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

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DE-A-2 119 730
FR-A-2 315 927
US-A-3 012 039

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

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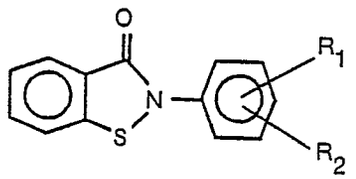
Description

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

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.

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). Benzisothiazolones are reported as spermicides (FR)—A—2,315,927. Other forms of therapeutic activity have never been reported.

It has now surprisingly been found that the benzisothiazoles 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 by 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. Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic 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 carrageenin (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 in 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			Indomethacin		
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 and dry. The anti-proliferative effect of an antiphologistic is reflected in light of the weights of the granulomas by comparison with untreated controls.

TABLE 2: Anti-proliferative effect

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one			Indomethacin		
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. 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		Indomethacin	
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 at the therapeutic dosage.

TABLE 4: Ulcer-inducing effect in rats

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

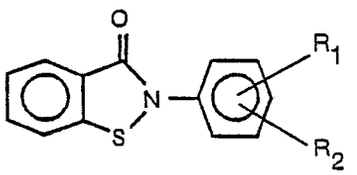
0 = no ulcer induction
\+ = moderate ulcer induction
++ = serious ulcer induction
+++ = very serious ulcer induction

TABLE 5: Toxicity

	2-(4-chlorophenyl)-1,2-benzisothiazol-3(2H)-one	Indomethacin
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.

Thus, the present invention is directed to the use of compounds of the following formula I



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in which R_1 represents a radical selected from chlorine, flourine and bromine, and R_2 represents a radical selected from hydrogen, chlorine, fluorine and bromine, as active principle for the preparation of pharmaceutical preparations for the teatment and prophylaxis of phlogistic and/or arteriosclerotic processes and resulting illnesses in humans or animals.

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, dragees, 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 prferably 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 and shellac. 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 and in the form of a syrup or an elixir. These are prepared in the usual way. Injectable formulations may be aqueous or oily suspensions or solutions, powder-form compositions containing a filler and freeze-dried preparations which are dissolved before application. 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 and Witepsol®. 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

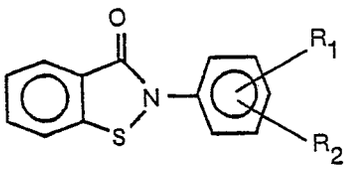
Capsules

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. The use of a compound corresponding to the following general formula:



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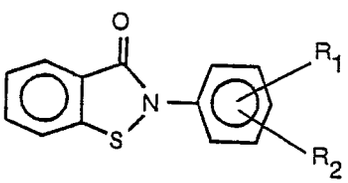
in which R_1 represents a radical selected from chlorine, fluorine and bromine, and R_2 represents a radical selected from hydrogen, chlorine, fluorine and bromine, as active principle for the production of pharmaceutical preparations for the treatment and prophylaxis of phlogistic and arteriosclerotic processes and resulting illnesses in humans or animals.

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

Patentansprüche

1. Verwendung einer Verbindung der allgemeinen Formel



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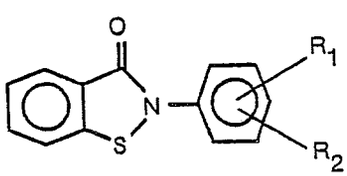
worin R_1 einen Rest, ausgewählt aus Chlor, Fluor und Brom, und R_2 einen Rest, ausgewählt aus Wasserstoff, Chlor, Fluor und Brom, darstellen, als aktives Prinzip (Wirkstoff) zur Herstellung von pharmazeutischen Präparaten für die Behandlung und Prophylaxe von phlogistischen und arteriosklerotischen Prozessen und den daraus resultierenden Erkrankungen bei Menschen oder Tieren.

2. Verwendung nach Anspruch 1, worin das Benzisothiazol 2-(4-Chlorophenyl)-1,2-benzisothiazol-3(2H)-on ist.

Revendications

1. Utilisation d'un composé correspondant à la formule générale suivante:



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dans laquelle R_1 représente un radical choisi entre le chlore, le fluor et le brome et R_2 représente un radical choisi entre l'hydrogène, le chlore, le fluor et le brome en tant que principe actif pour la fabrication de préparations pharmaceutiques pour le traitement et la prophylaxie de processus inflammatoires et artérioscléreux et des maladies en résultant chez l'homme ou l'animal.

2. Utilisation selon la revendication 1 caractérisée en ce que le benzisothiazole et la 2-(4-chlorophényl)-1,2-benzisothiazol-3(2H)-one.