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(12) # EUROPEAN PATENT APPLICATION

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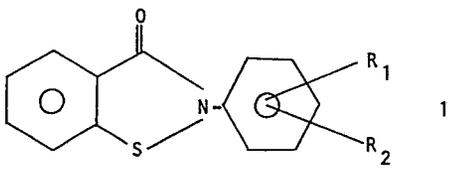
(54) **The use of N-halogenophenyl-benzisothiazoles.**

(57) The invention relates to the new use of certain benzisothiazoles corresponding to the following general formula:



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wherein R_1 represents chlorine, fluorine or bromine, and R_2 represents hydrogen, chlorine, fluorine or bromine, in the treatment of phlogistic and/or arteriosclerotic processes.

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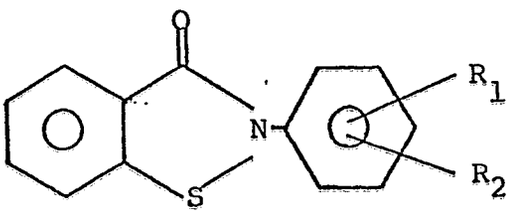
BACKGROUND OF THE INVENTION

This invention relates to the use of certain benzisothiazoles in the treatment and prophylaxis of phlogistic and/or arteriosclerotic processes and in the control of the illnesses which they cause, particularly in human beings or even in animals.

SUMMARY OF THE INVENTION

The benzisothiazoles used in accordance with the invention correspond to the following general formula:



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in which R_1 represents chlorine, fluorine or bromine and R_2 represents hydrogen, chlorine, fluorine or bromine.

The following are examples of compounds such as these:

2-(4-fluorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(2-chlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(3-chlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(2,3-dichlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(2,6-dichlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(3,4-dichlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(2,4-dichlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(2,5-dichlorophenyl)-1,2-benzisothiazol-3(2H)-one
2-(4-bromophenyl)-1,2-benzisothiazol-3(2H)-one,
but more particularly
2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one.

DETAILED DESCRIPTION OF THE INVENTION

The benzisothiazoles corresponding to general formula I are for the most part known compounds (German Patent No. 2,119,730) or may be obtained by the process described therein using corresponding starting materials.

Some of the known compounds show bactericidal and fungicidal activity (Arzneimittel-Forsch. 1964, 14, 1301-06). Other forms of therapeutic activity have never

been reported.

It has now surprisingly been found that the benziso-thiazoles corresponding to general formula I show pronounced antiphlogistic and anti-arteriosclerotic activity and are distinguished from the therapeutically used inflammation-inhibiting compounds by their low toxicity and by their extremely high compatibility with the stomach as reflected in the absence of ulcers.

The outstanding antiphlogistic properties and high compatibility of the benzisothiazoles used in accordance with the invention were determined, for example, by the following tests. Indometacin (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indole acetic acid) was used for comparison.

1. Rat paw oedema test

Determination of antiphlogistic activity by HILLEBRECHT's rat paw oedema test (J. HILLEBRECHT, Arzeim. Forsch. 1954, Vol. 4, page 607). An oedema was produced in one of the rear paws of rats weighing from 120 g to 150 g by the subplantar injection of carragenin (0.5% in a 0.9% NaCl-solution) in a quantity of 0.1 ml of solution per paw. After administration of the test substance, which generally should not exceed a volume of 10 ml per kg of body weight, the volume of the paw is determined in an overflow. After 3 hours, the final value is determined. For each dose, the test is carried out with 10 test animals and 10 control animals of one sex and repeated with the same number of animals of the other sex. For the purposes of evaluation, inhibition of the oedema is expressed as a percentage on relation to the control group. The following values were obtained:

Table 1: Oedema inhibition in rats

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one			Indometacin	
Dose (mg/kg p.o.)	0.01	0.1	1.0	3.8	5.6
Inhibition (%)	-13	-22	-36	-26	-45

Dose (mg/kg i.m.)	0.1	1.0	10	1.0	3.2	10
Inhibition (%)	-36	-26	-33	-9	-23	-33

Granuloma test (Cotton pellet test)
according to R. MEIER et al. Experientia 6, 469 (1950)

In this test, cottonwool pellets impregnated with croton oil were implanted subcutaneously in the test animals (rats) to induce the formation of granulomas in the connective tissue. After the animals had been killed, the granulomas were excised and weighed moist or dry. The anti-proliferative effect of an antiphlogistic is reflected in light weights of the granulomas by comparison with untreated controls.

Table 2: Anti-proliferative effect

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one			Indometacin		
Dose (mg/kg p.o.)	0.1	1.0	10	1	3.2	5.6
Reduction in weight of the granulomas(%)	-26	-43	-44	-21	-7	-6

3. Adjuvant arthritis
(C.M. PEARSON, proc.Soc.exp.Biol. 91, 95-101 (1956)

10 Wistar rats weighing from 120 g to 150 g are used per dose. The same number of animals is used for control purposes. An arthritis is induced by the administration of 0.5 ml of Freund's adjuvant by subplantar injection. The test lasts 17 days. At the beginning of the test, the paw volume of all four extremities is determined and

used as the starting value. Further volume measurements are carried out on the 8th, 14th and 17th days of the test. For evaluation purposes, the difference between the starting volume and final volume of the paws both of the test group and of the control group is calculated and inhibition expressed as a percentage.

Table 3: Adjuvant arthritis in rats (p.o.)

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one		Indometacin	
Dose (mg/kg p.o.)	1	3.2	0.32	1.0
Inhibition (%)				
7th day p.i.	-27	-46	-20	-50
14th day p.i.	-44	-51	-26	-40
17th day p.i.	-45	-56	-33	-40

4. Ulcer test

Ulcer formation was determined in accordance with W.J.R. WHITTLE, Brit.J.Pharmacology 1975, Vol. 55, pages 242 to 243; L. MARIANI, Europ. J. Toxicol. Environ, 1975, Vol. 8, pages 335-339; R. MENGUY and L. DESBAILLETS, Proc.Soc.Exp.Bio. Vol. 125, page 1108. In the tests, 10 female and 10 male Wistar rats (120 g-150 g which had been fed on a pure carbohydrate diet for 2 days and subsequently kept without food for 16 hours) were used per dose and control. A bleeding stomach ulcer is induced by oral administration of the active principle. After 3.5 hours, the animals are killed, their stomachs removed, cut open along the major curvature and stretched across a Styropor plate. The frequency and extent of average ulcer formation in the test and control groups is determined. Under these conditions, all hitherto known, therapeutically useable, non-steroidal antiphlogistics induce ulcerations of the stomach mucosa in the therapeutic dosage.

Table 4: Ulcer-inducing effect in rats

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one			Indometacin		
Dose (mg/kg p.o.)	1	10	100	3.2	5.6	7.5
Effect	0	0	0	++	+++	+++

0 = no ulcer induction
\+ = moderate ulcer induction
++ = serious ulcer induction
+++ = very serious ulcer induction

Table 5: Toxicity

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one		Indometacin
Mice, oral			
Dose (mg/kg p.o.)	3	160	38
Lethality (%)	0		50

As can be seen from the pharmacological tests, the benzisothiazoles corresponding to general formula I above, even when administered in very small doses, show pronounced antiphlogistic activity, extremely low toxicity and, even when administered in fairly large doses, no ulcer formation.

The active principle may be used in any form, for example systemic, in human or veterinary medicine, provided that the build up and maintenance of adequate levels of active principle in the blood or tissue is guaranteed. This result may be achieved by oral, rectal or parenteral administration in suitable doses. The active principle is with advantage pharmaceutically formulated in individual doses adapted to the required form of administration, such as for example tablets, dragrees, capsules, suppositories, granulates, solutions, emulsions, suspensions, sols or gels. For building up and maintaining

adequate blood or tissue levels, the daily dose amounts to between 30 and 300 mg and preferably to between 50 and 200 mg and may be administered one or more times a day, preferably 2 to 3 times a day.

For producing pharmaceutical preparations containing benzisothiazoles of general formula I as their active component, the active principle may be used either as such or in combination with suitable pharmaceutical vehicles and formulated in the usual way.

Suitable vehicles for the preparation of oral formulations, for example in the form of tablets, capsules, granules or powders, are calcium carbonate, calcium phosphate, starch, sugar, lactose, talcum, magnesium stearate, gelatin, polyvinyl pyrrolidone, gum arabic, sorbitol, microcrystalline cellulose, polyethylene glycol, carboxy methyl cellulose, shellac and the like. The tablets may be coated in the usual way. Liquid formulations for oral administration may be made up in the form of aqueous or oily suspensions or solutions, in the form of a syrup, an elixir and the like. These are prepared in the usual way. Injectable formulations may be aqueous or oilysuspensions or solutions, powder-form compositions containing a filler and freeze-dried preparations which are dissolved before application, and the like. These formulations are prepared in the usual way.

The benzisothiazoles used in accordance with the invention may also be used in the form of suppositories for rectal administration, the suppositories containing pharmaceutically compatible vehicles which are known per se, for example polyethylene glycol, lanolin, cocoa butter, Witepsol^{R}, etc. External preparations are preferably made up in the form of ointments or creams which are prepared in the usual way using standard ingredients.

EXAMPLE 1

Tablets

2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one	30 mg
Lactose	150 mg
Crystalline cellulose	50 mg
Calcium carboxymethyl cellulose	7 mg
Magnesium stearate	3 mg

The substances listed above are mixed and pressed in the usual way. The pressings obtained may optionally be coated with a standard film.

EXAMPLE 2

Capsules

2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one	30 mg
Lactose	102 mg
Crystalline cellulose	56 mg
Colloidal silicon dioxide	2 mg

The substances listed above are mixed, granulated and introduced into hard gelatin capsules by standard methods.

EXAMPLE 3

Tablets

2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one	50 mg
Microcrystalline cellulose	150 mg
Cutina HR	15 mg
Hydroxypropyl methyl cellulose phthalate	20 mg

EXAMPLE 4

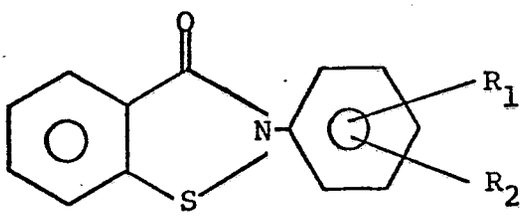
Capsules

2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one	50 mg
Talcum	5 mg
Aerosil 200	10 mg

are mixed, granulated and introduced into hard gelatin capsules.

CLAIMS:

1. A method for the treatment and prophylaxis of phlogistic and arteriosclerotic processes and resulting illnesses in humans or animals, which comprises administering to an animal an effective amount of a benzisothiazole corresponding to the following general formula:



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in which R_1 represents a radical selected from the group consisting of chlorine, fluorine and bromine, and R_2 represents a radical selected from the group consisting of hydrogen, chlorine, fluorine and bromine.

2. A method according to claim 1, wherein the benzisothiazole is 2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one.

3. A pharmaceutical composition for the treatment and prophylaxis of phlogistic and arteriosclerotic processes and resulting illnesses in animals, which comprises a benzisothiazole corresponding to the general formula I as defined in claim 1, together with a non-toxic, pharmaceutically acceptable vehicle therefor.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number: EP 81 10 8458

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
DX	DE - A - 2 119 730 (THE SHERWIN WILLIAMS CO.) * Claim 1; page 13 *	3
X	US - A - 3 012 039 (JOHN SELWYN MORLEY) * Columns 1-3 *	3
DX	ARZNEIMITTEL FORSCHUNG, vol. 14, no. 12, December 1964 Aulendorf, DE R. FISCHER et al. "On benzisothiazolones: A series with a wide range of bacteriostatic and fungistatic activity", pages 1301-1306. * Page 1301, page 1302, compounds 19,20,21; page 1303, compounds 41,42,43 *	3
	FR - A - 2 315 927 (PREPHAR PROSPECTION DE RECHERCHES PHARMACEUTIQUES) * Claims 1,2; page 14, examples 18,19 *	3

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

A 61 K 31/425
C 07 D 275/04

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

A 61 K 31/425
C 07 D 275/04

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 3
Claims searched incompletely:
Claims not searched: 1,2
Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See Art. 52(4) of the European Patent Convention)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
The Hague	25-01-1982	HENRY