(12) UK Patent (19) GB (11) 2 262 739 (13) B

(54) Title of Invention

Benzofuranylimidazole derivatives

(51) INT CL[6]; **C07D 405/04, A61K 31/415** // (**C07D 405/04 233:54 307:78**)

(21) Application No
9226997.6

(22) Date of filing
24.12.1992

(30) Priority Data

(31) **9127430**

(32) **27.12.1991**

(33) **GB**

(43) Application published
30.06.1993

(45) Patent published
17.05.1995

(52) Domestic classification
(Edition N)
C2C CAA CWD CZB C1410 C1473 C213 C215 C246 C247 C25Y C250 C252 C253 C28X C29X C29Y C30Y C305 C31Y C314 C337 C36Y C364 C365 C43X C50Y C509 C623 C624 C672 C80Y C802
U1S S1317

(56) Documents cited
US3927023 A
J. Med.Chem. 27 (5) 570-6 (1984)
Indian J.Chem., Sect.B, 18B (3), 254-6 (1979)

(58) Field of search

As for published application 2262739 A *viz:*
UK CL(Edition L) **C2C CWD CZB**
INT CL[5] **C07D**
Online databases: CAS ONLINE
updated as appropriate

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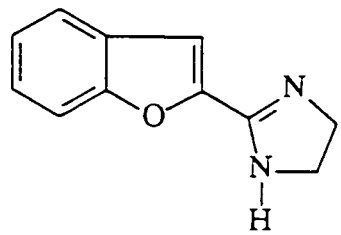
TITLE

Benzofuranylimidazole Derivatives

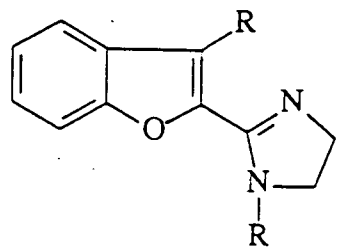
DESCRIPTION

The invention relates to benzofuranylimidazole derivatives, to a process for their preparation and to pharmaceutical compositions containing them. The benzofuranylimidazole derivatives of the invention have a high selectivity for imidazoline receptors.

Some series of benzofuranylimidazole derivatives have been described in the literature. Thus, in Indian J. Chem. 1979, 18B, 254, the following compound is disclosed.

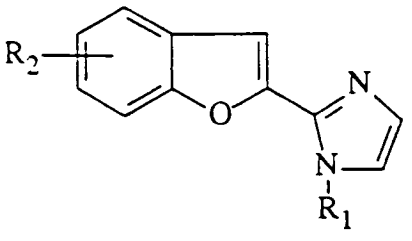


This compound was evaluated for antibacterial and antifungal activity without showing any noteworthy activity. In the US patent 3927023 there are disclosed compounds of the following formula



indicated for the treatment of gastric ulcers. Recently, it has been found that some α_2-adrenoceptor antagonists also show affinity for the so-called "imidazoline receptor" (see for instance: Laugien et al., Mol. Pharmacol, 1990, 37,1876). The imidazoline receptors are related to the regulation of blood pressure, modulation of insulin release and other biological functions (see for instance: Bousquet et al., Am. J. Med. 1989, (supp 3C), 105. Moreover, it seems that the imidazoline compounds are able to inhibit the noradrenaline release in aorta and pulmonary arteries, involving purinoceptors P_1 and prostaglandin receptors (see for instance: Göthert et al., Naunyn-Schmied. Arch. Pharmacol. 1991, 343, 271).

The invention provides benzofuranylimidazole derivatives of the general formula (1)



(1)

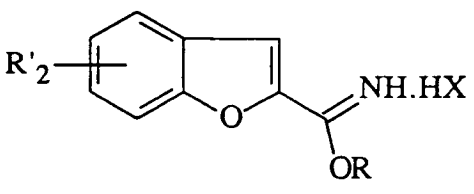
wherein

R_1 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, and R_2 represents a hydroxy group or a group R'_2 wherein R represents a hydrogen or halogen atom, an alkyl group having from 1 to 6 carbon atoms or an alkoxy group having from 1 to 5 carbon atoms; and further provides pharmaceutically acceptable salts of such derivatives. Said salts may be those formed with both organic and inorganic acids such as hydrochloric, sulphuric, phosphoric, acetic, citric, propionic, malonic, succinic, fumaric, tartaric, cinnamic, methanesulphonic and p-toluene-sulphonic acids, and preferably hydrochloric acid.

The compounds of the invention possess affinity for imidazoline receptors and very low affinity for the α_2-adrenergic receptors.

The invention also provides processes for the preparation of the benzofuranylimidazole derivatives of the general formula (1). In particular, those benzofuranylimidazole derivatives (1) wherein R_1 represents a hydrogen atom and R_2 represents a group R'_2 as above defined may be prepared by

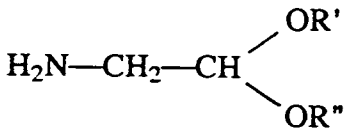
reacting a compound of the general formula (2)



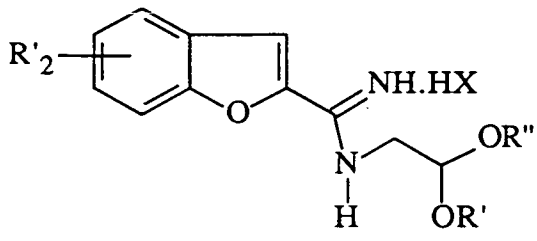
(2)

wherein R'_2 is as above defined, R represents an alkyl group having from 1 to 4 carbon atoms and HX represents an acid,

with at least one molar equivalent of an aminoacetaldehyde dialkyl acetal of the general formula



wherein each of R' and R" independently represents an alkyl group having from 1 to 4 carbon atoms, in a polar solvent for 1 to 24 hours at a temperature of from -5°C to the boiling point of the reaction mixture, and
cyclising the resultant compound of the general formula (3)



(3)

in an aqueous acidic medium for from 1 to 24 hours at a temperature of from 15 to 80°C.

In the compounds (2), R preferably represents a methyl or ethyl group and HX preferably represents hydrochloric acid. The aminoacetaldehyde dialkyl acetal is preferably the dimethyl or diethyl acetal, that is R' and R" are both methyl or both ethyl. The reaction of the compound (2) with the acetal is preferably conducted in a polar solvent, such as methanol or ethanol; more preferably, it is conducted for from 15 to 17 hours in refluxing methanol. The cyclisation is preferably conducted at from 40 to 60°C for from 16 to 20 hours in 10% aqueous hydrochloric acid.

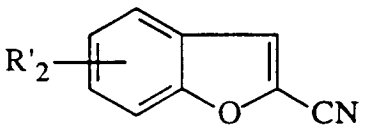
The benzofuranylimidazole derivatives (1) wherein R_1 represents an alkyl group having from 1 to 6 carbon atoms and R_2 is as above defined may be prepared by treating a compound of the general formula (1) wherein R_1 represents a hydrogen atom and R_2 is as above defined first with a base in an aprotic solvent at a temperature of from -10 to 25°C and secondly with an alkyl halide having from 1 to 6 carbon atoms or with an alkyl sulphonate having from 1 to 6 carbon atoms.

Preferably the base used in the first treatment is sodium hydride. The reaction may be

conducted in an aprotic solvent such as dimethylformamide (DMF), preferably at 0°C.

The benzofuranylimidazole derivatives (1) wherein R_1 is as above defined and R_2 represents a hydroxy group may be prepared by treating a compound of the general formula (1) wherein R_1 is as above defined and R_2 represents an alkoxy group having from 1 to 5 carbon atoms with a dealkylating agent. A suitable dealkylating agent is trimethylsilyl iodide or aqueous hydrogen bromide.

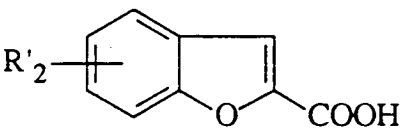
The compounds of the general formula (2) may be prepared from the corresponding cyano compounds of the general formula (4)



(4)

by treatment with an alcohol of the formula ROH wherein R is as above defined, in the presence of an acid HX. Most conveniently, the alcohol used is methanol and the acid HX is hydrochloric acid.

The cyano compounds (4) may in turn be prepared from the corresponding carboxylic acid of the general formula (5)



(5)

by treatment with a halogenating agent and subsequent reaction with ammonia, followed by dehydration with phosphorus pentoxide. The acids (5) are obtained according to the method described in J. Am. Chem. Soc. 1951, 73, 872.

Finally, the invention provides a pharmaceutical composition comprising a benzofuranylimidazole derivative of the general formula (1) as above defined or a pharmaceutically acceptable salt of such a derivative in admixture with a pharmaceutically acceptable diluent or carrier.

The following examples illustrate the invention. In these examples, the various compounds and intermediates were characterised by their NMR spectra recorded on a Varian (Trade Mark) Gemini 200 spectrometer at 200MHz for ^{1}H and at 50MHz for ^{13}C and are reported in ppm downfield from the resonance of tetramethylsilane. Melting points were measured on a Buchi melting point apparatus in glass capillary tubes and are uncorrected. IR spectra were recorded on a Nicolet (Trade Mark) 5PC FT-IR spectrophotometer.

EXAMPLE 1:

2-(benzofuran-2-yl)imidazole hydrochloride

R_1= H R_2= H

a) preparation of benzofuran-2-carbonyl chloride

Thionyl chloride (12.5 ml) was added to a suspension of benzofuran-2-carboxylic acid (20g) in anhydrous benzene (250 ml). The mixture was refluxed for 3 hours, then allowed to cool down to room temperature. Removal of the volatiles left the desired acid chloride (21.8g, 98%).

b) preparation of benzofuran-2-carboxamide

Benzofuran-2-carbonyl chloride (21.8 g) was added in small portions to an ice cold solution of ammonia (200 ml, d=0.91). Upon completion of the addition the reaction mixture was allowed to reach room temperature and the desired carboxamide formed a precipitate. The solid was collected by filtration, washed with water and dried in vacuo (17.8g, 91%). IR: (KBr): 1661 cm^{-1}

^{1}H-NMR (DMSO-d_6): 7.35 (t,1H), 7.45 (t,1H), 7.60 (s,1H), 7.65 (d,1H), 7.75 (d,1H), 7.70-8.20 (d,2H).

c) preparation of 2-cyanobenzofuran

Phosphorus pentoxide (86g) was added to a suspension of benzofuran-2-carboxamide (17.8g) in anhydrous toluene (500 ml) and the mixture was refluxed for 3 hours. After cooling the supernating solution was decanted off and the resulting residue extracted with toluene. The combined toluene fractions were evaporated to leave the cyano compound as an oil (10.7g, 68%). IR: (NaCl): 2231 cm^{-1}

^{1}H-NMR (DMSO-d_6): 7.45 (t,1H), 7.55 (t,1H), 7.75 (d,1H), 7.85 (d,1H), 8.10 (s,1H).

d) preparation of methyl benzofuran-2-carboximidate hydrochloride

2-Cyanobenzofuran (10.7g) was dissolved in ethereal HCl (150 ml, 5M) and methanol (12 ml). The resulting mixture was kept at 4°C for 48 hours. The resulting solid was filtered, washed with ether and dried (13.4g, 85%).

^{1}H-NMR (DMSO-d_6): 4.30 (s,3H), 7.50 (t,1H), 7.70 (t,1H), 7.80 (d,1H), 7.90 (d,1H), 8.40 (s,1H).

e) preparation of 2-(benzofuran-2-yl)-imidazole hydrochloride

A solution of aminoacetaldehyde dimethylacetal (7.3 g) and methyl benzofuran-2-carboximidate hydrochloride (13.4 g) in methanol (135 ml) was stirred at 60°C for 16 hours. The mixture was then evaporated to dryness. Hydrochloric acid (750 ml, 2M) was added and the resulting mixture was stirred at 60°C for 16 hours. After cooling, the solution was washed with dichloromethane. The aqueous layer was basified with sodium hydroxide and the free base was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried. Evaporation of the solvent gave a solid residue which was dissolved in diethyl ether/ethanol. Ethereal HCl was added to solution and the precipitated salt was collected by filtration (12.5g, 90%).

m.p.= 225-227°C

^{1}H-NMR (DMSO-d_6):

7.40 (t,1H), 7.50 (t,1H), 7.75 (d,1H), 7.85 (s,2H), 7.90 (d,1H), 8.20 (s,1H).

^{13}C-NMR (DMSO-d_6):

110.4, 112.1, 121.2, 123.4, 124.9, 127.6, 127.8, 135.4, 141.1, 155.1.

EXAMPLE 2:

1-methyl-2-(benzofuran-2-yl)imidazole hydrochloride

R_1= CH_3- R_2= H

To a solution of the free base (7.0g) generated from 2-(benzofuran-2-yl)imidazole hydrochloride in DMF (50ml) at 0°C was added sodium hydride (1.4g) 80% in mineral oil in three equal portions. After 30 minutes at room temperature, methyl iodide (2.5ml) was added dropwise over 15 minutes at 0°C. The mixture was then stirred for 30 minutes at room temperature, poured into water and extracted with ethyl acetate. The organic layer was washed with water and the product was extracted with hydrochloric acid (1M). The aqueous layer was basified with sodium hydroxide and the free base was extracted with ethyl acetate, washed with saturated brine and dried. Evaporation of the solvent gave a solid residue which was dissolved in diethyl ether/ethanol. Ethereal HCl was added to solution and the precipitated salt was collected by filtration (8.1g, 91%).

m.p.= 232-235°C

^{1}H-NMR (DMSO-d_6):

4.20 (s,3H), 7.45 (t,1H), 7.55 (t,1H), 7.80 (d,1H), 7.90 (d,1H), 8.00 (d,1H), 8.20 (s,1H).

^{13}C-NMR (DMSO-d_6):

38.4, 112.0, 112.2, 120.3, 123.3, 125.0, 126.1, 127.2, 128.0, 135.2, 140.2, 155.0.

EXAMPLE 3:

2-(6-methoxybenzofuran-2-yl)imidazole hydrochloride

R_1 = H R_2 = 6-methoxy

This was prepared from 6-methoxybenzofuran-2-carboxylic acid according to the methods a - e as described in example 1; m.p.= 245-248°C.

^{1}H-NMR (DMSO-d_6):

3.90 (s,3H), 7.05 (dd,1H), 7.25 (d,1H), 7.75 (d,1H), 7.80 (s,2H), 8.10 (s,2H).

^{13}C-NMR (DMSO-d_6):

56.1, 96.2, 110.7, 114.2, 120.6, 120.8, 123.6, 135.6, 140.0, 156.5, 160.4.

EXAMPLE 4:

2-(6-hydroxybenzofuran-2-yl)imidazole hydrochloride

R_1 = H R_2 = 6-hydroxy

The free base (3.0 g) generated from 2-(6-methoxy-benzofuran-2-yl)imidazole hydrochloride was treated with 47% w/v hydrobromic acid solution (30 ml) and the mixture heated at 100°C for 7 hours with stirring. After cooling the resulting solid was filtered, dissolved in water and basified with sodium bicarbonate. The free base was extracted with ethyl acetate, washed with saturated brine and dried. Evaporation of the solvent gave a solid residue which was dissolved in diethyl ether/ethanol. Ethereal HCl was added to solution and the precipitated salt was collected by filtration (2.2g, 66%).

^{1}H-NMR (DMSO-d_6):

6.95 (dd,1H), 7.10 (d,1H), 7.65 (d,1H), 7.80 (s,2H), 8.00 (s,1H).

^{13}C-NMR (DMSO-d_6):

97.9, 110.8, 114.8, 119.4, 120.7, 123.6, 135.9, 139.2, 156.7, 158.9.

EXAMPLE 5:

1-ethyl-2-(benzofuran-2-yl)imidazole hydrochloride

R_1= C_2H_5- R_2= H

This was prepared from 2-(benzofuran-2-yl)imidazole hydrochloride and ethyl bromide according to the procedure of example 2 ; m.p.= 183-185°C.

^{1}H-NMR (DMSO-d_6):

1.55 (t,3H), 4.60 (q,2H), 7.45 (t,1H), 7.55 (t,1H), 7.80 (d,1H), 7.90 (d,1H), 7.95 (d,1H), 8.10 (d,1H), 8.20 (s,1H).

^{13}C-NMR (DMSO-d_6):

15.4, 44.6, 112.2, 112.2, 121.0, 123.2, 124.4, 124.9, 127.1, 127.9, 134.4, 140.1, 155.1.

EXAMPLE 6:

2-(5-bromobenzofuran-2-yl)imidazole hydrochloride

R_1 = H R_2 = 5-bromo

This was prepared from 5-bromobenzofuran-2-carboxylic acid according to the methods a - e as described in example 1 ; m.p.= 280°C.

^{1}H-NMR (DMSO-d_6):

7.65 (dd,1H), 7.75 (d,1H), 7.85 (s,2H), 8.10 (s,1H), 8.15 (d,1H).

^{13}C-NMR (DMSO-d_6):

109.3, 114.1, 117.1, 121.6, 125.8, 129.9, 130.3, 135.0, 142.5, 154.0.

EXAMPLE 7:

2-(5-methoxybenzofuran-2-yl)imidazole hydrochloride

R_1 = H R_2 = 5 - methoxy

This was prepared from 5-methoxybenzofuran-2-carboxylic acid according to the methods a - e as described in example 1 ; m.p.= 232-235°C.

^{1}H-NMR (DMSO-d_6):

3.80 (s,3H), 7.10 (dd,1H), 7.40 (d,1H), 7.65 (d,1H), 7.80 (s,2H), 8.10 (s,1H).

^{13}C-NMR (DMSO-d_6):

56.0, 104.7, 110.3, 112.7, 116.9, 121.2, 128.3, 135.6, 141.8, 150.0, 157.0.

EXAMPLE 8:

2-(5-hydroxybenzofuran-2-yl)imidazole hydrochloride

R_1 = H R_2 = 5 - hydroxy

This was prepared from the free base generated from 2-(5-methoxybenzofuran-2-yl)imidazole hydrochloride according to the procedure of example 4.

^{1}H-NMR (DMSO-d_6):

7.00 (dd,1H), 7.15 (d,1H), 7.55 (d,1H), 7.80 (s,2H), 8.00 (s,1H).

^{13}C-NMR (DMSO-d_6):

106.8, 110.3, 112.4, 117.1, 121.1, 128.4, 135.7, 141.2, 149.4, 155.1.

EXAMPLE 9:

1-ethyl-2-(6-methoxybenzofuran-2-yl)imidazole hydrochloride

$R_1 = C_2H_5$- $R_2 = 6$ - methoxy

This was prepared from 2-(6-methoxybenzofuran-2-yl) imidazole hydrochloride and ethyl bromide according to the procedure of example 2 ; m.p.= 259-261°C.

^{1}H-NMR (DMSO-d_6):

1.50 (t,3H), 3.90 (s,3H), 4.50 (q,2H), 7.15 (dd,1H), 7.35 (d,1H), 7.75 (d,1H), 7.85 (d,1H), 7.95 (d,1H), 8.10 (s,1H).

^{13}C-NMR (DMSO-d_6):

15.4, 44.4, 56.1, 96.0, 112.2, 114.5, 120.1, 120.5, 123.3, 123.8, 134.5, 138.8, 156.3, 160.2.

The pharmacological activities of the compounds of the invention have been determined according to the following procedures.

Binding studies

Initial biological evaluation of alpha$_1$- and alpha$_2$-adrenoceptor and imidazoline preferring receptor (IR) affinities and selectivities in homogenized rat cerebral cortex were assessed by determining the K_i values of the compounds to displace ^{3}H-prazosin ^{3}H-clonidine as well as ^{3}H-idazoxan in the presence of (-)-adrenaline according to the method of Olmos et al. (J. Neurochem. 1991, 57: 1811-1813).

This in vitro model is particularly useful as an initial screening for studying the affinity and the selectivity of these compounds on the imidazoline receptors. The K_i (nM) values of the tested compounds to displace the binding of ^{3}H-idazoxan (4 nM) in the presence of (-)-adrenaline (10^{-6} M) (IR affinity), ^{3}H-clonidine (2 nM) and ^{3}H-prazosin (0.5 nM), (alpha$_2$- and alpha$_1$-adrenoceptors affinity respectively), are summarized in table 1; this table shows the potential affinities and selectivities of compounds and two standard drugs regarding these receptors.

Theremore, the affinities of compounds of the invention for other receptors were also evaluated by determining the K_i values of compounds to displace the binding of ^{3}H-pyrilamine (1.1 nM) and ^{3}H-tiotidine (11.8 nM) in homogenized guinea-pig cerebral cortex (H_1 and H_2 histamine receptors, respectively). The K_i values for these compounds resulted to be higher than 10 µM in both subtypes of histamine receptors.

In vivo activity

At present, certain compounds of the invention (Examples 1, 2 and 3) have shown an in vivo CNS functional activity, such as : feeding behaviour in rats. These compounds induced an acute (1-4 h after the intraperitoneal administration at 25 mg/kg) hyperphagic effect respect to the control group (7-10-fold, $P<0.05$), which was lower in potency than those induced by idazoxan (10 mg/kg, i.p.) (cf Table 2 : cummulative food intake (g/kg body weight) at 1,2 and 4 hours after intraperitoneal administration of the compounds and the standard drug idazoxan).

However, Example 2 was equally potent than idazoxan for the I_2-imidazoline receptors according to the data derived from binding studies but much more selective (cf Table 1). Also, the selectivity ratio for IR/alpha$_2$ and IR/alpha$_1$ are indicated.

Thus, these compounds may have a therapeutic potential as appetite stimulants and/or antianorexics. Other data obtained in different laboratories also support the therapeutic potential of imidazoline drugs acting upon imidazoline receptors as appetite stimulants and/or antianorexics (Jackson et al., Br. J. Pharmacol. 1991, 104, 258-262).

The compounds of the invention have been found deprived of action on serotonin receptors.

On the other hand, an approximative LD_{50} was obtained from the Irwin test performed in mice (4 animals, 50% males and females), where compounds of the invention (all at 100 mg/kg, i.p.) did not caused any death during 72 h. So, the approximative intraperitoneal LD_0 in mice for these compounds was higher than 100 mg/kg.

In accordance to their physical, chemical and pharmaceutical characteristics, these compounds may be prepared in a form suitable for oral, rectal or parenteral administration. Such oral compositions may be in the form of capsules, tablets, granules or liquid preparations such as elixirs, syrups or suspensions.

Tablets contain a compound or a non-toxic salt thereof in admixture with excipients which are suitable for the manufacture of tablets. These excipients may be inert diluents such as calcium phosphate, microcrystalline cellulose, lactose, sucrose or dextrose ; granulating and disintegrating agents such as starch ; binding agents such as starch, gelatine, polyvinylpyrrolidone or acacia ; and lubricating agents such as magnesium stearate, stearic acid or talc.

Compositions in the form of capsules may contain the compound or a non-toxic salt thereof mixed with an inert solid diluent such as calcium phosphate, lactose or kaolin in a hard gelatine capsule.

Compositions for parenteral administration may be in the form of sterile injectable preparations such as solutions or suspensions, for example : water or saline.

For the purposes of convience and accuracy of doing the compositions are adventageously employed in a unit dosage form. For oral administration the unit dosage form contains from 0.5 to 300 mg, preferably 1 to 100 mg of the compounds or a

non-toxic salt thereof. Parenteral unit dosage forms contain from 0.05 to 20 mg of the compounds or a non-toxic salt thereof per 1 mL of the preparation.

Table 1

Compound	Affinity (K_i, nM)			Selectivity	
	IR	Alpha$_2$	Alpha$_1$	IR/α_2	IR/α_1
Example 1	89	100 148	36 540	1 125	410
Example 2	15	62 061	26 169	4 137	1 744
Example 3	151	56 150	17 800	372	118
Example 6	117	68 350	33 258	584	284
Example 7	163	98 719	4 405	605	27
Example 9	123	71 320	22 615	580	184
Idazoxan	14	5	91	0.4	6.5
RX 821002	44 902	0.7	ND	0.00002	–

The results are the mean of 10 experiments. RX 821002 is the methoxy derivative of idazoxan.

ND : not determined

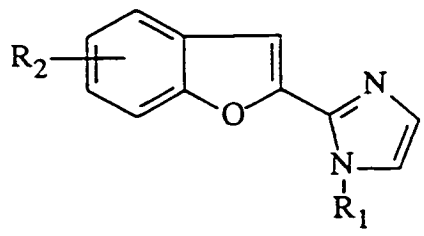
Table 2

Compounds	Dose mg/kg	N	Time(h) 1	2	4
Carboxymethylcellulose 0.5 %	—	5	0.04 ± 0.01	0.2 ± .05	0.6 ± 0.1
Idazoxan	10	5	3.7 ± 1.2**	5.6 ± 2.1**	7.4 ± 2.3**
Example 1	25	5	3.0 ± 2.0**	4.0 ± 2.1**	4.8 ± 2.0**
Example 2	25	5	2.7 ± 1.5**	3.0 ± 1.5	3.6 ± 1.4*
Example 3	25	5	1.3 ± 1.0*	3.4 ± 1.2*	3.8 ± 1.2*

* significant - ** highly significant

CLAIMS

1. A benzofuranylimidazole derivative of the general formula (1)



(1)

wherein

R_1 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, and R_2 represents a hydroxy group or a group R'_2 wherein R'_2 represents a hydrogen or halogen atom, an alkyl group having from 1 to 6 carbon atoms or an alkoxy group having from 1 to 5 carbon atoms;

or a pharmaceutically acceptable salt of such a derivative.

2. 2-(Benzofuran-2-yl)-imidazole or its hydrochloride.

3. 1-Methyl-2-(benzofuran-2-yl)-imidazole or its hydrochloride.

4. 2-(6-Methoxybenzofuran-2-yl)-imidazole or its hydrochloride.

5. 2-(6-Hydroxybenzofuran-2-yl)-imidazole or its hydrochloride.

6. 1-Ethyl-2-(benzofuran-2-yl)-imidazole or its hydrochloride.

7. 2-(5-Bromobenzofuran-2-yl)-imidazole or its hydrochloride.

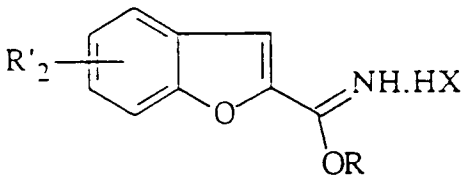
8. 2-(5-Methoxybenzofuran-2-yl)-imidazole or its hydrochloride.

9. 2-(5-Hydroxybenzofuran-2-yl)-imidazole or its hydrochloride.

10. 1-Ethyl-2-(6-methoxybenzofuran-2-yl)-imidazole or its hydrochloride.

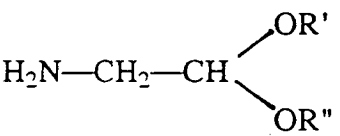
11. A process for the preparation of a benzofuranylimidazole derivative of the general formula (1) wherein R_1 represents a hydrogen atom and R_2 represents a group R'_2 as defined in claim 1, the process comprising

reacting a compound of the general formula (2)

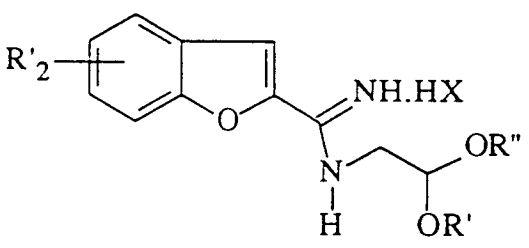


(2)

wherein R'_2 is as defined in claim 1, R represents an alkyl group having from 1 to 4 carbon atoms and HX represents an acid,
with at least one molar equivalent of an aminoacetaldehyde dialkyl acetal of the general formula



wherein each of R' and R" independently represents an alkyl group having from 1 to 4 carbon atoms, in a polar solvent for 1 to 24 hours at a temperature of from -5°C to the boiling point of the reaction mixture, and
cyclising the resultant compound of the general formula (3)



(3)

in an aqueous acidic medium for from 1 to 24 hours at a temperature of from 15 to 80°C.

12. A process according to claim 11, wherein the compound (2) and the acetal are reacted for from 15 to 17 hours in refluxing methanol.

13. A process according to claim 11 or claim 12, wherein the cyclisation is conducted at from 40 to 60°C for from 16 to 20 hours in 10% aqueous hydrochloric acid.

14. A process for the preparation of a benzofuranylimidazole derivative of the general formula (1) wherein R_1 represents an alkyl group having from 1 to 6 carbon atoms and R_2 is as defined in claim 1, the process comprising treating a compound of the general formula (1) wherein R_1 represents a hydrogen atom and R_2 is as defined in claim 1 first with a base in an aprotic solvent at a temperature of from -10 to 25°C and secondly with an alkyl halide having from 1 to 6 carbon atoms or with an alkyl sulphonate having from 1 to 6 carbon atoms.

15. A process according to claim 14, wherein the first treatment is effected with sodium hydride in dimethylformamide at 0°C.

16. A process for the preparation of a benzofuranylimidazole derivative of the general formula (1) wherein R_1 is as defined in claim 1 and R_2 represents a hydroxy group, the process comprising treating a compound of the general formula (1) wherein R_1 is as defined in claim 1 and R_2 represents an alkoxy group having from 1 to 5 carbon atoms with a dealkylating agent.

17. A process according to claim 16 wherein the dealkylating agent is trimethylsilyl iodide or aqueous hydrogen bromide.

18. A pharmaceutical composition comprising a benzofuranylimidazole derivative according to any of claims 1 to 10 or a pharmaceutically acceptable salt of such a derivative in admixture with a pharmaceutically acceptable diluent or carrier.

19. A pharmaceutical composition according to claim 18, the composition being in unit dose form for oral administration and containing from 0.5 to 300 mg of the benzofuranylimidazole derivative or its salt.

20. A pharmaceutical composition according to claim 18, the composition being in unit dose form for parenteral administration and containing from 0.05 to 20 mg of the benzofuranylimidazole derivative or its salt.

RENEWAL DETAILS

PUBLICATION NUMBER GB2262739

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DATE FILED 24.12.1992

DATE GRANTED 17.05.1995

DATE NEXT RENEWAL DUE 24.12.1996

DATE NOT IN FORCE

DATE OF LAST RENEWAL

YEAR OF LAST RENEWAL 00

STATUS PATENT IN FORCE

**** END OF REPORT ****

REGISTER ENTRY FOR GB2262739

Form 1 Application No GB9226997.6 filing date 24.12.1992

Priority claimed:
27.12.1991 in United Kingdom - doc: 9127430

Title BENZOFURANYLIMIDAZOLE DERIVATIVES

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Classified to
C2C U1S
C07D A61K

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Publication No GB2262739 dated 30.06.1993

Examination requested 05.07.1993

Patent Granted with effect from 17.05.1995 (Section 25(1)) with title
BENZOFURANYLIMIDAZOLE DERIVATIVES

**** END OF REGISTER ENTRY ****