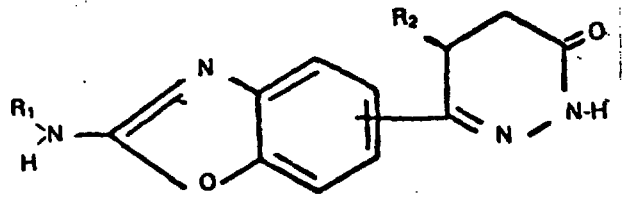
10G146-841T

Specification

The present invention relates to new benzoxazoles of general formula



(I)

the physiologically acceptable acid addition salts thereof with inorganic or organic acids and processes for preparing them and pharmaceutical compositions containing these compounds.

The compounds of general formula I above have valuable pharmacological properties, in particular cardiovascular effects, namely cardiotonic, hypotensive and/or antithrombotic properties.

In general formula I above

R_1 represents a hydrogen atom, a straight-chained or branched alkyl group containing 1 to 7 carbon atoms which may be substituted by an alkoxy group with 1 to 3 carbon atoms; a cycloalkyl group with 3 to 7 carbon atoms; an alkyl group with 1 to 3 carbon atoms substituted by a phenyl group which may be substituted by 1 or 2 alkoxy groups with 1 to 3 carbon atoms; or a phenyl group which may be substituted by an alkyl or alkoxy group with 1 to 3 carbon atoms or by a trifluoromethyl, nitro or cyano group or by a fluorine, chlorine or bromine atom, whilst in addition one of the above-mentioned monosubstituted phenyl groups may be substituted by one or two alkyl groups with 1 to 3 carbon atoms or by an alkoxy group with 1 to 3 carbon atoms or

by a fluorine, chlorine or bromine atom; and

R_2 represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms.

Thus, as examples of definitions of the groups R_1 and R_2 given hereinbefore, R_1 may represent a hydrogen atom, a methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, n-pentyl, isopentyl, neopentyl, tert.-pentyl, hexyl, heptyl, methoxyethyl, methoxypropyl, methoxybutyl, methoxypentyl, methoxyheptyl, ethoxyethyl, propoxypropyl, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, methylphenyl, dimethylphenyl, trimethylphenyl, ethylphenyl, propylphenyl, isopropylphenyl, methoxyphenyl, dimethoxyphenyl, isopropoxyphenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, trifluoromethylphenyl, nitrophenyl, cyanophenyl, methyl-fluorophenyl, methyl-chlorophenyl, methoxy-chlorophenyl, methoxy-bromophenyl, methoxy-cyanophenyl, methoxy-trifluoromethylphenyl, methoxy-nitrophenyl, ethoxy-nitrophenyl, propoxy-nitrophenyl, benzyl, 1-phenylethyl-3-phenylethyl, methoxybenzyl, dimethoxy-benzyl, 2-dimethoxyphenylethyl, 2-diethoxyphenylethyl, 2-dipropoxyphenylethyl, 2-(methoxy-ethoxyphenyl)-ethyl or 3-dimethoxy-phenylpropyl group and R_2 may represent a hydrogen atom or a methyl, ethyl, propyl or isopropyl group.

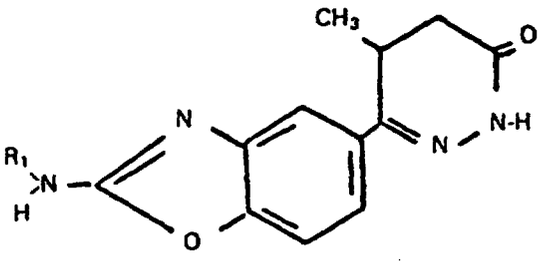
The preferred compounds of general formula I above are those wherein

R_1 represents a hydrogen atom, an alkyl group with 1 to 5 carbon atoms which may be substituted by a methoxy group, a phenyl group which may be substituted by a methyl, methoxy, trifluoromethyl, cyano or nitro group or by a chlorine or bromine atom, a dichlorophenyl, dibromophenyl, dimethoxyphenyl, methoxy-nitrophenyl, trimethylphenyl, cyclohexyl or dimethoxyphenylethyl group and

R_2 represents a methyl group, but particularly

those wherein the pyridazinone group is in position 5 of the benzoxazole, and the physiologically acceptable acid addition salts thereof.

Particularly preferred compounds are the compounds of general formula



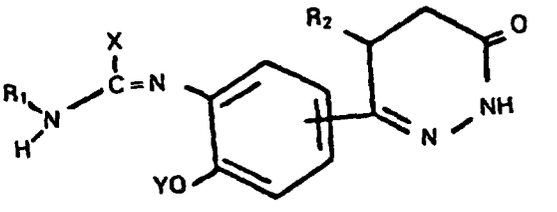
(Ia)

wherein

R_1 represents an alkyl group with 1 to 5 carbon atoms, a cyclohexyl group or a phenyl group optionally substituted by one or two methoxy groups, and the physiologically acceptable acid addition salts thereof.

According to the invention, the new compounds of general formula I are obtained by the following processes:

a) Cyclising a thiourea of general formula



(II)

wherein

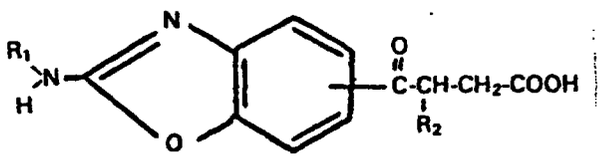
R_1 and R_2 are as hereinbefore defined and

X represents a mercapto, alkylmercapto, arylmercapto or aralkylmercapto group and

Y represents a hydrogen atom or an acyl group.

The reaction is conveniently carried out in a solvent such as tetrahydrofuran, dioxan, benzene, toluene or dimethylethyleneglycol, preferably in the presence of a condensing agent such N,N'-dicyclohexyl-carbodiimide, carbonyl-diimidazole, p-toluenesulphonic acid, phosphorusoxychloride, thionylchloride, hydrochloric acid, sulphuric acid, phosphoric acid or polyphosphoric acid at temperatures of between 25 and 200°C, but preferably at the boiling temperature of the reaction mixture, e.g. at temperatures of between 50 and 150°C. The reaction may, however, also be carried out in a melt.

b) Reacting a carboxylic acid of general formula



(III)

wherein

R_1 and R_2 are as hereinbefore defined, or the esters, thioesters, amides or halides thereof with hydrazine.

The reaction is conveniently carried out in a solvent such as ethanol, isopropanol, glacial acetic acid, propionic acid and/or in an excess of hydrazine or hydrazine hydrate at temperatures of between 50 and 200°C, preferably at the boiling temperature of the reaction mixture, e.g. at temperatures of between 75 and 150°C, and optionally in the presence of an acid as condensing agent such as sulphuric acid or p-toluenesulphonic acid. However, the reaction may also be carried out without a solvent.

A compound of general formula I obtained by process a) or b) wherein R_1 represents a hydrogen

atom may subsequently be converted by alkylation into a corresponding compound of general formula I wherein R_1 has the meanings given hereinbefore, with the exception of the hydrogen atom and the phenyl groups.

The subsequent alkylation is carried out with a corresponding alkylating agent such as a phenylalkylhalide, alkylhalide, dialkylsulphate or trialkyloxonium tetrafluoroborate, e.g. with benzylchloride, phenylethylbromide, methyliodide, dimethylsulphate, diethylsulphate or ethylbromide, conveniently in a solvent such as methanol, ethanol, methanol/water or dioxan, optionally in the presence of a base such as sodium carbonate, sodium bicarbonate, sodium hydroxide, sodium methoxide or potassium carbonate at temperatures up to the boiling temperature of the solvent used.

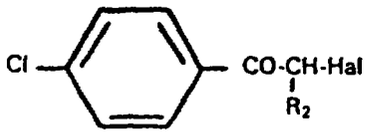
Moreover, in view of their optically active carbon atom in position 5 of the pyridazinone ring, the compounds of general formula I obtained may be resolved into their optically active enantiomers by racemate splitting. The racemate splitting is conveniently carried out by fractional crystallisation of the corresponding salts with optically active acids such as tartaric, dibenzoyl tartaric, malic, camphor or camphorsulphonic acid or by chromatography on optically active adsorbents.

Moreover, the compounds of general formula I obtained may be converted into their physiologically acceptable salts with inorganic or organic acids. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric or maleic acid.

The compounds of general formulae II and III used as starting materials are obtained by methods known from the literature. Thus, for example, a compound of general formula II is obtained by

reacting a corresponding 3-(nitrohydroxybenzoyl)-butyrate with hydrazine, subsequently reducing the nitro group and then reacting the resulting compound with a corresponding thioisocyanate.

A compound of general formula III is obtained by reacting a compound of general formula



(IV)

with malonates. The resulting compound is subsequently saponified, decarboxylated, nitrogenated, the chlorine atom is replaced by a hydroxy group, the nitro group is reduced and the resulting amino compound is reacted with a corresponding thioisocyanate and then cyclised to give the desired benzoxazole.

The new compounds of general formula I and the optically active enantiomers thereof and the physiologically acceptable acid addition salts thereof with inorganic or organic acids have valuable pharmacological properties, as already mentioned hereinbefore, particularly cardiovascular effects, namely cardiotonic, hypotensive and/or antithrombotic activities.

For example, the following compounds:
A = 5-Methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)pyridazinone,
B = 5-Methyl-6-[2'-cyclohexylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)pyridazinone,
C = 5-Methyl-6-[2'-n-butylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)pyridazinone and
D = 5-Methyl-6-[2'-(4-methoxyphenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)pyridazinone

were tested for their biological properties as follows:

1. Determination of the thrombocyte aggregation according to Born and Cross (J. Physiol. 170, 397 (1964)):

The thrombocyte aggregation was measured in platelet-rich plasma from healthy test subjects. The decrease in optical density was measured photometrically and recorded after the addition of commercial collagen made by Messrs. Sigma, St. Louis, U.S.A., which contains 1 mg of collagen fibrils per ml. The velocity of aggregation (Vmax) was determined by the angle of inclination of the density curve . The point of the curve where the most light was transmitted was used to determine the optical density (o.d.). To provoke maximum aggregation approx. 0.01 ml of the collagen solution was added to 1 ml of platelet-rich plasma.

The following table shows the results obtained:

Table I:

Compound	EC_{50} in µmol/l
A	1.4

(15)

2. Determination of the hypotensive and positive inotropic activity in the anaesthetised cat

The tests were performed in cats which had been anaesthetised with sodium pentobarbital (40 mg/kg i.p.). The animals breathed spontaneously. The arterial blood pressure was measured in the aorta abdominalis by a Statham pressure transducer (P 23 Dc). The positive inotropic effect was determined by measuring the pressure in the left auricle by means of a catheter tip manometer (Millar PC 350 A). The contractility parameter dp/dt_{max} was obtained from this using an analog differentiating circuit.
The substances under test were injected into the vena femoralis. Physiological saline solution or polydiol 200 was used as solvent. Each substance was tested in at least 3 cats, dose 0.1 or 2.0 mg/kg i.v. The tested substances showed an activity lasting at least 45 minutes.

The following table contains the average values:

Test Compound	Dose mg/kg i.v.	Change in blood pressure in mmHg	Increase in dp/dt in %
A	0.1	-40/33	+ 79
B	0.1	-32/32	+ 39
C	0.1	-27/27	+ 62
D	2.0	-32/42	+ 92

3. Acute toxicity:

The acute toxicity of the test compounds was determined in white mice after oral administration of a single dose (observation time: 14 days).

Table III:

Test compound	acute toxicity mg/kg p.o.
A	> 300 (2 out of 6 animals died)
B	> 300 (0 out of 6 animals died)
C	> 300 (1 out of 6 animals died)
D	> 300 (0 out of 6 animals died)

In view of their pharmacological properties the compounds of general formula I, prepared according to the invention, and their optically active enantiomers and their physiologically acceptable acid addition salts with inorganic or organic acids are suitable for the treatment of chronic heart insufficiency or angina pectoris and/or for the prophylaxis of arterial occlusion and thrombosis.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible acid addition salts may be incorporated into the conventional preparations such as tablets, coated tablets, powder, suspensions, suppositories or ampoules. The single dose for adults contains from 10 - 50 mg

preferably from 20 to 40 mg, (i.v. application) and from 50 to 150 mg, preferably from 75 to 100 mg (oral application).

The following Examples serve to illustrate the invention:

(18)

Example I

N-Ethyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea

10.8 g (50 mmol) of 2-amino-4-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenol were suspended in 250 ml of tetrahydrofuran. The suspension was mixed with 25 ml (0.29 mol) of ethyl isothiocyanate and the mixture was refluxed for 3.5 hours, whilst a clear solution formed after only a short time. After the reaction time the mixture was evaporated and the yellow oily residue was crystallized by addition of ether. The precipitated product was suction filtered, washed with ether and dried at room temperature.
Yield: 13.0 g (91.5 % of theory)
M.p.: 137 - 139°C

$C_{14}H_{18}N_4O_2S$ (306.4)

Calc.:	C 54.88	H 5.92	N 18.29	S 10.47
Found:	55.10	6.10	17.90	10.30

Example II

2-Ethylamino-5-(3-methyl-4-oxo-butyric acid-4-yl)-benzoxazole

3.24 g (10.0 mmol) of N-ethyl-N'-[2-hydroxy-5-(3-methyl-4-oxo-butyric acid-4-yl)-phenyl]thiourea were dissolved in 150 ml of tetrahydrofuran. The solution was mixed with 4.17 g (20.0 mmol) of N,N'-dicyclohexyl carbodiimide and refluxed for 5 hours. After refluxing, the solution was evaporated down to half the quantity, boiled again for a short time and cooled until crystals were formed. The product obtained was suction filtered, recrystallized from tetrahydrofuran and dried at room temperature.
Yield: 0.71 g (24.3 % of theory)
M.p.: 160 - 162°C.

(19)

Example 1

5-Methyl-6-[2'-methylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

3.36 g (11.5 mmol) of N-methyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl thiourea were dissolved in 150 ml of tetrahydrofuran. The solution was mixed with 3.13 g (15 mmol) of N,N'-dicyclohexyl carbodiimide and refluxed for 5 hours. After refluxing, the reaction mixture was evaporated down to half the original volume, boiled again for a short time and cooled until crystals were formed. The product obtained was suction filtered, recrystallized from methanol and dried at room temperature.

Yield: 0.84 g (28.3 % of theory)

M.p.: 241 - 242°C

$C_{13}H_{14}N_4O_2$ (258.3)

Calc.:	C 60.46	H 5.46	N 21.69
Found:	60.28	5.61	21.50

Example 2

5-Methyl-6-[2'-n-butylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-n-butyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.

Yield: 39.7 % of theory

M.p.: 186 - 188°C

$C_{16}H_{20}N_4O_2$ (300.4)

Calc.:	C 63.98	H 6.71	N 18.65
Found:	63.99	6.96	18.54

Example 3

5-Methyl-6-[2'-isopropylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-isopropyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 52 % of theory
M.p.: 239 - 241°C
$C_{15}H_{18}N_4O_2$ (286.34)

Calc.:	C 69.92	H 6.34	N 19.57
Found:	62.65	6.33	19.25

Example 4

5-Methyl-6-[2'-cyclohexylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-cyclohexyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinone-6-yl)-phenyl]thiourea.
Yield: 59.1 % of theory
M.p.: 235 - 237°C
$C_{18}H_{22}N_4O_2$ (326.4)

Calc.:	C 66.24	H 6.79	N 17.16
Found:	66.00	6.90	16.99

Example 5

5-Methyl-6-[2'-(3,4-dimethoxyphenethylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-3,4-dimethoxyphenethyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 48.2 % of theory
M.p.: 70 - 72°C
$C_{22}H_{24}N_4O_4$ x hydrochloric acid (444.93)

Calc.:	C 59.39	H 5.87	N 12.59	Cl 7.99
Found:	59.40	5.69	12.89	8.00

Example 6

5-Methyl-6-[2'-phenylamino-benzoxazole-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

5 ml of hydrazine hydrate (99 %) were added in batches at approx. 20°C to 20 ml of glacial acetic acid with stirring and cooling with ice. Subsequently 6.5 g (20.0 mmol) of 2-phenylamino-5-(3-methyl-4-oxo-butyric acid-4-yl)-benzoxazole were added to the reaction mixture and the resulting suspension was refluxed. After 1 hour the suspension was cooled to room temperature and diluted with water. The precipitated product was suction filtered, washed with water and dried at 80°C.
Yield: 2.80 g (43.7 % of theory)
M.p.: 214 - 217°C
$C_{18}H_{16}N_4O_2$ (320.34)

Calc.:	C 67.49	H 5.03	N 17.49
Found:	67.00	5.32	17.12

(22)

Example 7

5-Methyl-6-[2'-(2-chloroanilino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-2-chlorophenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 33.9 % of theory
M.p.: 193 - 195°C
$C_{18}H_{15}N_4O_2Cl$ (354.8)

Calc.:	C 60.93	H 4.26	N 15.79	Cl 9.99
Found:	60.90	4.25	15.93	10.20

Example 8

5-Methyl-6-[2'-(4-trifluoromethylphenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-4-trifluoromethylphenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 57.3 % of theory
M.p.: 249 - 251°C
$C_{19}H_{15}N_4O_2F_3$ (388.36)

Calc.:	C 58.76	H 3.89	N 14.42
Found:	59.00	4.13	14.31

Example 9

5-Methyl-6-[2'-(3,4-dichlorophenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-3,4-dichlorphenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.

Yield: 73.5 % of theory
M.p.: 253 - 256°C
$C_{18}H_{14}N_4O_2Cl_2$ (389.3)

Calc.:	C 55.54	H 3.63	Cl 18.22
Found:	55.40	3.83	18.14

Example 10

5-Methyl-6-[2'-(4-bromophenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-4-bromophenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 65.4 % of theory
M.p.: 243 - 245°C
$C_{18}H_{15}N_4O_2Br$ (390.27)

Calc.:	C 55.40	H 3.87	N 14.36	Br 20.48
Found:	55.00	4.05	13.95	20.76

Example 11

5-Methyl-6-[2'-(4-methoxyphenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogusly to Example 1 from N-4-methoxyphenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 40.3 % of theory
M.p.: 220 - 222°C
$C_{19}H_{18}N_4O_3$ (350.4)

Calc.:	C 65.13	H 5.18	N 15.99
Found:	65.30	5.20	15.83

Example 12

5-Methyl-6-[2'-(2-methoxy-4-nitrophenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-2-methoxy-4-nitrophenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl thiourea.

Yield: 65.6 % of theory

M.p.: 223 - 225°C

$C_{19}H_{17}N_5O_5$ (395.4)

Calc.:	C 57.82	H 4.33	N 17.71
Found:	58.27	4.25	18.17

Example 13

5-Methyl-6-[2'-(4-methylphenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-4-methylphenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.

Yield: 52.1 % of theory

M.p.: 273 - 275°C

$C_{19}H_{18}N_4O_2$ (334.39)

Calc.:	C 68.25	H 5.43	N 16.76
Found:	68.10	5.59	16.88

Example 14

5-Methyl-6-[2'-(2,4,6-trimethylphenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-2,4,6-trimethylphenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.

Yield: 76.4 % of theory
M.p.: 225 - 228°C
$C_{21}H_{22}N_4O_2$ (362.4)

Calc.:	C 69.59	H 6.12	N 15.46
Found:	69.79	6.37	15.65

Example 15

5-Methyl-6-[2'-(4-cyanophenylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-4-cyanophenyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 59.7 % of theory
M.p.: 318 - 320°C
$C_{19}H_{15}N_5O_2$ (345.37)

Calc.:	C 66.08	H 4.38	N 20.28
Found:	66.14	4.58	20.03

Example 16

5-Methyl-6-[2'-n-pentylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-n-pentyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 52.3 % of theory
M.p.: 154 - 155°C
$C_{17}H_{22}N_4O_2$ (314.4)

Calc.:	C 64.95	H 7.05	N 17.82
Found:	65.26	7.12	17.88

Example 17

5-Methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-ethyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl thiourea.
Yield: 71.9 % of theory
M.p.: 244 - 246°C
$C_{14}H_{16}N_4O_2$ (272.3)

Calc.:	C 61.75	H 5.92	N 20.57
Found:	61.95	5.98	20.85

Example 18

5-Methyl-6-[2'-(3-methoxypropylamino)-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-3-methoxypropyl-N'-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.

Yield: 55.5 % of theory
M.p.: 153 - 154°C

$C_{16}H_{20}N_4O_3$ (316.4)			
Calc.:	C 60.75	H 6.37	N 17.71
Found:	61.00	6.40	17.56

Example 19

5-Methyl-6-[2'-amino-benzoxazol-5'-yl -4,5-dihydro-3(2H)-pyridazinone

Prepared analogously to Example 1 from N-[2-hydroxy-5-(5-methyl-4,5-dihydro-3(2H)-pyridazinon-6-yl)-phenyl]thiourea.
Yield: 42.1 % of theory
M.p.: 285 - 287°C

Example A

Tablets containing 100 mg of 5-methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Composition:
1 tablet contains:

Active ingredient	100.0 mg
Lactose	50.0 mg
Polyvinyl pyrrolidone	5.0 mg
Carboxymethyl cellulose	19.0 mg
Magnesium stearate	1.0 mg
	175.0 mg

The active ingredient and the lactose were homogeneously moistened with an aqueous solution of the polyvinyl pyrrolidone.
Moist screening: 1.5 mm
Drying: in a circulation air drier at 50°C
Dry screening: 1 mm
The granulate and the remaining excipients were mixed and pressed into tablets.
Weight of tablet: 175 mg
Punch: 8 mm ø

Example B

Coated tablets containing 50 mg of 5-methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

1 coated tablet core contains:

Active ingredient	50.0 mg
Corn starch (dried)	20.0 mg
Soluble starch	2.0 mg
Carboxymethyl cellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

The active ingredient and the starch were homogeneously moistened with an aqueous solution of the soluble starch.
Moist screening: 1.0 mm
Dry screening: 1.0 mm
Drying: in a circulation air drier at 50°C
The granulate and the remaining excipients were mixed and pressed into cores.
Weight of core: 80 mg
Punch: 6 mm
Radius of curvature: 5 mm

The finished cores were covered with a sugar coating in conventional manner.
Weight of coated tablet: 120 mg

Example C

Suppositories containing 75 mg of 5-methyl-6-[2'-ethyl-amino-benzoxazol-5'-yl -4,5-dihydro-3(2H)-pyridazinone

1 suppository contains:

Active ingredient:	75.0 mg
Suppository mass (e.g. Witepsol H 19 and Witepsol W 45)	1625.0 mg
	1700.0 mg

Method of preparation:

The suppository mass was melted. At 38°C the ground active ingredient was homogeneously dispersed in the melt. The suppository mass was cooled to 35°C and poured into pre-cooled moulds.
Weight of suppository: 1.7 g

Example D

Ampoules containing 25 mg of 5-methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone

Composition:
1 ampoule contains:

Active ingredient	25.0 mg
Sodium chloride	45.0 mg
Polyethylene glycol 600	1.0 ml
Dissolving intermediary (e.g. hydroxy-ethylated hydrated castor oil)	0.5 ml
Water for injection purposes ad	5.0 ml

Method of preparation:

The active ingredient was dissolved in a mixture of polyethylene glycol, dissolving intermediary and approx. half the water in a suitable volume-calibrated vessel whilst stirring. The solution was mixed with the isotonane of sodium chloride and made up with water to the given volume.

Example E

Suspension containing 75 mg of 5-methyl-6-[2'-ethylamino-benzoxazol-5'-yl]-4,5-dihydro-3(2H)-pyridazinone per 5 ml

100 ml of suspension contain:

Active ingredient	1.5 g
Carboxymethyl cellulose	0.1 g
Methyl p-hydroxybenzoate	0.05 g
Propyl p-hydroxybenzoate	0.03 g
Cane sugar	10.0 g
Glycerine	5.0 g
Sorbitol solution (70%)	20.0 g
Flavouring	0.3 g
Water, dist.	100.0 ml

Method of preparation:

Distilled water was heated up to 70°C, and methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, glycerine and carboxymethyl cellulose were dissolved therein with stirring. This solution was cooled to room temperature, the active ingredient was added with stirring and homogeneously dispersed. Subsequently, the sugar, the sorbitol solution, and flavouring were added and dissolved and the suspension was evaporated in vacuo with stirring.