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(54) Title: PYRIMIDINE DERIVATIVES

(57) Abstract

The present invention relates to novel pyrimidine derivatives, to processes for preparing them, to intermediates useful in preparing them, to pharmaceutical compositions containing them and to uses for them as pharmaceuticals.

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Pyrimidine Derivatives

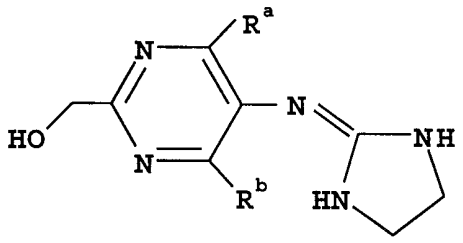
This application claims the benefit of U.S. Provisional Application No. 60/057,472, filed September 3, 1997.

The present invention relates to novel pyrimidine derivatives, to processes for preparing them, to intermediates useful in preparing them, to pharmaceutical compositions containing them and to uses for them as pharmaceuticals.

United States patent number 4,323,570 discloses a group of aminopyrimidine derivatives having antihypertensive activity. One of the compounds, 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine, is commercially available in some countries under the generic name moxonidine for the treatment of hypertension. This compound may interconvert with its tautomer, 4-chloro-5-(imidazolidin-2-ylideneimino)-6-methoxy-2-methylpyrimidine.

We have now found a novel pyrimidine derivative having a 2-hydroxymethyl substituent which possesses anti-hypertensive activity.

The present invention provides a compound of formula

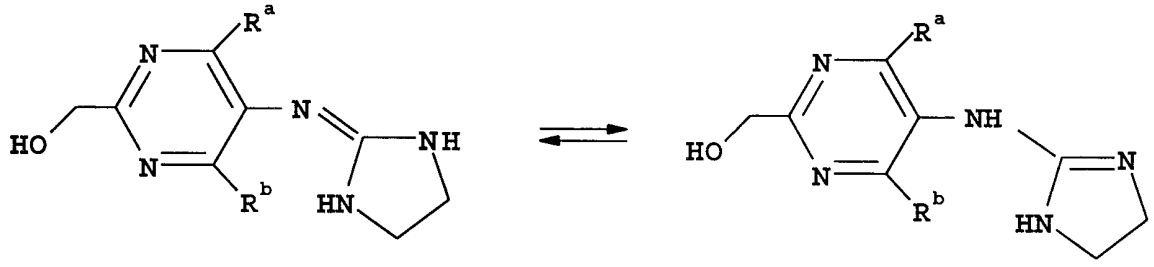


I

in which each of R^a and R^b independently represents a C_1-C_6 alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide.

The compound 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidene)-6-methoxypyrimidine has been found to lower blood pressure and heart rate when administered intravenously to spontaneously hypertensive rats at a dose of 3 mg/kg when tested according to the method described by A. D. Palkowitz *et al.*, *J. Med. Chem.*, Vol. 37, p. 4508-4521, 1994.

It will be appreciated by those skilled in the art that the compounds of formula I can exist in tautomeric form as shown below.



The invention includes each tautomeric form of the compound.

Pharmaceutically acceptable salts of the compound of formula I include acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric and phosphoric acid, as well as organic acids such as *para*-toluenesulfonic, methanesulfonic, oxalic, *para*-bromophenylsulfonic, carbonic, succinic, citric, benzoic, and acetic acid, and related inorganic and organic acids. The pharmaceutically acceptable salts thus include the hydrogen chloride, hydrogen bromide and hydrogen iodide acid addition salts.

Pharmaceutically acceptable metabolically labile ester and amides of the compound of formula I are ester or amide derivatives of the compound of formula I that are hydrolyzed <u>in vivo</u> to afford the compound of formula I and a

pharmaceutically acceptable carboxylic acid. Examples of labile esters include esters formed with the hydroxyl group in the compound of formula I and an alkanoic acid, such as acetic acid. Example of metabolically labile amides include amides formed with an NH group in the compound of formula I and an alkanoic acid such as acetic acid.

A particular value for a C_1-C_6 alkoxy group represented by R^a or R^b is methoxy.

A particular value for a halogen atom represented by R^a or R^b is chlorine.

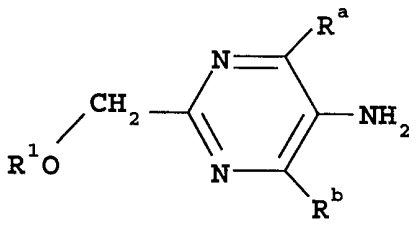
Preferably R^a represents methoxy and R^b represents chlorine.

A particularly preferred compound is 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidene)-6-methoxypyrimidine.

The compound 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidene)-6-methoxypyrimidine was originally isolated as a metabolite of moxonidine from the urine of rats and dogs. Another aspect of the invention is, therefore, a compound of formula I in a pharmaceutically acceptable state of purity.

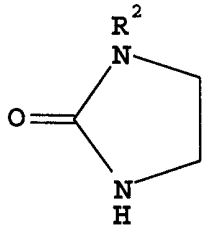
The compounds according to the invention may also be prepared by a process which comprises:

(a) reacting a compound of formula



II

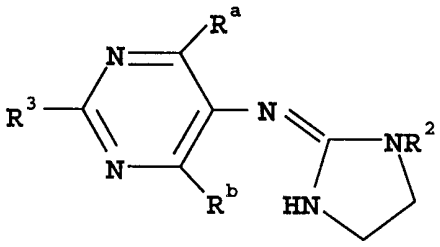
or a salt thereof, with a compound of formula



III

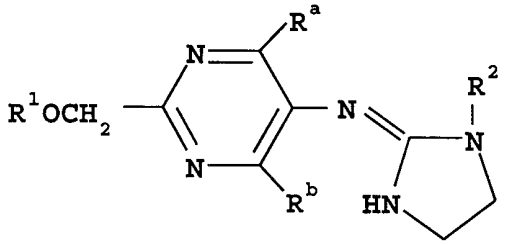
in which R^1 represents a hydrogen atom or a hydroxyl protecting group and R^2 represents a hydrogen atom or an amino protecting group; or

(b) reducing a compound of formula



IV

in which R^3 represents a carboxyl group or an ester derivative thereof, or a salt thereof;
to afford a compound of formula



Ia

of a salt thereof;
whereafter, as necessary, optionally

(i) replacing a halogen atom represented by R^a or R^b with a C_1-C_6 alkoxy group by reaction with a C_1-C_6 alkanol in the presence of a base; and further optionally

(ii) removing any remaining protecting groups; and further optionally

(iii) forming a pharmaceutically acceptable metabolically labile ester or amide; or

(iv) forming a pharmaceutically acceptable salt.

The protection of hydroxyl and amino groups, is generally described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley

& Sons, NY, 1991. Examples of hydroxyl protecting groups include acyl groups, such as groups of formula R^4CO in which R^4 represents C_1-C_6 alkyl, (3-10C) cycloalkyl, phenyl C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy, phenyl C_1-C_6 alkoxy, or (3-10C) cycloalkoxy, wherein a phenyl group may be unsubstituted or substituted by one or two substituents independently selected from amino, hydroxy, nitro, halogeno, C_1-C_6 alkyl, C_1-C_6 alkoxy, carboxy, C_1-C_6 alkoxycarbonyl, carbamoyl, C_1-C_6 alkanoylamino, C_1-C_6 alkylsulphonylamino, phenylsulphonylamino, toluenesulphonylamino, and C_1-C_6 fluoroalkyl. Examples of amine protecting groups include acyl groups of formula R^5CO, in which R^5 is as defined for R^4.

Examples of particular values for R^1 and R^2 are hydrogen and C_1-C_6 alkanoyl such as acetyl.

Examples of particular values for R^3 are carboxy and C_1-C_6 alkoxycarbonyl such as methoxycarbonyl or ethoxycarbonyl.

In process step (a), the compound of formula II is conveniently reacted with the compound of formula III in the presence of a dehydrating agent, such as phosphorous oxychloride. The reaction is conveniently conducted at a temperature in the range of from 20 to 150°C, preferably at 90 to 110°C. An excess of phosphorous oxychloride may be used as reaction solvent.

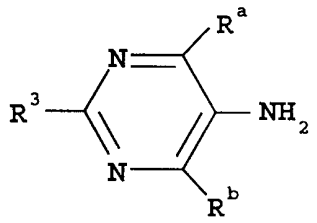
The reduction process step (b) may conveniently be performed using a reducing agent such as lithium aluminum hydride. Suitable solvents include ethers such as tetrahydrofuran.

In the replacement of a halogen atom with an alkoxy group, the base is conveniently an alkali metal alkoxide, such as a sodium alkoxide or potassium alkoxide. The reaction is conveniently performed in an alkanol as a reaction solvent, and under reflux conditions.

Any protecting groups may conveniently be removed employing a method well known in the art. For example, an acyl group protecting the hydroxyl or an amino group may conveniently be removed by acid or base catalyzed hydrolysis or methanolysis, for example by reaction with methanol in the presence of an alkali metal methoxide. In this connection, it will be appreciated that an acyl group protecting the hydroxyl or an amino group in a compound of formula Ia may be removed during the replacement of a halogen atom with an alkoxy group.

Pharmaceutically acceptable metabolically labile esters or amides of the compound of formula I, and pharmaceutically acceptable salts thereof may be prepared by methods well known in the art.

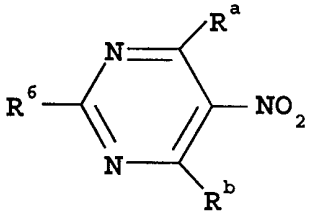
The compounds of formula IV may be prepared by reacting a compound of formula



V

or a salt thereof with a compound of formula III, following the method of process step (a).

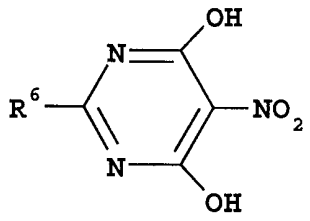
The compounds of formula II and V may be prepared by reducing a compound of formula



VI

in which R^6 represents R^1OCH_2 or R^3, as appropriate. The reduction is conveniently performed using hydrogen and a group VIII metal catalyst, for example Raney nickel.

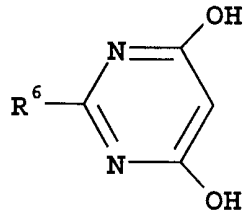
The compounds of formula VI may be prepared by reacting a compound of formula



VII

with a halogenating agent, for example a phosphorus oxyhalide. The reaction is conveniently performed in the presence of a base, such as N,N-diethylaniline. One or two atoms may subsequently be replaced with alkoxy by reaction with an alkali metal alkoxide in an alkanol.

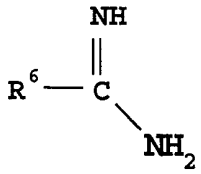
The compounds of formula VII may be prepared by reacting a compound of formula



VIII

with a nitrating agent, for example a mixture of fuming nitric acid and glacial acetic acid.

The compounds of formula VIII may be prepared by reacting a compound of formula



IX

or a salt thereof, such as the hydrochloride with a malonate, such as diethylmalonate, in the presence of a strong base, such as an alkali metal alkoxide, for example sodium ethoxide.

The compounds of formula III and IX are known, for example from US 4,323,570, or may be prepared by well-known methods.

Certain intermediates described herein, for example the compounds of formula IV are believed to be novel and are provided as further aspects of the invention.

The compounds according to the invention are preferably formulated in a pharmaceutical composition prior to administration.

According to another aspect, therefore, the present invention provides a compound of formula I, a pharmaceutically acceptable metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions may be prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, micro-crystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxy-benzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents,

preserving agents, sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation example is illustrative only and is not intended to limit the scope of the invention in any way.

Formulation Example

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The

solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

The compounds according to the invention are useful in the treatment of hypertension, congestive heart failure, non-insulin dependent diabetes mellitus, smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal and atherosclerosis. According to other aspects of the invention therefore, the present invention provides the use of the compounds of the invention for the treatment of each of the conditions in a warm blooded mammal, such as a human. The following example illustrates the invention.

Example

Biological Activity in Hypertensive Rats

Telemetry Implantation

Spontaneously hypertensive rats (Tac:N(SHR)fBR) were obtained from Taconic Farms (Germantown, NY) at 14-16 weeks of age (295-325 gm) and housed under a 12-hour light/dark cycle (lights on from 0600 to 1800 hours). Following a 1-week acclimation period, rats were anesthetized with 2% isoflurane (Aerrane, Anaquest, Madison, WI) for implantation of blood pressure transmitters (model TA11PA-C40, Data Sciences Int (DSI), St Paul, MN) as follows: The abdomen was shaved, scrubbed with Betadine®, and a 4.5-cm abdominal incision was made beginning just caudal to the approximate location of the kidneys. The abdominal aorta was isolated and gently cleaned of connective tissue with a sterile cotton swab. A small spatula was used to raise a portion of the aorta away from the vena cava in an area just rostral to

the iliac artery bifurcation. A bulldog clamp was placed caudal to the left renal artery, and the aorta was punctured rostral to the common iliac using a 21-gauge needle (bent at a 45° angle with the bevel down). A fluid-filled catheter (0.7 mm OD, 8 cm in length) attached to the hermetically sealed transmitter was inserted and advanced to the bulldog clamp using the bent needle as a guide. The area was dried with a cotton swab and tissue adhesive applied at the entry point while the clamp was removed. The entry point was further sealed using tissue adhesive and a cellulose fiber patch (Vetland, 3M Co). The body of the transmitter was sutured to the muscles of the inner abdominal wall using non-absorbable 4-0 silk, the muscle layers were approximated with sterile 3-0 silk, and the final incision closed with sterile metal wound clips. All animals were administered 10,000 units of penicillin intramuscularly (Ambi-Pen®, Butler), housed individually in shoe box cages with food and water ad libitum, and permitted to recover for at least one week before study. Digitized pressure signals were acquired for 30 seconds every 10 minutes using DSI Dataquest IV 2.0 software. Mean pressure was calculated as the arithmetic mean of the sample waveform sampled at a frequency of 500 Hz. The digitized values were stored and manipulated on a Compac Deskpro 486/33MHz computer.

Protocol

Animals were briefly sedated with 2% isoflurane. Test compounds or vehicle were administered via the tail vein in a total volume of 0.3-0.4 ml. The hydroxymethyl metabolite was administered in a water vehicle made by adding approximately 50 µl of 1N HCL to the metabolite base and slowly diluting with water to appropriate concentration. Rats were then returned to telemetry cages and blood pressure was monitored for the subsequent 24 hours. Monitoring was initiated immediately except that the values for 15 min prior and subsequent to dosing were omitted.

Results

The hydroxymethyl metabolite lowered mean blood pressure compared to vehicle in the SHR.

Table 1

Time (hours) MAP	Hydroxymethyl Metabolite	Vehicle
1.00	-15.80	10.10
2.00	-16.80	0.40
3.00	-9.40	4.00
4.00	-8.50	0.90
5.00	-7.80	-3.40
6.00	-7.80	-4.00
7.00	-7.00	-1.80
8.00	-5.80	-1.90
9.00	-5.20	5.60
10.00	-4.20	2.30
11.00	-2.60	-0.70
12.00	-7.50	1.80
13.00	-6.00	-0.10
14.00	-6.30	-0.60
15.00	-3.80	1.80
16.00	-4.50	-1.20
17.00	-3.00	-2.50
18.00	-5.60	2.10
19.00	-1.80	0.80
20.00	-4.50	2.20
21.00	-2.50	-1.60
22.00	-13.30	-1.10
23.00	-9.80	-5.20
24.00	-9.80	-2.90

The effect of the hydroxymethyl metabolite lasted for approximately 4 hours. Accompanying the effect of hydroxymethyl metabolite on blood pressure was pronounced falls in heart rate (Table 2) that were most prominent 4 hours after dosing.

Table 2

Time (hours) H r	Hydroxymethyl Metabolite	Vehicle
1.00	-32.10	24.90
2.00	-2.40	4.00
3.00	8.70	2.50
4.00	6.20	-1.90

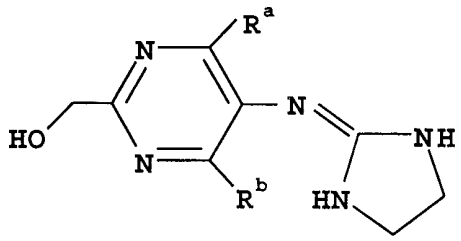
5.00	18.10	0.80
6.00	6.40	-8.30
7.00	7.20	4.70
8.00	21.40	16.60
9.00	23.20	39.50
10.00	32.80	41.50
11.00	37.00	46.50
12.00	36.80	36.50
13.00	25.80	33.60
14.00	31.00	34.40
15.00	29.80	20.80
16.00	37.00	31.10
17.00	12.70	23.40
18.00	7.60	12.60
19.00	24.50	24.90
20.00	25.80	19.60
21.00	6.10	16.80
22.00	-7.20	10.10
23.00	-10.80	-17.60
24.00	1.40	-10.00

Consistent with the shorter effect of the hydroxymethyl metabolite on blood pressure, there was also a significant fall compared to vehicle in heart rate apparent during the first hour after dosing.

Conclusion

The moxonidine hydroxymethyl metabolite has been identified in urine of rats, dogs, mice and humans. Moxonidine and the hydroxymethyl metabolite are shown to be analagous in that they both possess antihypertensive and bradycardic activity in conscious unrestrained hypertensive rats. This analogy can also be drawn from moxonidine to the hydroxymethyl metabolite in other treatments, as well, as would be apparent to those skilled in the art. Moxonidine has been shown to be an effective treatment for hypertension (U.S. Patent No. 4,323,570), smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal (U.S. Patent No. 5,732,717), congestive heart failure (PCT publication WO97/46241), non-insulin dependent diabetes (U.S. Patent No. 5,712,283), and atherosclerosis (PCT

publication WO96/26728). Therefore, another embodiment of this invention is the use of a compound of the formula



I

in which each of R^a and R^b independently represents a C_1-C_6 alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide for the treatment of hypertension, smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal, congestive heart failure, non-insulin dependent diabetes, and atherosclerosis.

The particular dose of compound administered according to this invention for the treatment of the indications alone or in combination will of course be determined by the particular circumstances surrounding the case, including the compound administered, the warm blooded mammal being treated, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from 0.005 mg/kg to 50 mg/kg of the active compound of this invention. Preferably, daily doses will be 0.01 mg/kg to 25 mg/kg, more preferably from 0.1 mg/kg to 10 mg/kg.

The following Example illustrates the invention.

Example 1

2-Hydroxymethyl-4-chloro-5-(imidazolin-2-ylideneimino)-6-methoxypyrimidine

(a) Preparation of 4,6-dihydroxy-2-hydroxymethylpyrimidine:

To a solution of sodium ethoxide prepared from sodium (1.38 g, 60.0 mmol) and ethanol (29 mL), was added hydroxyacetamidine hydrochloride (McCasland, G. E. and Tarbell, S. - *J. Amer. Chem. Soc.*, 1946, **68**, 2393-2395) (2.21 g, 20.0 mmol) and after 5 min ethyl malonate (3.2 g, 20.0 mmol). The reaction mixture was refluxed for 3 hours then cooled to room temperature, diluted with water (10 mL) and acidified with concentrated hydrochloric acid (4 mL). The precipitate was filtered off, washed with water (10 mL), ethanol (5 mL) and ether (5 mL), and dried under vacuum to give 2.24 g (79%) of the title compound as a light-brown solid. IR (KBr): 527, 1106, 1324, 1571, 1639, 1682, 2910, 3029, 3084 cm^{-1}·, UV (EtOH) λ max(ε): 256 (4235), 239 nm (3398); ^{1}H-NMR (DMSO-d_6) δ 4.28(s), 5.14(s), 5.66(s); MS(FD): 142 (M^+, 100%).

(b) Preparation of 4,6-dihydroxy-2-hydroxymethyl-5-nitropyrimidine:

To a stirred mixture of nitric acid (fuming, 4.2 mL) and acetic acid (glacial, 2.1 mL) was added the product of Step (a) (2.3 g, 16.2 mmol) over the period of 40 min at 10-15°C. The reaction mixture was stirred for 5.5 hours at room temperature then cooled down to 5°C and diluted with cold water (3 mL). The precipitate was collected by filtration, washed with ethanol (5 mL) and ether (5 mL), and dried under vacuum to give 2.44 g (80.5%) of title compound as a colorless solid. IR (KBr): 539, 789, 1105, 1297, 1358, 1630, 1674, 2828, 2920, 3402, 3460 cm^{-1}·, UV (EtOH) λ max(ε): 322 (3354), 213 nm (17626); ^{1}H-NMR (DMSO-d_6) δ 4.42 (s,CH_2); MS (FD): 187 (M^+, 100%).

(c) Preparation of 2-acetoxymethyl-4,6-dihydroxy-5-nitropyrimidine:

A mixture of the product of Step (b) (2.35 g, 12.56 mmol), acetic acid (glacial, 15 mL), and acetic anhydride (15 mL) was heated at 105°C for 2 hours, then evaporated under vacuum, and re-evaporated with toluene (3 times). The residue was dried under vacuum to give 2.843 g (99%) of title compound as a yellow solid. IR (KBr): 545, 787, 1212, 1326, 1354, 1367, 1493, 1650, 1673, 1758, 2939, 3082, 3141 cm^{-1}., UV (EtOH) λ max(ε): 327 nm (3365); ^{1}H-NMR (DMSO-d_6) δ 2.14 (s, 3H, CH_3), 4.98 (s, 2H, CH_2); MS (FD): 229 (M^+, 100%).

(d) Preparation of 2-acetoxymethyl-4,6-dichloro-5-nitropyrimidine:

To a mixture of the product of Step (c) (2.75 g, 12.0 mmol) and phosphorus oxychloride (13 mL) was added N,N-diethylaniline (2.5 mL, 15.7 mmol) dropwise. The reaction mixture was refluxed for 2 hours and evaporated under vacuum. The residue was diluted with ether (15 mL) and poured onto ice. After stirring for 3 min organic layer was separated, washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, then dried over sodium sulfate and evaporated under vacuum. Flash chromatography of the residue on silica gel (20% ether in hexane) gave 2.446 g (77%) of title compound as a white solid, R_f 0.60 (hexane/ethyl acetate, 3:2). IR (KBr): 836, 853, 1218, 1550, 1755 cm^{-1}., UV (EtOH) λ max(ε): 259 nm (3290); ^{1}H-NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 5.33 (s , 2H, CH_2). Analysis calculated for $C_7H_5Cl_2N_3O_4$: C, 31.60; H, 1.89; N, 15.79. Found: C, 31.84; H, 1.85; N, 15.69.

(e) Preparation of 2-acetoxymethyl-4,6-dichloro-5-aminopyrimidine:

A mixture of the product of Step (d) (255 mg, 0.96 mmol) and Raney nickel (30 mg) in ethanol (25 mL) was hydrogenated in Parr apparatus (50 pSi of hydrogen) for 5.5 h. The resulting suspension was filtered through celite and evaporated under vacuum. Flash chromatography of the residue on silica gel (40% ethyl acetate in hexane) gave 202 mg (89%) of title compound as a colorless solid, R_f 0.41 (hexane/ethyl acetate, 3:2). IR (KBr): 793, 907, 1249, 1366, 1459, 1513, 1621, 1731, 3332, 3428 cm^{-1}., UV (EtOH) λ max(ε): 314 (5676), 253 nm (11629); ^{1}H-NMR ($CDCl_3$) δ 2.21 (s, 3H, CH_3), 4.55 (s, 2H, NH_2), 5.16 (s, 2H, CH_2); MS (FD): 235 (M^+, 100%).

(f) Preparation of 2-acetoxymethyl-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)pyrimidine:

To a solution of the product of Step (e) (191 mg, 0.81 mmol) in phosphorus oxychloride (1 mL) was added N-acetyl-2-imidazolidone (114 mg, 0.89 mmol) in one portion. The reaction mixture was heated at 105-110°C (bath) for 3 hours and evaporated under vacuum. The residue was diluted with ice water (2 mL), made alkaline with aqueous sodium hydroxide (5*N*, 2 mL) and extracted with dichloromethane (3 x 5 mL). The extract was washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, dried over sodium sulfate and evaporated under vacuum. Flash chromatography of the residue on silica gel (from 50 to 60% of ethyl acetate in hexane) gave 166 mg (59%) of title compound as a colorless solid, R_f 0.21 (hexane/ethyl acetate, 1:1). IR (KBr): 815, 1033, 1074, 1219, 1355, 1378, 1414, 1497, 1657, 1675, 1752, 3254, cm^{-1}., UV (EtOH) λ max(ε): 245 nm (12118); ^{1}H-NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3COO), 2.70 (s, 3H, CH_3CON), 3.58 (t, J = 7.98 Hz, 2H,

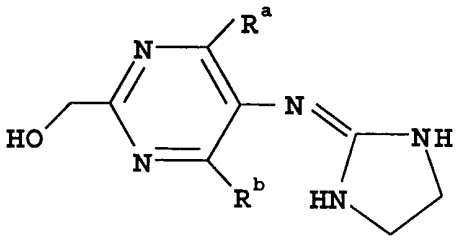
CH_2N), 4.11 (t, J = 7.98 Hz, 2H, CH_2N), 4.74 (s, 1H, NH), 5.19 (s, 2H, CH_2O); HRMS (FAB): calculated for $C_{12}H_{13}Cl_2N_5O_3$: 346.0474. Found: 346.0481.

(g) Preparation of 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxypyrimidine

A solution of the product of Step (f) (87 mg, 0.25 mmol) and sodium methoxide (14 mg, 0.26 mmol) in methanol (1.2 mL) was refluxed for 3 hours. The reaction mixture was evaporated under vacuum to one half of the initial volume and cooled to 5°C. The precipitate was collected by filtration, washed with water (1 mL) and dried under vacuum to give 32 mg (50%) of title compound as a colorless solid. IR (KBr): 720, 1042, 1091, 1283, 1307, 1376, 1440, 1471, 1533, 1659, 3030, 3225, 3340 cm^{-1}., UV (EtOH) λ max(ε): 254 nm (8577); ^{1}H-NMR (DMSO-d_6) δ 3.34 (s, 4H, CH_2N), 3.87 (s, 3H, CH_3), 4.39 (d, J = 6.18 Hz, 2H, CH_2O), 5.19 (t, J = 6.18 Hz, 1H, OH), 6.26 (s, 2H, NH), HRMS (FAB): calculated for $C_9H_{12}ClN_5O_2$: 258.0758. Found: 258.0759.

We Claim:

1. A compound of formula



I

in which each of R^a and R^b independently is a C_1-C_6 alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide.

2. A compound as claimed in Claim 1, in which R^a is methoxy and R^b is chlorine.

3. The compound of Claim 1, which is 2-hydroxymethyl-4-chloro-5-(imidazolin-2-ylideneimino)-6-methoxypyrimidine.

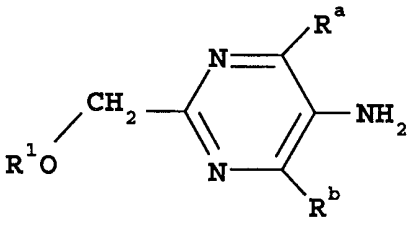
4. A compound as claimed in any one of Claims 1 to 3, which is in a pharmaceutically acceptable state of purity.

5. A pharmaceutical composition, which comprises a compound as claimed in Claim 1 together with a pharmaceutically acceptable diluent or carrier.

6. A method of treating hypertension, congestive heart failure, non-insulin dependent diabetes, smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal, or atherosclerosis in a warm blooded mammal requiring such treatment, which comprises administering an effective amount of a compound as claimed in Claim 1.

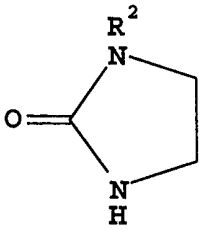
7. A process for preparing a compound as claimed in Claim 1, which comprises:

(a) reacting a compound of formula



II

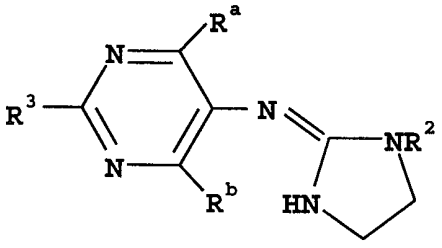
or a salt thereof, with a compound of formula



III

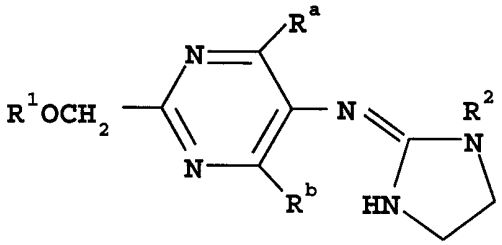
in which R^1 is a hydrogen atom or a hydroxyl protecting group and R^2 is a hydrogen atom or an amino protecting group; or

(b) reducing a compound of formula



IV

in which R^3 is a carboxyl group or an ester derivative thereof, or a salt thereof;
to afford a compound of formula



Ia

of a salt thereof; and optionally,

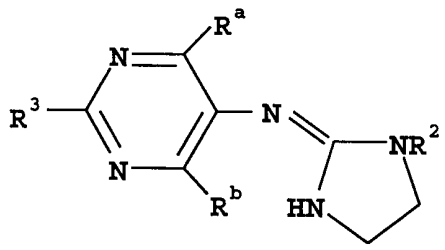
(i) replacing a halogen atom of R^a or R^b with a C_1-C_6 alkoxy group by reaction with C_1-C_6 alkanol in the presence of a base; and optionally

(ii) removing any remaining protecting groups; and optionally

(iii) forming a pharmaceutically acceptable metabolically labile ester or amide; and optionally

(iv) forming a pharmaceutically acceptable salt.

8. A compound of formula

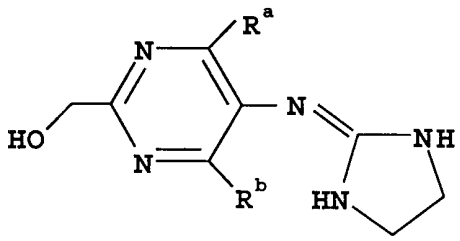


IV

in which R^a and R^b each independently are a C_1-C_6 alkoxy group or a halogen atom, R^2 is a hydrogen atom or an amino protecting group, and R^3 is a carboxyl group or an esterified carboxyl group, or a salt thereof.

9. A compound as claimed in Claim 10, in which R^2 is a hydrogen atom or a C1-C6 alkanoyl group and R^3 represents a carboxyl group or a C_1-C_6 alkoxycarbonyl group.

10. A compound of formula



I

in which each of R^a and R^b independently represents a (1-6C)alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide.

11. A compound as claimed in Claim 10, in which R^a is methoxy and R^b is chlorine.

12. The compound of Claim 10, which is 2-hydroxymethyl-4-chloro-5-(imidazolin-2-ylideneimino)-6-methoxypyrimidine.

13. A compound as claimed in any one of Claims 10 to 12, which is in a pharmaceutically acceptable state of purity.

14. A pharmaceutical composition, which comprises a compound as claimed in Claim 10 together with a pharmaceutically acceptable diluent or carrier.

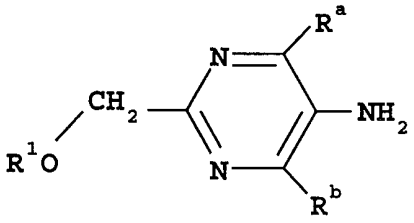
15. A compound as claimed in Claim 10 for use in therapy.

16. The use of a compound as claimed in Claim 10 for the manufacture of a medicament for the treatment of hypertension, congestive heart failure, non-insulin

dependent diabetes, smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal or atherosclerosis.

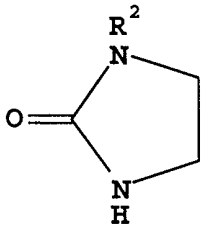
17. A process for preparing a compound as claimed in Claim 10, which comprises:

(a) reacting a compound of formula



II

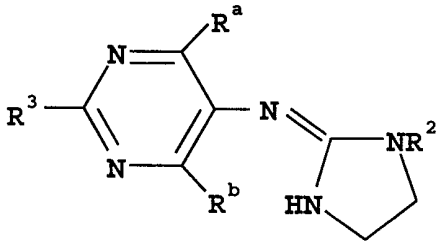
or a salt thereof, with a compound of formula



III

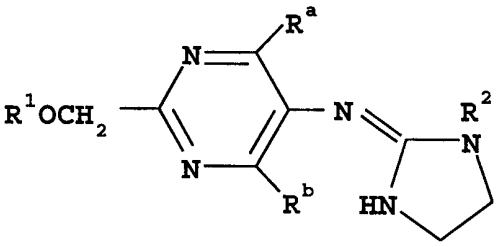
in which R^1 represents a hydrogen atom or a hydroxyl protecting group and R^2 represents a hydrogen atom or an amino protecting group; or

(b) reducing a compound of formula



IV

in which R^3 represents a carboxyl group or an ester derivative thereof, or a salt thereof;
to afford a compound of formula



Ia

of a salt thereof;
whereafter, as necessary,

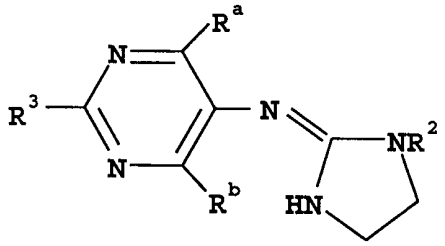
(i) replacing a halogen atom represented by R^a or R^b with a (1-6C)alkoxy group by reaction with (1-6C)alkanol in the presence of a base;

(ii) removing any remaining protecting groups;

(iii) forming a pharmaceutically acceptable metabolically labile ester or amide; and

(iv) forming a pharmaceutically acceptable salt.

18. A compound of formula

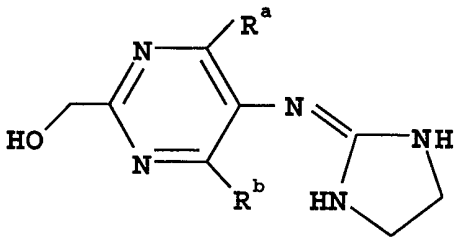


IV

in which R^a and R^b each independently represent a (1-6C)alkoxy group or a halogen atom, R^2 represents a hydrogen atom or an amino protecting group, and R^3 represents a carboxyl group or an esterified carboxyl group, or a salt thereof.

19. A compound as claimed in Claim 18, in which R^2 represents a hydrogen atom or a C_{1-6} alkanoyl group and R^3 represents a carboxyl group or a (1-6C)alkoxycarbonyl group.

20. A compound of formula



I

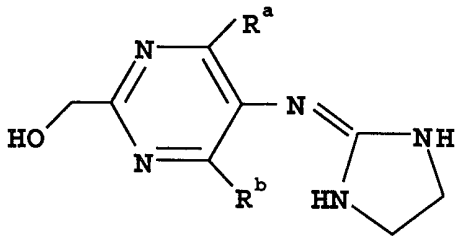
in which each of R^a and R^b independently represents a (1-6C)alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide.

21. A compound as claimed in Claim 20, in which R^a is methoxy and R^b is chlorine.

22. The compound of Claim 20, which is 2-hydroxymethyl-4-chloro-5-(imidazolin-2-ylideneimino)-6-methoxypyrimidine.

23. A compound as claimed in any one of Claims 20 to 22, which is in a pharmaceutically acceptable state of purity.

24. A pharmaceutical formulation adapted for the treatment of hypertension, congestive heart failure, non-insulin dependent diabetes, smoking cessation, opioid withdrawal, ethanol withdrawal or atherosclerosis comprising as an active ingredient a compound having the Formula



I

in which each of R^a and R^b independently represents a (1-6C)alkoxy group or a halogen atom; a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt of said compound, said ester or said amide.

25. The formulation of Claim 24 adapted for the treatment of hypertension, congestive heart failure, non-insulin dependent diabetes, smoking cessation, nicotine withdrawal, opioid withdrawal, ethanol withdrawal or atherosclerosis comprising as an active ingredient a compound having the Formula comprising as an active ingredient a compound of Formula I wherein which R^a is methoxy and R^b is chlorine.

26. The formulation of Claim 24 adapted for the treatment of hypertension, congestive heart failure, non-insulin dependent diabetes, smoking cessation, opioid withdrawal, ethanol withdrawal or atherosclerosis comprising as an active ingredient a compound having the Formula comprising as an active ingredient a compound of Formula I wherein the compound is 2-hydroxymethyl-4-chloro-5-(imidazolin-2-ylideneimino)-6-methoxypyrimidine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18381

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505; C07D 239/42
US CL :544/322, 319; 514/269, 256
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/322, 319; 514/269

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 4,323,570 A (STENZEL ET AL.) 06 April 1982, see columns 1-2.	7, 17, 5, 6, 14, 24, 25, 26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
04 DECEMBER 1998	29 DEC 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOHN M. FORD aco Telephone No. (703) 308-1235

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