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Synthesis and biological activities of meribendan and related heterocyclic benzimidazolo-pyridazinones

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Summary — The synthesis of new heterocyclic benzimidazolo-pyridazinones is described. The new compounds were evaluated as inotropic agents with 'calcium-sensitizing' effects. 5-Methyl-6-[2-(3-pyrazolyl)-5-benzimidazolyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride (meribendan) turned out to be the most interesting compound and was chosen for development as a positive inotrope.

benzimidazole / calcium sensitivity / cardiotonics / inotropes / phosphodiesterase / papillary muscle / pyridazinone

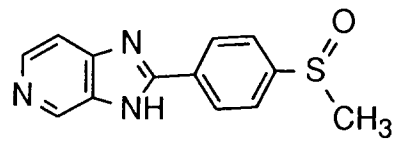
Introduction

Congestive heart disease is one of the major causes of deaths in the industrialized western countries and it affects roughly 1% of the population. This disease has turned out to be a rather common clinical syndrome with a very poor prognosis in its advanced stages. For the population aged 75 years and older, its prevalence is about 10%, indicating an age-dependence. In the past, the established therapy was treatment with digitalis glycosides. During the last decade major advances were made in the search for a better treatment. Vasodilators have been found which selectively either reduce preload or afterload and have been welcomed as effective armaments in the treatment of this serious disease. Therapeutic advances have been made in inotropic therapy as well. Here, the newer sympathomimetic agents play an important role in the clinical setting, but they unfortunately suffer severely from oral ineffectiveness and tachyphylaxis [1] due to receptor desensitization.

Recently several specific cardiac phosphodiesterase-III inhibitors have been developed which improve ventricular performance and exercise tolerance, as exemplified by Amrinone [2] and its congeners [3]. Conceptually, phosphodiesterase (PDE)-inhibitors combine positive inotropy and vasodilation [4]. The newly coined term 'inodilator' describes this dualism [5–7]. These unique features make them very attractive, although some serious questions as to long-term efficacy and reduction in mortality have not been answered definitively [8–10].

E Merck has been pursuing research in this area for quite a while. The first new drug, isomazole [11] (fig 1), is in clinical phase III. It is a selective PDE-III inhibitor characterized by a strong positive inotropic effect combined with moderate vasodilation. A new agent with an evenly balanced ratio of veno- and arteriodilation combined with a sufficient positive inotropic action was desired. It was thought that the class of the pyridazinones (fig 2) might be able to provide suitable candidates because, in the past, quite a few new drugs belonging to this class of drugs were designed [12–15].

Although in this paper we shall refrain from discussing the putative phosphodiesterase receptor [16], some facts are worth mentioning. The so called '5-point model' [17, 18] incorporates a strong dipole, an adjacent acidic proton, a small lipophilic space and a basic hydrogen-acceptor site opposite the dipole. This model was supported by similar conclusions [19] and somehow advanced by the introduction of a binding site for an electron-rich system [18].



Isomazole

Fig 1. Substituted imidazopyridine, isomazole.

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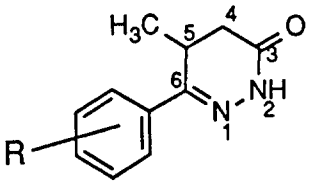
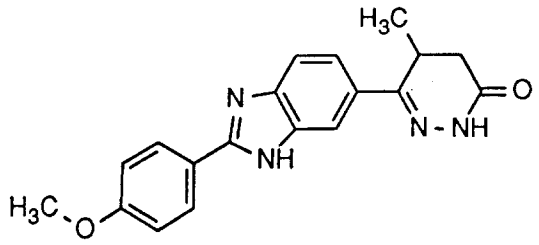


Pyridazinone

Fig 2. Cardiotonic 2,3,4,5-tetrahydro-pyridazin-3-ones.



Pimobendan

Fig 3. Pimobendan, a substituted benzimidazolo-pyridazinone.

Fairly recently, even structurally rather diverse cardiotonics have been fitted onto this putative PDE-receptor incorporating all the quantitative structure–activity relationship (QSAR) features elaborated so far [20].

As a rule of thumb, one can state that the 5-point model still is a good approximation of the PDE receptor, regardless of the refinements which have been made. Apparently, the basically flat inhibitor molecule can adopt, to a certain extent, some deviation from coplanarity of the pyridazinone- and phenyl rings, suggesting a fair amount of conformational flexibility. Since no X-ray structure of the enzyme phosphodiesterase-III is known to date, we think it is premature to discuss a receptor–inhibitor relationship with regard to the positive inotropic effect.

One prominent fact is the increase in positive inotropic potency exerted by the introduction of a substituent into the pyridazinone ring in position 5 and thus introducing chirality into the molecule. It has been shown that the optimum was reached with a methyl group [21].

Computer-assisted molecular modelling has been used to elucidate the influence of other parameters on the biological activity [19].

Chemistry

Due to the favorable results obtained with isomazole and some known facts of pimobendan [22] (fig 3), it seemed interesting to investigate substances similar to pimobendan carrying heterocyclic residues instead of the substituted phenyl ring.

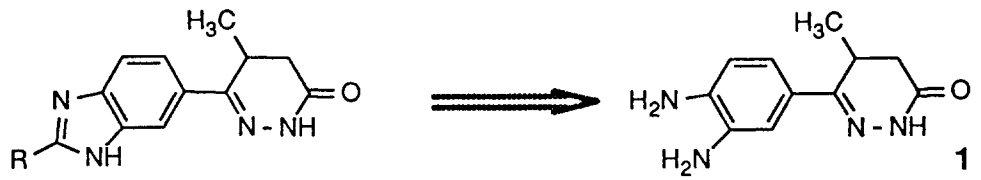
When the synthetic strategy was planned, a highly flexible approach was desired. In order to gain easy access to a wide variety of new benzimidazoles, retrosynthetic preparation of the parent diamine **1** (scheme 1) was envisioned as key intermediate.

Although the literature contains a host of procedures for the synthesis of benzimidazoles [11, 23–25], in our hands, the adaptation of a published method, *ie*, the condensation of aldehydes in *N,N*-dimethylformamide or *N,N*-dimethylacetamide in the presence of pyrosulfite gave the best results [26]. However, it must be stated that the desired benzimidazole derivatives were frequently contaminated with some by-product *N*-alkylated in the imidazole ring (scheme 2).

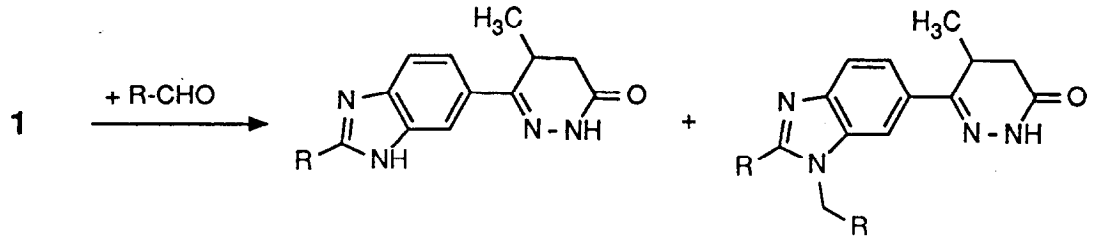
Scheme 3 provides a possible explanation. The first step in this condensation is the formation of an imine which may be in equilibrium with the corresponding dihydrobenzimidazole. In forming the by-product, the imine must react with another aldehyde molecule to form a di-imine, which, in turn, *via* disproportionation leads to the product. The other possibility is the addition of the dihydrobenzimidazole in an excess of aldehyde. The thus-formed hemiaminal then loses one element of water, followed by a 1,3-hydride shift to form a new carbenium ion. The latter is then stabilized by the loss of a proton leading to the final product.

Synthesis of the diamine 1

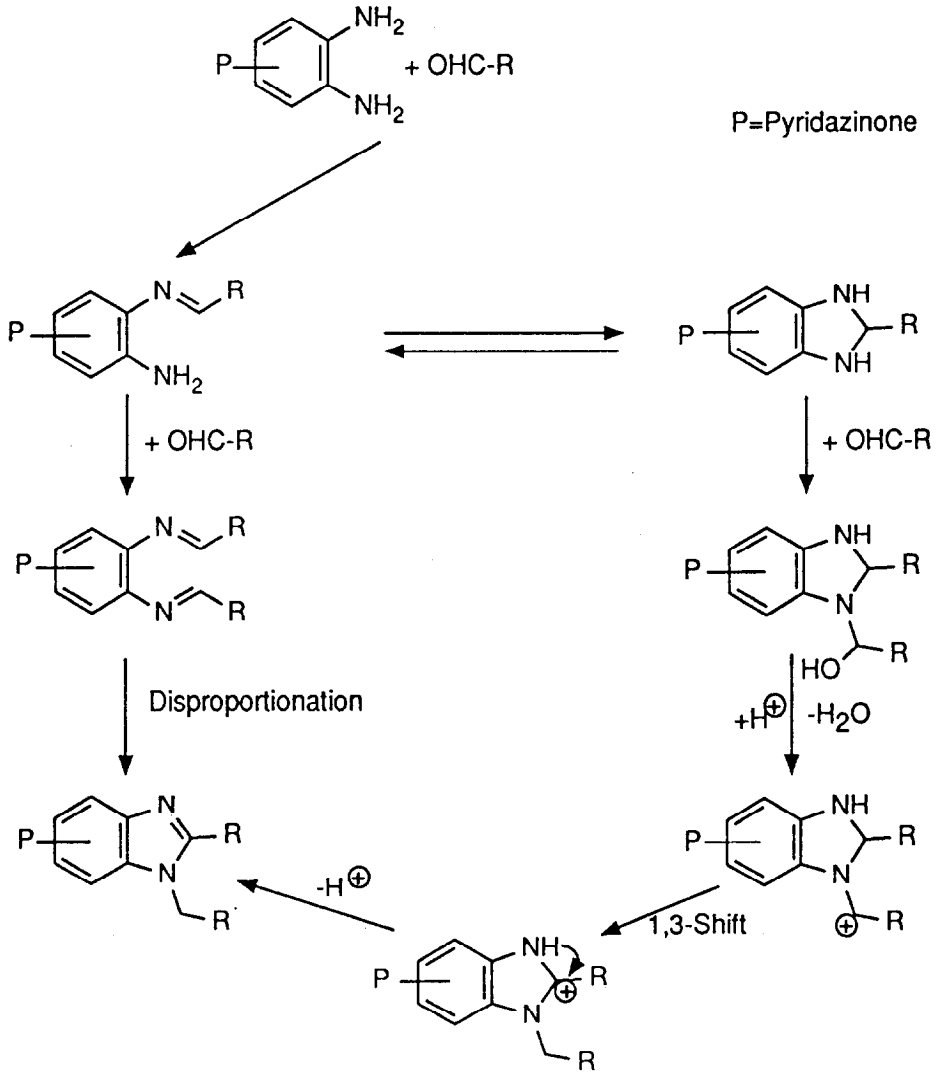
The introduction of an extra methyl group into position 5 of the pyridazinone ring makes this class of



Scheme 1. Retrosynthetic scheme for the construction of benzimidazolo-pyridazinones.



Scheme 2. *N*-Alkylated by-product in the condensation of aldehydes with phenylenediamine **1**.



Scheme 3. Possible mechanistic explanation for the formation of *N*-alkylated by-products.

substances generally more potent in their positive inotropic effect, but renders the system racemic as well. Different syntheses for 5-alkyl-pyridazinones have been reported in the literature [27–29]. A modified version of Stetter and Schreckenberg's procedure [30] considerably shortened the synthesis and is outlined in the scheme 4.

The key step is the direct Michael-addition of the aldehyde to crotononitrile using cyanide anion as the catalyst. This reaction seems to be extremely sensitive to electronic and steric factors. We were very fortunate that, in our hands, this reaction, which used an *in situ Umpolung*, worked so well with 4-chlorobenzaldehyde, even in large scale.

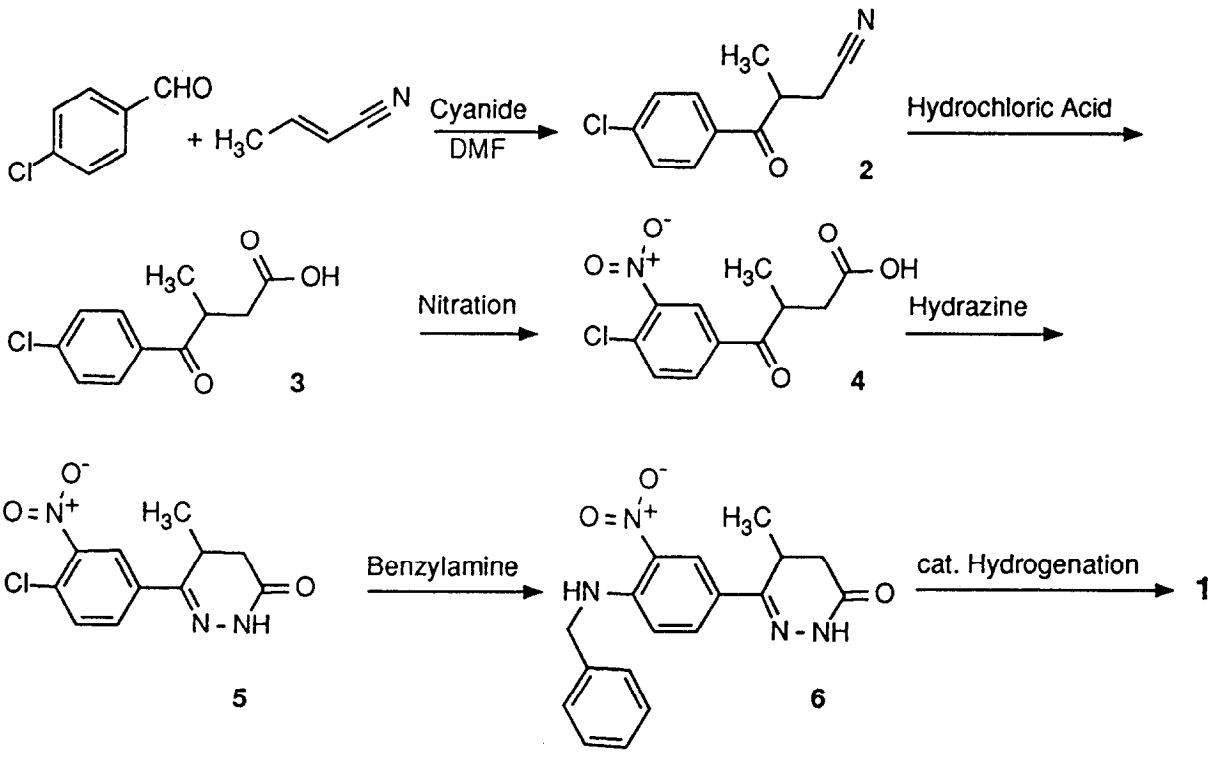
The following steps were less difficult. The hydrolysis of Michael-adduct **2** with hydrochloric acid gave acid **3** which served as the substrate for a nitration reaction. The resulting 4-chloro-3-nitro-acid **4** cyclized smoothly with hydrazine to give the pyridazinone **5**. The 3-nitro-group rendered the system sufficiently reactive to undergo nucleophilic aromatic substitution with benzylamine to yield **6**. Hydrogenolysis of **6** then liberated the diamine **1**, the precursor for a series of new benzimidazoles, by condensation with suitable aldehydes. All the new compounds **7–21** are listed in table I.

From this list, meribendan (fig 4), 5-methyl-6-[2-(3-pyrazolyl)-5-benzimidazolyl]-2,3,4,5-tetrahydropyridazin-3-one **13** as its hydrochloride was chosen for further development.

The pyrazole-3-carboxaldehyde used for the synthesis of meribendan has been known in the literature for a long time [31]. But for the increased demand due to large scale syntheses, the published procedure left something to be desired. The key step is the condensation of pyruvic aldehyde dimethylacetal with dimethylformamide dimethylacetal to give the enamine 1,1-dimethoxy-4-dimethylamino-but-3-ene-2-one which was cylized with hydrazine to give pyrazole-3-carboxaldehyde dimethylacetal. The original synthesis could be modified by using the cheap 'Gold's salt' [32, 33] instead of the expensive dimethylformamide dimethylacetal. 'Gold's salt' is a vinylogous immonium salt and is formed easily in the reaction of dimethylformamide with cyanuric chloride at high temperature.

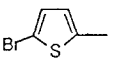
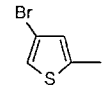
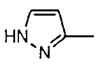
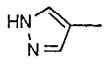
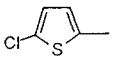
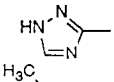
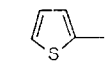
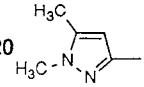
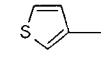
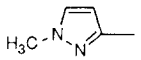
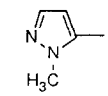
Enantiomers of meribendan

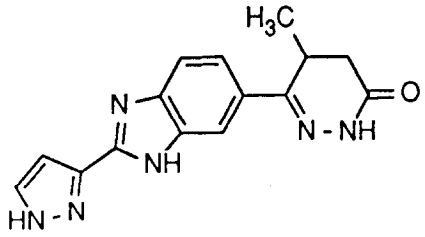
Because of the racemic nature of meribendan, synthesis of the pure enantiomers for pharmacological evaluation was desired. The literature precedent pimobendan had been resolved into its enantiomers using



Scheme 4. Synthetic scheme for construction of phenylenediamine **1**.

Table I. Heterocyclic residues in new benzimidazolo-pyridazinones.

No	Residue	No	Residue	No	Residue
7		12		17	
8		13		18	
9		14		19	
10		15		20	
11		16		21	



Meribendan

Fig 4. 5-Methyl-6-[2-(3-pyrazolyl)-5-benzimidazolyl]-2,3,4,5-tetrahydro-pyridazin-3-one, meribendan.

tartaric acid [34]. Meribendan, on the contrary, could not be resolved with tartaric acid and even a wide variety of chirally modified tartaric acids or other commercially available chiral carboxylic acids failed.

Since the advent of chirally modified sorbents, many successful separations of a great variety of chemical substances have been reported. In order to reduce the synthetic effort, a chromatographic separation of meribendan was attempted. In summary, it can be stated that all attempts with the unmodified meribendan were discouraging, although some partial separations were obtained. For the preparation of gram amounts of either enantiomer, other ways had to be found.

Separation of the direct precursor of diamine **1**, the 4-benzylamino-3-nitro-pyridazinone **6**, was possible using Pirkle-phase [35]. Even the parent diamine **1** could be separated using either Pirkle-phase or a cellulose–triacetate column [36, 37]. Due to the column sizes and loadability, chromatography on chiral columns only served for analytical purposes.

If instead of 4-benzylamino-3-nitro-pyridazinone **6** the corresponding diastereoisomeric phenethylamino or naphthylethylamino derivatives were used, only a partial separation could be achieved on plain silica high-performance liquid chromatography (HPLC) columns which precluded preparative application. Later, it turned out that this disappointing result was apparently due to some racemization of the optically active amines under the reaction conditions used (24 h reflux in *n*-butanol).

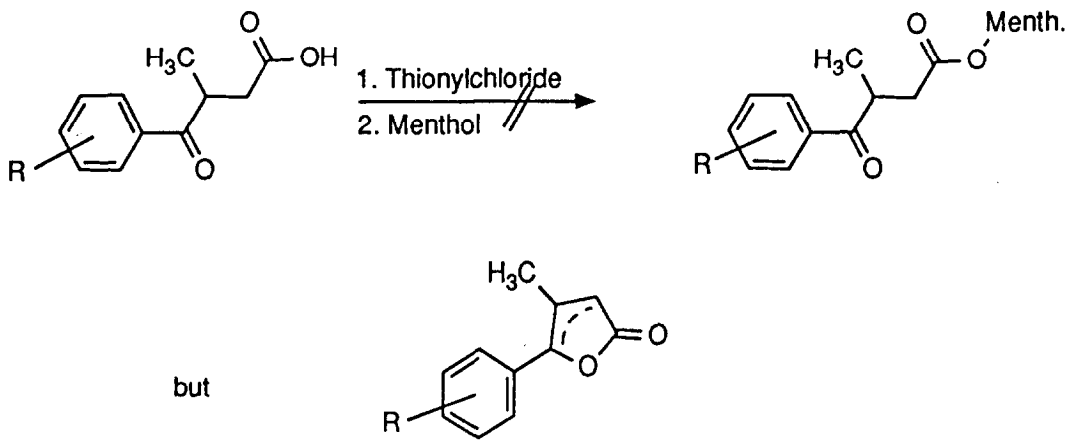
The other obvious approach was to make use of the carboxylic acid function. Because in some other work a menthyl ester had been successfully separated [38], the menthyl ester of 4-chlorobenzene-oxybutyric acid **3** was desired. But it has to be conceded that, in our hands, this esterification could not be brought about: an intermolecular lactonization leading to the corresponding butenolide (scheme 5) had occurred. The same applied to the 4-chloro-3-nitro acid **4**.

Finally, the desired resolution could be obtained with the plain acid **4**. From the precipitate formed from **4** and (*S*)(−)-1-phenethylamine in ethanol, the pure diastereisomeric salt **22** was obtained after several recrystallizations (scheme 6). Liberation with hydrochloric acid gave the enantiomerically pure oxybutyric acid **4** which was processed further to the optically pure meribendan. From the mother liquors of the diastereoisomeric salt preparation the other enantiomer was obtained using (*R*)(+)-1-phenethylamine.

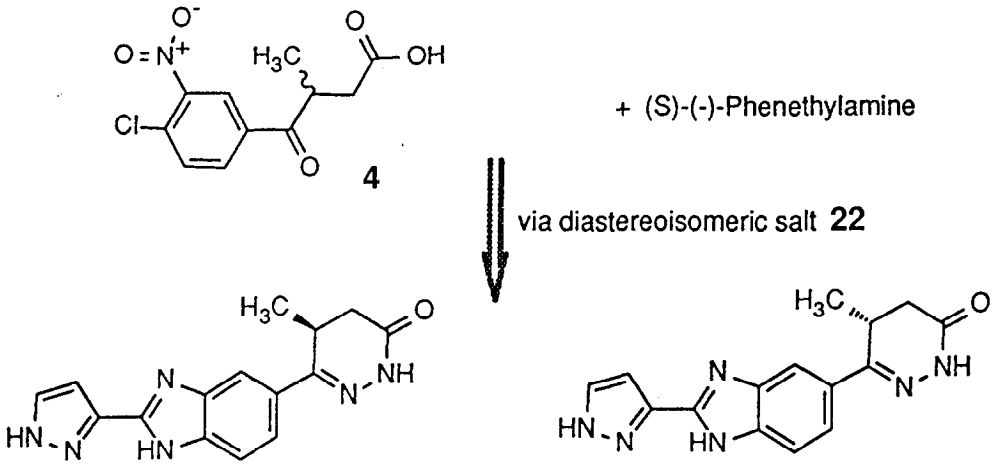
Different approaches to chiral pyridazinones have been described recently. In the first case, the chiral Michael-addition of a chirally modified amino-acetonitrile, which was derived from 4-chlorobenzaldehyde and a chiral amine, to crotononitrile gave chiral **2** in high enantiomeric excess [39]. This then principally can be taken through to chiral meribendan with defined absolute configuration depending upon the amine used. In the second example, the key step was the Friedel–Crafts acylation of a suitable aromatic compound with a chiral acid chloride [40] which led to a new chiral ketone, which could then be further converted, after some experimentation, into chiral pyridazinones of high enantiomeric purity.

X-ray structure and absolute configuration of meribendan

From a methanolic solution of meribendan, some crystals suitable for a X-ray analysis could be grown. It can be seen from the computer plot (fig 5) that the



Scheme 5. Attempted formation of menthylesters for the preparation of optically active pyridazinones.



Scheme 6. Synthetic scheme for the preparation of optically active meribendan.

benzimidazole is protonated and the whole molecule is fairly flat. Only the pyridazinone ring with its methyl group is arranged almost perpendicularly to the bulk of the molecule.

Meribendan did not form diastereoisomeric salts with chiral acids. Therefore, a pure specimen of the salt **22** had to be used for the X-ray crystallographic determination of the absolute configuration.

From the computer plot (fig 6) of the (*S*)-configuration, it can be deduced when (*S*)-1-phenethylamine was used. Since the (+)-meribendan was obtained from (*S*)(–)-**4** the latter must also be (*S*). The conversion of (*S*)(–)-**4** into meribendan occurred without any inversion. This was proven indirectly by conversion of (*S*)(–)-**4** into (*S*)(+)-pimobendan.

Biological results and discussion

Biological evaluation of the new compounds was undertaken by *in vitro* and *in vivo* tests. The newer positive inotropes being studied have been shown to inhibit myocardial cAMP phosphodiesterase (PDE) isoenzyme III, generally referred to as PDE III [41, 42]. This subfraction was isolated from guinea pig hearts and tested for inhibition.

In table II, the inhibitory concentrations of compounds **7–21** are expressed as IC_{50}-values (50% inhibition of PDE III in the presence of 0.25 μM cAMP). For comparison reasons, the values of some reference substances are given. Solely based upon the results of this assay, it was not possible to differentiate among

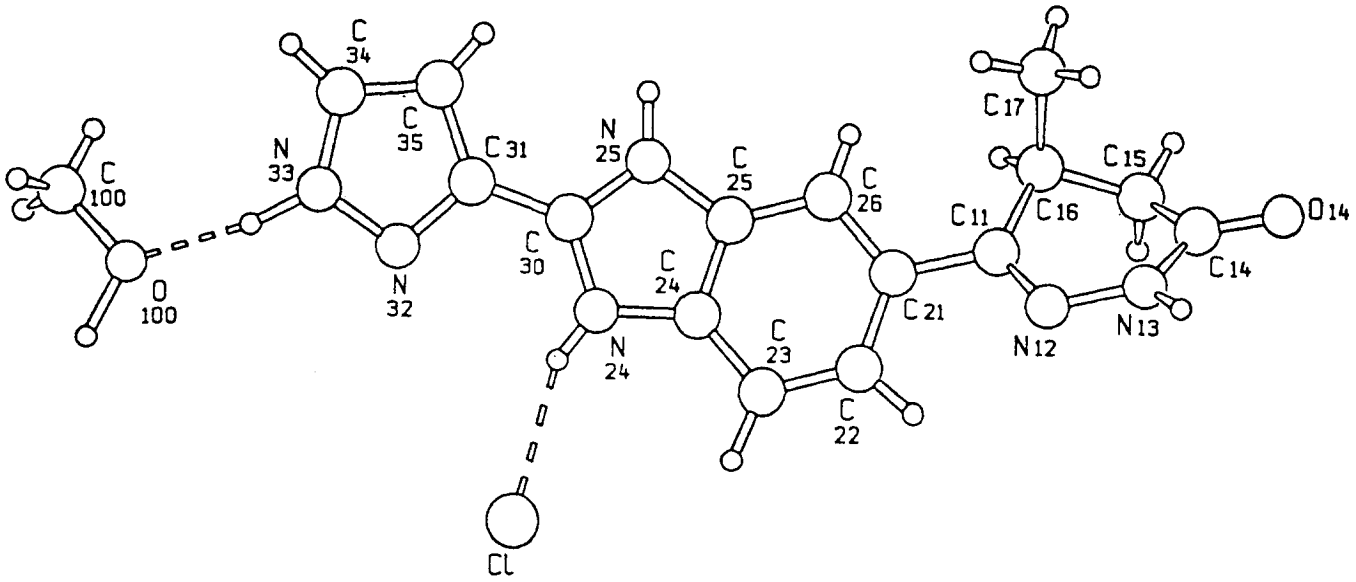


Fig 5. Computer plot of the X-ray structure of racemic meribendan containing one molecule of methanol.

the various derivatives because all turned out to be potent PDE III inhibitors.

For the first selection, positive inotropy was assayed in guinea pig papillary muscle [43]. All compounds with an EC_{100} of 10^{-4} M or lower in this assay were considered active [44]. The results together with two reference substances are given in the table II.

Compound **13** was active in increasing the force of contraction starting at the concentration of 3 μM. At the concentration of 1000 μM, the force was increased 17-fold. The force of contraction was doubled (EC_{100}) with ~ 4 μM.

Compounds **7–15** performed best in the papillary muscle test and were further examined for their effects on cardiac contractility [cardiac index (CI = dP/dt/P)] after oral administration to conscious dogs [45, 46]. As can be seen from table II, compounds **10**, **11** and **13** showed the most favorable results in terms of positive inotropic action as well as duration of action. From these, **13** (EMD 49 931), with the generic name meribendan, was elected for further development.

Most notable is the observed 'calcium sensitizing' effect [47, 48]. In the test with skinned fibers [43, 49], meribendan developed a concentration-dependent and reversible increase in contractility. The 25% increase of force (EC_{25}) was reached with 59 μM substance. A similar 'calcium-sensitizing' effect was observed with regard to the myofibrillar actomyosin ATPase. Meribendan activated bovine cardiac myofibrillar actomyosin ATPase concentration-dependently; the activation was observed over the entire range of Ca^{2+}-concentrations tested [50].

From table II it can be seen that the values of either meribendan enantiomer, (+)-**13** or (–)-**13**, did not differ strikingly from that of the racemic material. Only in the PDE III-values was a difference in the order of one magnitude seen.

Experimental protocols

All analytical data were obtained from the E Merck central analytical department. NMR spectra were measured on a Bruker AC 200 or WM 250 instrument, IR spectra on a Bruker FT-IR spectrometer IFS 45 and mass spectra on a Varian MAT 711 or a Vacuum Generators VG 70-250 instrument. The melting points were determined with an automatic Mettler FP 61 instrument. Petroleum ether (40–60°C fraction) is referred to as petrol and diethyl ether is referred to as ether. The chromatography was performed on E Merck silica gel 60 (230–400 mesh) and all solvents used were of E Merck grade. The aldehydes used in the syntheses were either commercially available or prepared according to published procedures. Microanalyses indicated by the symbols of the elements were within ±0.4% of theoretical values.

4-(4-Chlorophenyl)-3-methyl-4-oxobutyronitrile **2**

Sodium cyanide (5.2 g, 106 mmol) was added to absolute dimethylformamide (484 ml) in a nitrogen atmosphere. Under stirring at 35–38°C, a solution of 4-chlorobenzaldehyde (150 g, 1.07 mol) in dimethylformamide (242 ml) was added dropwise

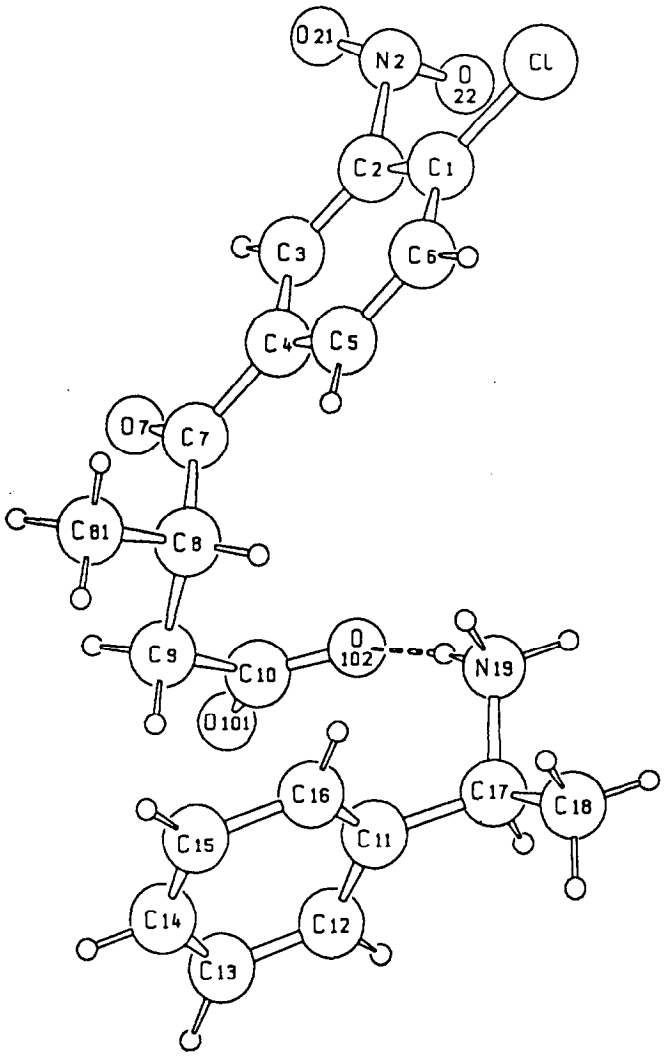


Fig 6. Computer plot of diastereoisomeric salt **22** for elucidation of the absolute configuration.

within 90 min. After continued stirring at 38°C for 30 min, 1-cyano-1-propene (72 g, 1.07 mmol) in dimethylformamide (242 ml) was added dropwise within 1 h maintaining the temperature at 38°C. The reaction mixture was stirred for another 2 h during which time the temperature did not have to rise above 40°C. Then the dark reaction mixture was poured on crushed ice–water (6000 ml) and the orange solid formed was collected by filtration. The bulk of this material was used for the next step. A small portion was purified for analytical purposes: mp: 52–53°C. Microanalysis: (C, H, Cl, N) $C_{11}H_{10}ClNO$. IR: 3000, 2295, 1673, 1589, 1087, 979 cm^{-1}. MS (MG 207.66): 207 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.40(3H, d, CH_3), 2.63(1H, dd), 2.74 (1H, dd, CH_2) and 3.75(1H, m, CH), 7.50 and 7.90(3H, m, aromatic-H).

4-(4-Chlorophenyl)-3-methyl-4-oxobutyric acid ***3***

The crude nitrile **2** was heated under reflux with conc hydrochloric acid (798 ml) containing water (260 ml). After cooling the reaction mixture was extracted 3 times with *tert*-butylmethylether (2000 ml). The combined organic extracts were washed exhaustively with saturated sodium bicarbonate solution and the pooled aqueous extracts were back-extracted with *tert*-butylethylether. After acidification to pH 1 with conc hydrochloric acid, the desired oxobutyric acid **3** was extracted with *tert*-butylmethylether. After washing with water and drying over sodium sulfate, the combined acidic extracts were evaporated to yield a pale oil which on trituration with petrol gave crystalline acid **3** (123 g, 54.6 %) with mp: 80–81°C. Microanalysis: (C, H, Cl) $C_{11}H_{11}ClO_3$. IR: 3067, 2972, 1714, 1683, 1591, 1221, 981 cm^{-1}. MS (MG 226.66): 226 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.20(3H, d, CH_3), 2.50(1H, dd) and 3.00(1H, dd, CH_2), 3.85(1H, m, CH), 7.45 and 7.90(3H, m, aromatic-H).

4-(4-Chloro-3-nitrophenyl)-3-methyl-4-oxobutyric acid ***4***

To absolute nitric acid (300 ml) cooled to –15°C was added thoroughly dried oxo-acid **3** (132 g, 580 mmol) portionwise in such a manner that the temperature could be maintained between –10 and –15°C. After an additional 30 min, the reaction mixture was poured onto crushed ice (3000 g) and the precipitate was collected. After washing with water the substance was dried at 50°C *in vacuo*. Yield: 156 g (98%), mp: 114–116°C. Microanalysis: (C, H, Cl, N) $C_{11}H_{10}ClNO_5$. IR: 3102, 2981, 2882, 1707, 1690, 1600, 1534, 1356, 1051 cm^{-1}. MS (MG 271.66): 271 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.10(3H, d, CH_3), 2.45(1H, m) and 2.73(1H, m, CH_2), 3.91(1H, m, CH), 7.95(1H, d), 8.25(1H, d) and 8.55(1H, s, aromatic-H), 12.2(1H, s, carboxylic-H).

6-(4-Chloro-3-nitrophenyl)-5-methyl-2,3,4.5-tetrahydro-pyridazin-3-one ***5***

To acetic acid (1142 ml) was added under cooling with ice hydrazine hydrate (86 g, 1.71 mol) in such a manner that the temperature was kept below 30°C. Then oxybutyric acid **4** (156 g, 570 mmol) was added and the mixture heated to 100°C for 2.5 h. For work-up, the reaction mixture was poured onto crushed ice (3000 g) and the precipitate was collected. After washing with water, the substance was dried at 50°C *in vacuo*. Yield: 156 g (98%), mp: 188–190°C. Microanalysis: (C, H, Cl, N) $C_{11}H_{10}ClN_3O_3$. IR: 3448, 3214, 1716, 1536, 1340 cm^{-1}. MS (MG 267.67): 267 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.18(3H, d, CH_3), 2.30(1H, d), 2.70(1H, d) and 2.80(1H, d, CH_2), 3.45(1H, m, CH), 7.82(1H, d), 8.05(1H, dd) and 8.40(1H, d, aromatic-H), 11.2(1H, s, NH).

6-(4-Benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one ***6***

The stirred solution of nitro-chloro compound **5** (1.51 g, 560 mmol) and benzylamine (125 g, 1.16 mol) in 1-butanol (740 ml) was heated under reflux for 20 h. After cooling to room temperature, water (370 ml) was added and the precipitate formed was collected to yield **6** (163 g, 86%) mp: 207–209°C. Microanalysis: (C, H, N) $C_{18}H_{18}N_4O_3$. IR: 3368, 3216, 1694, 1629, 1223, 1144 cm^{-1}. MS (MG 338.37): 338 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.05(3H, d, CH_3), 2.21(1H, d) and 2.65(1H, dd, CH_2), 3.33(1H, m, CH), 4.68(2H, d, benzyl-H), 7.01(1H, d), 7.87(1H, d) and 8.43(1H, s, aromatic-H), 7.38(5H, m, benzyl-H), 8.83(1H, t, benzyl-NH), 8.83(1H, t, benzyl-NH), 10.83(1H, m, pyridazinone-NH).

6-(3,4-Diaminophenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one ***1***

The benzylamino-nitro compound **6** from the foregoing reaction (165 g, 480 mmol) was hydrogenated over a 5% Pd on charcoal catalyst (30 g) in a mixture of methanol (550 ml) and

Table II. Summary of *in vitro* and *in vivo* results.

Compound	*In vitro*			*In vivo*	
	PDE III[a] *(IC_{50}, μM)*	*Pap (EC_{100}, μM)*	*Ca-sens (EC_{25}, mM)*	*Cardiac index (ED_{50}, mg/kg)*	*Duration (h)*
7	0.08	4.6	7	>1	–
8	0.07	5.8	–	>1	–
9	1	15	100	>3	–
10	1	16	30	0.45	4
11	0.1	30	60	0.7	4
12	0.04	32	100	–	–
13	0.1	40	59	0.25	>24
14	0.3	55	70	–	–
15	0.04	100	100	–	–
16	0.13	160	300	–	–
17	0.08	180	–	–	–
18	0.1	240	300	–	–
19	0.15	250	–	–	–
20	0.75	320	–	–	–
21	0.03	–	300	–	–
Pimobendan	0.3	21	41	0.4	7–24
Isomazole	17	100	440	0.4	6
(–)-**13**	0.03	120	68	0.3	>6
(+)-**13**	2	155	230	>3	5

[a]PDE III: phosphodiesterase isoenzyme III; Pap: guinea pig papillary muscle; Ca-sens: calcium-sensitizing effect.

1 N hydrochloric acid (480 ml). After the hydrogen uptake had ceased (2 h, thin-layer chromatography (TLC) control), the catalyst was removed by filtration and washed with methanol/water, 1/1. The filtrate was rendered alkaline (pH 8) using 2 N sodium hydroxide (245 ml) and the precipitate was collected and dried overnight. From the mother liquor, a second crop could be collected after concentration to 500 ml. Collected yield: 94.6 g, 88.6%, mp: 183–185°C. Microanalysis: (C, H, N) $C_{11}H_{14}N_4O$. IR: 3398, 3268, 2963, 1673, 1653, 1625, 1342, 1293, 744 cm^{-1}. MS (MG 218.26): 218 M^+. ^{1}H-NMR (DMSO–d_6): δ = 1.10(3H, d, CH_3), 2.15(1H, d) and 2.58(1H, dd CH_2), 3.23(1H, m, CH), 4.80(2H, s, N-H), 6.63(1H, d), 6.87(1H, d), 7.06(1H, s).

Pyrazole-3-carboxaldehyde

Stirred absolute dimethylformamide (3880 ml, 50.4 mol) was treated at 80°C portionwise with cyanuric chloride (1330 g, 7.2 mol). During the addition the temperature was maintained between 80 and 110°C. The next portion of cyanuric chloride was added after the CO_2 evolution had ceased. After the final addition the reaction mixture was stirred for another 30 min at 100°C. After cooling overnight the crystalline product was taken up in methanol (13000 ml). To the homogeneous solution was added pyruvic aldehyde dimethylacetal (2550 ml, 21.6 mol). To this mixture was added within 5 min 30% sodium methylate in methanol (4010 ml, 21.6 mol). During the addition the temperature rose to 35°C. The mixture was stirred for another 2 h at ambient temperature followed by a 1 h period of heating under reflux. For work-up the cooled reaction mixture was filtered over Kieselguhr and evaporated to give 4440 g of crude product. The product was dissolved in water (15 000 ml) and, after addition of hydrazinium hydroxide (1050 ml, 21.6 mol), was stirred for 24 h at ambient temperature. After the addition of hydrazine the temperature initially rose to 41°C. For workup the aqueous mixture was saturated with sodium chloride (5400 g) and extracted twice with methyl *tert*-butyl ether (8000 ml, 4000 ml). The combined organic layers were dried and evaporated to give 3240 g of crude oily product. This was dissolved in water (15 000 ml) and treated with glacial acetic acid (650 ml). After standing overnight pale crystals deposited which were collected by filtration. After washing with water and acetone the crystals were dried *in vacuo* to give 1000 g of pyrazole-3-carboxaldehyde (48%) mp: 151–152°C.

General procedure for condensation: 5-methyl-6-[2-(3-pyrazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride (meribendan) ***13***

The stirred mixture of pyrazole-3-carboxaldehyde (35.6 g, 370 mmol), diamine **1** (73.3 g, 330 mmol) and sodium bisulfite (70.3 g, 350 mmol) in *N,N*-dimethylformamide (370 ml) was heated for 2 h under reflux. When all the starting material had been consumed (TLC-control), the reaction mixture was cooled to 100°C and poured onto chipped ice (1200 g). The collected precipitate was treated successively with 2.5% sodium bicarbonate solution and water. Finally, the pale product was briefly heated in acetone (600 ml) to the boiling point and filtered hot. After drying, the desired product **13** was obtained (83 g, 84%; mp: 330°C dec). The dried material was suspended in methanol (835 ml) and 6 N hydrochloride gas in methanol (83 ml) was added quickly. A clear solution was obtained from which after roughly 5 min crystals deposited. The reaction mixture was cooled in an ice bath and after 1 h the hydrochloride could be collected. After washing with methanol the product was dried *in vacuo* at 110°C until a constant weight was reached. Yield: 76.6 g (69%) mp: > 320°C dec. Microanalysis: (C, H, Cl, N)

$C_{15}H_{14}N_6O$•H, Cl. IR: 3239, 3107, 2853, 1690,1342 cm^{-1}. MS (MG 294 x HCl): 294(40) M^+, 279(12). ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.31(1H, d) and 2.80(1H, dd, CH_2), 3.55(1H, m, CH), 7.45(1H, d, pyrazole-H), 7.80(1H, d), 7.98(1H, d) and 8.10(1H, s, aromatic-H), 8.15(1H, d, pyrazole-H), 11.05(1H, s, NH), 14.3(1H, s, HCl).

5-Methyl-6-[2-(2-{5-bromothienyl})-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride ***7***
Yield: 50%, mp: 313–315°C. Microanalysis: (C, H, Br, Cl, N, S) $C_{16}H_{13}BrN_4OS$•HCl. IR: 3221, 2537, 1695, 1418, 867 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.33(1H,d) and 2.84(1H, dd, CH_2), 3.55(1H, m, CH), 7.51(1H, d, thiophene), 7.74(1H, d), 7.90(1H, d) and 8.02(1H, s, aromatic-H), 8.13(1H, d, thiophene-H), 11.0(1H, s, NH), 8.8(1H, s, HCl).

5-Methyl-6-[2-(2-{4-bromothienyl})-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride semihydrate ***8***
Yield: 68%, mp: 304–306°C. Microanalysis: (C, H, Br, Cl, N, S) $C_{16}H_{13}BrN_4OS$•HCl•0.5H_2O. IR: 3272, 2512, 1693, 1342, 874 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.16(3H, d, CH_3), 2.33 (1H, d) and 2.81(1H, dd, CH_2), 3.53(1H, m, CH), 7.75(1H, d), 7.95(1H, d) and 8.10(1H, s, aromatic-H), 8.20 and 8.40(each 1H, s, thiophene-H), 11.10(1H, s, NH), 11.5(1H, s, HCl).

5-Methyl-6-[2-(2-{5-chlorothienyl})-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***9***
Yield: 35%, mp: 310–313°C. Microanalysis: (C, H, N, S) $C_{16}H_{13}ClN_4OS$. IR: 3179, 1666, 1480, 1334, 812 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.30(1H, d) and 2.75(1H, dd, CH_2), 3.52(1H, m, CH), 7.30 and 7.75(each 1H, d, thiophene-H), 7.60(1H, m), 7.9(1H, m), 8.05(1H, M, aromatic-H), 11.1(1H, s, NH).

5-Methyl-6-[2-(2-thienyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride ***10***
Yield: 63%, mp: 316°C dec. Microanalysis: (C, H, Cl, N, S) $C_{16}H_{14}N_4OS$•HCl. IR: 3198, 2700, 1679, 1570, 1335, 821 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.11(3H, d, CH_3), 2.30(1H, d) and 2.78(1H. dd, CH_2), 3.52(1H, m, CH), 7.39(1H, t), 7.78(1H, d), 7.93(1H, d) and 8.04(1H, s, aromatic-H), 8.12(1H, d) and 8.39(1H, d, thiophene-H), 10.2(1H, s, NH).

5-Methyl-6-[2-(3-thienyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride ***11***
Yield: 83%, mp: > 300°C. Microanalysis: (C, H, N) $C_{16}H_{14}N_4OS$•HCl• 0.25H_2O. IR: 3200, 2702, 1681, 1338, 819, 708 cm^{-1}. MS (MG 310•HCl = 346.83): 310(100) M^+, 295(19), 267(7), 225(25), 199(7). ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.31(1H, d) and 2.80(1H, dd, CH_2), 3.53(1H, m, CH), 7.85(1H, d), 7.97(1H, d) and 8.13(1H, s, aromatic-H), 8.93(1H, d, thiophene-H), 11.1(1H, s).

5-Methyl-6-[2-(4-thiazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride ***12***
With thiazole-4-carboxaldehyde [51]. Yield: 15%, mp: > 300°C dec MS ($C_{15}H_{13}N_5OS$ = MG 311.4): 311(100) M^+, 296(18), 282(4), 268(8), 254(5), 240(7), 226(17). ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.31(d, 2H) and 2.80(1H, dd, CH), 3.55(1H, m, CH), 7.5–8.1(3H, m, aromatic-H), 8.48 and 9.38(each 1H, s, thiazole-H).

5-Methyl-6-[2-(2-furyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride ***14***
Yield: 74%, mp: > 276°C dec. Microanalysis: (C, H, Cl, N) $C_{16}H_{14}N_4O_2$•HCl. IR: 3400, 3200, 2480, 1682, 1338 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.12(3H, d, CH_3), 2.31(1H, d) and 2.80(1H, dd, CH_2), 3.55(1H, m, CH), 7.00(1H, d), 7.83(1H, d), 8.00(1H, d) and 8.10(1H, s, aromatic-H), 8.34(1H, d, furan-H), 11.1(1H, s, NH).

5-Methyl-6-[2-(2-pyrrolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***15***
Yield: 32%, mp: > 300°C dec. Microanalysis: (C, H, N) $C_{16}H_{15}N_5O_2$•0.25CH_3OH. IR: 3223, 2873, 1648, 1631, 1512, 1432, 1396, 1341, 1133, 1036 cm^{-1}. MS (MG 293): 293(100) M^+, 278(14), 264(18). ^{1}H-NMR (DMSO–d_6): δ = 1.12(3H, d, CH_3), 2.25(1H, d) and 2.80(1H, dd, CH_2), 3.52(1H, m, CH), 6.2–7.9(6H, m, aromatic- and pyrrole-H).

5-Methyl-6-[2-(3-{1-methyl}pyrazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***16***
With 1-methyl-pyrazole-3-caboxaldehyde [52]. Yield: 54%, mp: 319–320°C from acetone/ether. Microanalysis: (C, H, N) $C_{16}H_{16}N_6O$•0.25H_2O. IR: 3400, 3200, 2480, 1682, 1338 cm^{-1}. MS (MG 308.80): 308(100) M^+, 293(17), 223(31). ^{1}H-NMR (DMSO–d_6): δ = 1.12(3H, d, CH_3), 2.31(1H, d) and 2.74(1H, dd, CH_2), 3.54(1H, m, CH), 4.00(3H, s, N–CH_3), 6.90 and 7.60(each 1H, d, pyrazole-H), 7.5–8.1(3H, m, aromatic-H).

5-Methyl-6-[2-(2-thiazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one semihydrate ***17***
With thiazole-2-carboxaldehyde [51]. Yield: 29%, mp: 299–301°C. Microanalysis: (C, H, N) $C_{15}H_{13}N_5OS$•0.75H_2O. IR: 3172, 3098, 2638, 1679, 1642, 1364 cm^{-1}. MS (MG = 311): 311(100) M^+, 296(25), 268(11), 254(9), 240(9), 226(27). ^{1}H-NMR (DMSO–d_6): δ = 1.15(3H, d, CH_3), 2.54(1H, d) and 2.74(1H, dd, CH_2), 3.52(1H, m, CH), 7.55–8.15(5H, m, aromatic- and thiazole-H).

5-Methyl-6-[2-(4-pyrazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride semihydrate ***18***
Yield: 39%, mp: > 280°C dec. Microanalysis: (C, H, N) $C_{15}H_{14}N_6O$•HCl•0.5H_2O. IR: 3172, 3098, 2638, 1679, 1642, 1364 cm^{-1}. MS (MG 339.82 = 294•HCl•1/2H_2O): 294(9) M^+, 188(19). ^{1}H-NMR (DMSO–d_6): δ = 1.12(3H, d, CH_3), 2.30(2H, d) and 2.77(1H, dd, CH_2), 3.55(1H, m, CH), 7.77(1H, d), 7.96-(1H, d) and 8.05(1H, s, aromatic-H), 8.77(2H, s, pyrazole-H), 11.01(1H, s, NH).

5-Methyl-6-[2-(1,2,4-triazol-5-yl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***19***
With 1,2,4-triazole-5-carboxaldehyde [53]. Yield: 25%, mp: > 350°C from water. Microanalysis: (C, H, N) $C_{14}H_{13}N_7O$. IR: 3400, 3200, 2480, 1682, 1338 cm^{-1}. MS (MG 295.80): 295(34) M^+, 165(50), 134(100). ^{1}H-NMR (DMSO–d_6): δ =1.14(3H, d, CH_3), 2.25(1H, d) and 2.78(1H, dd, CH_2), 3.48(1H, m, CH), 7.5–8.3(4H, m, aromatic- and triazole-H).

5-Methyl-6-[2-(3-{1,5-dimethyl}-pyrazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one hydrochloride hydrate ***20***
With 1,5-dimethyl-pyrazole-3-carboxaldehyde [55]. Yield: 52%, mp: 237–240°C dec. Microanalysis: (C, H, Cl, N) $C_{17}H_{18}N_6O$•HCl•1.5H_2O. IR: 3430, 3215, 2984, 1684, 1358 cm^{-1}. ^{1}H-NMR (DMSO–d_6): δ = 1.13(3H, d, CH_3), 2.30(1H, d) and 2.77(1H, dd, CH_2), 3.50(1H, m, CH), 2.43 and 3.95-(each 3H, s, pyzazole-CH_3) 7.21(1H, s, pyrazole-H), 7.76(1H, d), 7.96(1H, d) and 8.05(1H, s, aromatic-H), 11.03(1H, s, NH).

5-Methyl-6-[2-(5-{1-methyl}-pyrazolyl)-5-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***21***
With 1-methyl-pyrazole-5-carboxaldehyde [54]. Yield: 68%, mp: 167°C from acetone/ether. Microanalysis: (C, H, N)

$C_{16}H_{16}N_6O \cdot 0.5C_3H_6O \cdot 0.25H_2O$. IR: 3400, 3200, 2480, 1682, 1338 cm^{-1}. MS (MG = 308.80): 308(100) M^+, 293(10), 222(21). ^{1}H-NMR (DMSO-d_6): δ =1.12(3H, d, CH_3), 2.31(2H, d) and 2.75(1H, dd, CH_2), 3.55(1H, m, CH), 4.35(3H, s, N-methyl), 7.02 and 7.60(each 1H, d, pyrazole-H), 7.5–8.1(3H, m, aromatic-H).

Preparation of optically active meribendan

A solution of 4-(4-chloro-3-nitrophenyl)-3-methyl-4-oxo-butyric acid **4** (90.3 g, 330 mmol) in ethanol (1645 ml) was treated with (*S*)(–)-1-phenethylamine (40 g, 330 mmol). Within 6 h a crystalline precipitate **22** (mp: 168–170°C) was formed which was collected and washed twice with ethanol (100 ml). The mother liquor was concentrated to 1000 ml and, after standing overnight, a second crop was collected. The combined crops (50.8 g) are taken up in dichloromethane (350 ml) and treated with 1 N hydrochloric acid (160 ml). After washing with brine (50 ml) the solvent was evaporated and the remaining oil triturated with petrol to yield pale crystals (33.8 g, 74.9%) with mp: 91–93°C and $[\alpha]_D^{20} = -22°$ (chloroform). From the mother liquor containing oily diastereoisomeric salt, the crude (+)-acid was liberated using the same procedure as before (180 ml 1N HCl). It (59.5 g) was then dissolved in ethanol (800 ml) and treated with (*R*)-(+)-1-phenethylamine (26 g, 215 mmol). After 24 h the precipitate (mp: 165–166°C) was collected and processed as before to yield the (+)-acid (29.9 g, 66.2%) with mp: 90–92°C and $[\alpha]_D^{20} = +23.4°$ (chloroform).

The (+)- and (–)-acids were processed through to the separate diamines (+)-**1** and (–)-**1**. (+)-**1**: mp: 230–233°C, $[\alpha]_D^{20}$ = +558.2° (DMSO); (–)-**1**: mp: 230–233°C, $[\alpha]_D^{20}$ = –555.5° (DMSO). (+)-**5**: mp: 140–167°C, $[\alpha]_D^{20} = +315.8°$ (chloroform); (–)-**5**: mp: 140–167 °C, $[\alpha]_D^{20} = -325.6°$ (chloroform). (+)-**6**: mp: 225–230°C, $[\alpha]_D^{20} = +250.6°$ (chloroform); (–)-**6**: mp: 224–230°C, $[\alpha]_D^{20} = -256.9°$ (chloroform). (+)-Meribendan: mp: 340°C dec, $[\alpha]_D^{20} = +358.3°$ (DMSO); (–)-Meribendan: mp: 340°C dec, $[\alpha]_D^{20} = -361.2°$ (DMSO).

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