 which is 2-Ethylamino 3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine.

47. A compound as claimed in claim 1 which is 3,4-dihydro-2-iso amylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.

48. A compound as claimed in claim 1 which is 2-methylamino-3,4-dihydro-5-methyl-7-isobutylimidazo[5,1-f]-as-triazine, hydrochloride.

49. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-4-phenyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

50. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4-(p-methoxyphenyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

51. A compound as claimed in claim 1 which is 4-allyl-2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrogen maleate.

52. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4,5-dimethyl-7-isobutylimidazo[5,1-f]-as-triazine, hydrochloride.

53. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4-ethyl-5-methyl-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.

54. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4,5-dimethyl-7-propylimidazo[5,1-f]-as-triazine and its hydrochloride.

55. A compound as claimed in claim 1 which is N-(4-benzyl-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-2-yl)acetamide, hydrochloride.

56. A compound as claimed in claim 1 which is 5-(2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4-yl)barbituric acid.

57. A compound as claimed in claim 1 which is 5-(2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazin-4-yl)barbituric acid, hydrochloride.

58. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4-(4,4-dimethyl-2,6-dioxocyclohexyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine.

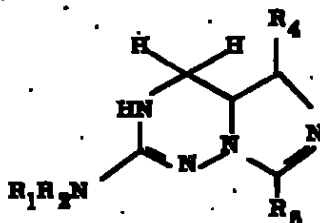
59. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-4-(p-methoxyphenacyl)-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

60. A compound as claimed in claim 1 which is 2-amino-3,4-dihydro-5-methyl-7-propylimidazo[5,1-f]-as-triazine-4-sulphonic acid.

61. A compound as claimed in claim 1 which is 2-diethylamino-5-methyl-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

62. A compound as claimed in claim 1 which is 2-amino-5-methyl-4-methylthio-7-propylimidazo[5,1-f]-as-triazine, hydrochloride.

63. The process for the preparation of compounds of the formula:

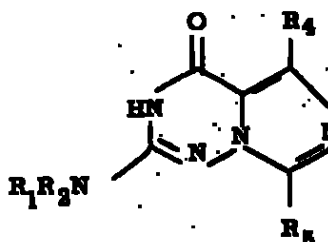


and physiologically acceptable salts and addition products thereof in which

R₁, R₂ which may be the same or different, represent a hydrogen atom, or a C₁₋₆ alkyl group which may optionally be substituted by a phenyl group, or represent a C₁₋₆ alkanoyl group or C₁₋₆ alkane sulphonyl group;

R₄ represents a hydrogen atom or a C₁₋₆ alkyl group; and

R₅ represents a hydrogen atom, a C₁₋₆ alkyl group, which alkyl group may optionally be substituted by a C₂₋₇ cycloalkyl group, or a phenyl group, which comprises the reduction with a metal hydride, diborane or sodium-dihydro-bis(2-methoxymethoxy)aluminate, of a compound having the formula:



in which

R₁, R₂, R₄ and R₅ have the meanings given above.

64. A process as claimed in claim 63 in which the reduction is effected with a metal hydride which is lithium aluminium hydride.

* * * * *

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

202075

Bogotá, D.C., 22 de Junio de 2007

Abogado**EMILIO FERRERO****(Apoderado)****Solicitante: BAYER HEALTHCARE AG.****ASUNTO****Radicación 03108302****Trámite 002****Evento 001****Actuación 430****Oficio****Folios 24**

8529

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

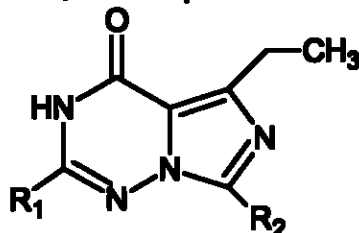
- 1.1. Descripción: Folios: 50 a 127 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 128 a 130 como se radicó inicialmente
- 1.3. Prioridad: Folios: 4 a 37 (01062001, GB,0113344.6).

2. Objeto de la invención

- **Título de la solicitud:** Derivados de imidazotriacinas y su uso contra procesos inflamatorios y/o enfermedades inmunitarias.

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos de 7-(4-terbutil-ciclohexyl)-imidazotriacinas.

Reivindicaciones 1– 3,6 : Compuesto de la fórmula (I):



- Reivindicación 4 : Procedimiento para prepararlo.
- Reivindicación 5 : Compuestos de la fórmula IV.
- Reivindicaciones 8,9 y 10 : De uso.
- Reivindicación 7 : Composición farmacéutica.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para el tratamiento y/o profilaxis de procesos inflamatorios y/o enfermedades inmunitarias.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula (I), procedimientos para su preparación, composiciones farmacéuticas que emplean dichos compuestos y métodos para utilizarlos.

La presente solicitud incluye las propiedades farmacológicas de los compuestos de la solicitud. Los compuestos de fórmula (I) son inhibidores de la fosfodiesterasa conduciendo a la acumulación de adenosinmonofosfato cíclico (cAMP) en las células. Por consiguiente la presente solicitud comprende el uso de compuestos en el tratamiento y prevención de los procesos inflamatorios agudos o crónicos como, toda clase de enfermedades obstructivas pulmonares crónicas, inflamación del tracto gastrointestinal, artritis reumatoidea, entre otras. Además incluye el uso de estos compuestos para el tratamiento y prevención de enfermedades inmunitarias como, rechazos a transplantes, esclerosis múltiple, leucemia, tumores y Sida entre otros.

El objeto de la invención definido anteriormente se clasifica de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K31/53, C07D487/04.

3. De la solicitud de Patente (según el caso)

3.1. Título :

El título de la solicitud no debería incluir el término "uso" de derivados de imidazotriacinas. Se solicita realizar la corrección respectiva.

3.2. Reivindicaciones (artículo 30 D 486)

En la reivindicación 1 el término "restos idénticos o diferentes" no se conoce en química. Se solicita hacer claridad al respecto.

En la reivindicación 6 no está definiendo los compuestos por una característica sino menciona el uso que eventualmente se les daría. Se solicita hacer claridad al respecto.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, no se puede otorgar patente al uso de las reivindicaciones 8-10, porque no es un producto ni un procedimiento tecnológico.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 01 de Junio de 2001, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

N°	Documento	Título	Fecha de Publicación*
D1	US4278673	Pharmacologically active compounds	14 de Julio de 1981
D2	US3841785	Imidazo[5,1-F]-s-triazines	2 de Marzo de 1976

6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

6.1. Nivel Inventivo (artículo 18 D486)

El documento del estado de la técnica más cercano es D1 (Pag.2. Folio 173) que enseña **Compuestos de Imidazotriacinas**, que son inhibidores de fosfodiesterasa PDE4.

La diferencia con D1 es que en esta solicitud los **Compuestos son de 7-(4-terbutil-ciclohexil)- Imidazotriacinas** y en la anterioridad son **Compuestos derivados de Imidazotriacinas**, sin tener el 4-terbutilo como sustituyente del anillo ciclohexilo.

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la Técnica más cercano; porque estos compuestos siguen teniendo efecto Inhibidor de la fosfodiesterasa PDE4.

Así que el Problema Técnico planteado en esta solicitud : La necesidad de compuestos de 7-(4-terbutil-ciclohexil)- imidazotriacinas útiles para el tratamiento y/o profilaxis de procesos inflamatorios y/o enfermedades inmunitarias, se había solucionado previamente mediante compuestos muy similares de derivados de imidazotriacinas, sin tener el 4-terbutil como reemplazo del anillo ciclohexilo. De manera que los nuevos compuestos son una alternativa a los compuestos conocidos porque no presentan un mayor efecto inhibidor de la fosfodiesterasa.

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D1 y D2 (Folio 181 a 191, enseña compuestos de Imidazo[5,1-F]-s-triazinas, su proceso de preparación, su uso en medicamentos y en particular su uso como inhibidores de la fosfodiesterasa PDE4), hubiera sugerido sin mucho esfuerzo de su parte, modificar los grupos de D1 mediante la sustitución en el anillo ciclohexilo en su cuarta posición un grupo H por un grupo terbutilo, para lograr los compuestos de 7-(4-terbutil-ciclohexil)-imidazotriacinas reivindicados que no parecen tener un mayor efecto Inhibidor de la fosfodiesterasa PDE4.

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

El procedimiento de la reivindicación 4 (Pag 3 Folio 174) que consiste en partir de un compuesto de fórmula IV (que se divulgaba previamente en D1) y hacerlo reaccionar con agente deshidratante como oxiclورو de fósforo para la formación de los compuestos reivindicados en 1-3, no está conformado por pasos sorprendentes para el Experto en la Materia; ni tampoco el producto obtenido es sorprendente, como ya se explicó. De manera que carece de Nivel Inventivo.

Para los compuestos de fórmula IV (reivindicación 5) ,la diferencia con D1 (Pag 3. Folio 174) es que en esta solicitud los compuestos tienen en R2 a 4-terbutil como sustituyente del anillo ciclohexilo y en la anterioridad son compuestos que tienen en R2 solo el anillo ciclohexilo.

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la Técnica más cercano; porque estos compuestos siguen siendo precursores de síntesis de los compuestos de la fórmula (I)

Así que el Problema Técnico planteado en esta solicitud : Compuestos de fórmula (IV), se había solucionado previamente mediante compuestos muy similares, sin tener el 4-terbutil como sustituyente del anillo ciclohexilo. De manera que los nuevos compuestos son una alternativa a los compuestos conocidos porque siguen siendo precursores de síntesis de los compuestos de fórmula I.

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D1 y D2, hubiera sugerido sin mucho esfuerzo de su parte, modificar los grupos de D1 mediante la sustitución en el anillo ciclohexilo en su cuarta posición un grupo H por un grupo terbutilo para lograr los compuestos de la fórmula (IV) reivindicados, que no parecen tener un mayor efecto porque siguen siendo precursores de síntesis de los compuestos de fórmula (I).

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

Las composiciones farmacéuticas que contienen el compuesto reivindicado (reivindicación 7), no tiene nivel inventivo porque el componente que lo caracteriza no es inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US4278673	1-7	Nivel Inventivo
D2	US3941785	1-7	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


CLARA CECILIA CASTELLAMOS DE JAIMES
Jefe de División de Nuevas Creaciones(E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

13 JUL 2007

CONCEPTO TECNICO No. 920	EXAMINADOR TECNICO Código No.202075
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EXAMEN TÉCNICO DE FONDOS			
Nº Radicación	03108302	Fecha de presentación	10-12-2003
Nº Prioridad	GB0113344 6	Fecha de prioridad	01-08-2001

Palabras clave	IMIDAZOTRIAZINONE COMPOUNDS	PHOSPODIESTERASE ACTIVE	PRODUCTION INHIBITORS
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
AK81K3153 C07D487/04

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES		
WO02098879	RU2003138078	CN1512993
EP1399447	MXP03010985	CA2449095
US2003139415	EE200300570	CZ295609
Países Originales		

BASES DE DATOS CONSULTADAS	
EPOLINE	MIMOSA
ESPAENET	
USPTO	

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EUROPEA	29-08-2002	1 10

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reivindicaciones afectadas
US4278673	Nivel Inventivo	17
US6476029	Nivel Inventivo	17

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Relv afectadas

Observaciones

Fecha de examen	Art. 45 22-08-07
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