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Synthesis of a new type of 'bent' heterocyclic benzimidazolo-pyridazinones

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Summary — The synthesis of some new heterocyclic benzimidazolo-pyridazinones starting from 2,1,3-benzothiadiazole-4-carboxaldehyde **2** is described. Biological evaluation of all new compounds proved them to be inhibitors of phosphodiesterase III with no marked positive inotropic effects.

benzimidazole / benzothiadiazole / cardiotonics / inotropes / phosphodiesterase / pyridazinone

Introduction

As an extension of the work described in the foregoing paper, it seemed interesting to synthesize new cardiotonic benzimidazolo-pyridazinones with a new substitution pattern, which brings the pyridazinone ring and the benzimidazole moiety bearing heterocyclic residues R closer together and thus makes the molecules less linear (fig 1). In close analogy to the synthesis of meribendan [1], the pyridazinone system should be constructed using amine **1**.

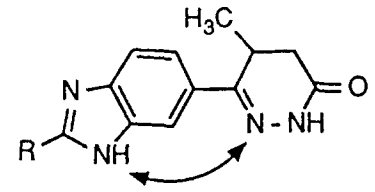
Chemistry

In the beginning, it became apparent that the synthesis of amine **1** was not straightforward. Due to the different functional-group manipulations necessary and the incompatible functionality of potential starting materials, some problems were encountered.

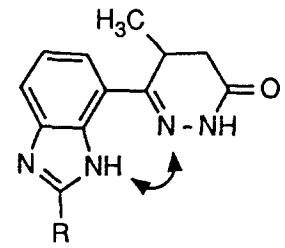
2,1,3-Benzothiadiazole-4-carboxaldehyde [2, 3] **2** was chosen as the starting material because it has been reported in the literature that 2,1,3-benzothiadiazoles can be cleaved reductively to their parent phenylene diamines [4]. Since this heterocyclic system is synthesized by reaction of a phenylene diamine with thionyl chloride, it can serve as a masking group for phenylene diamines (scheme 1).

The synthesis of the aldehyde seemed straightforward. Commercially available 2,3-diamino toluene was treated with thionyl chloride in the presence of triethyl amine to give the corresponding 4-methyl-2,1,3-benzothiadiazole as an oil [5]. The benzylic methyl group then could be converted to an aldehyde using conventional methods.

Due to the special properties of the thiadiazole ring only a few oxidation methods are applicable. Selenium dioxide has been described to oxidize the benzylic methyl group selectively [6], but, for large-scale synthesis, this reagent was not considered. NBS



Meribendan-series



"bent"-series

Fig 1. A new type of 'bent' benzimidazolo-pyridazinones.

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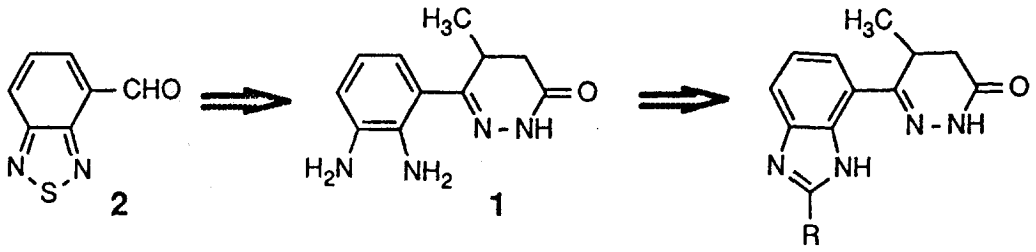
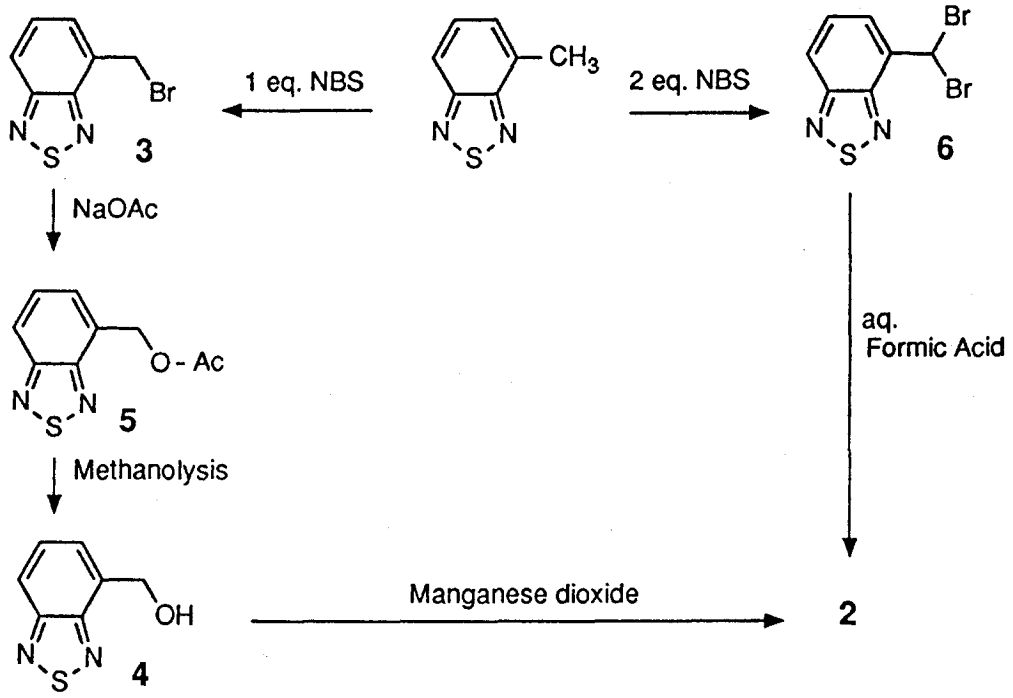


Scheme 1. Retrosynthetic scheme for the construction of 'bent' benzimidazolo-pyridazinones.

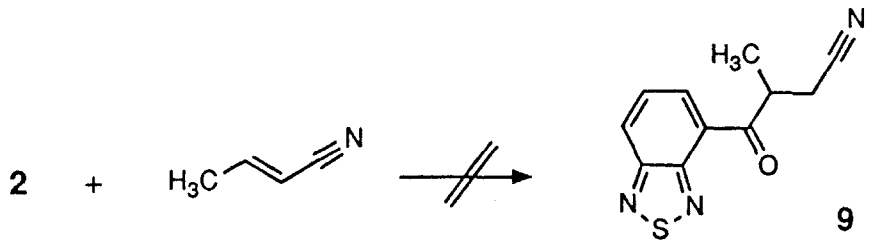
oxidation in carbon tetrachloride, according to a procedure reported in the literature [7], gave the corresponding 4-bromomethyl derivative **3** [8] which was subjected to a Sommelet reaction. This process indeed gave the desired aldehyde **2**, but by no means in satisfactory yield. When the bromomethyl compound **3** was treated with 2-nitropropane [9] in an alkaline solution, no aldehyde was obtained. Instead, the benzothiadiazole nucleus was attacked by the base and completely destroyed [10]. Treatment of the bromomethyl compound **3** with aqueous potassium carbonate led to the corresponding hydroxymethyl derivative **4** [5]. Due to the base sensitivity of the benzothiadiazole nucleus, the conversion of **3** into the acetate **5** followed by alcoholysis was preferred in the large-scale reaction. In a final oxidation with manganese dioxide, the desired aldehyde **2** was obtained. When two equivalents of NBS (*N*-bromosuccinimide) were used in the bromination step, the benzal bromide **6** was obtained. After some experimentation, this underwent a direct conversion into the aldehyde **2** in boiling aqueous formic acid (scheme 2).

With a good supply of 2,1,3-benzothiadiazole-4-aldehyde **2** on hand, the elaboration of the pyridazinone ring was undertaken. The Stetter reaction [1], which worked superbly with 4-chloro-benzaldehyde, failed completely (scheme 3).

As a way out, the aldehyde **2** had to be treated with morpholine hydrochloride in acetic acid, followed by cyanide anion. This gave the corresponding

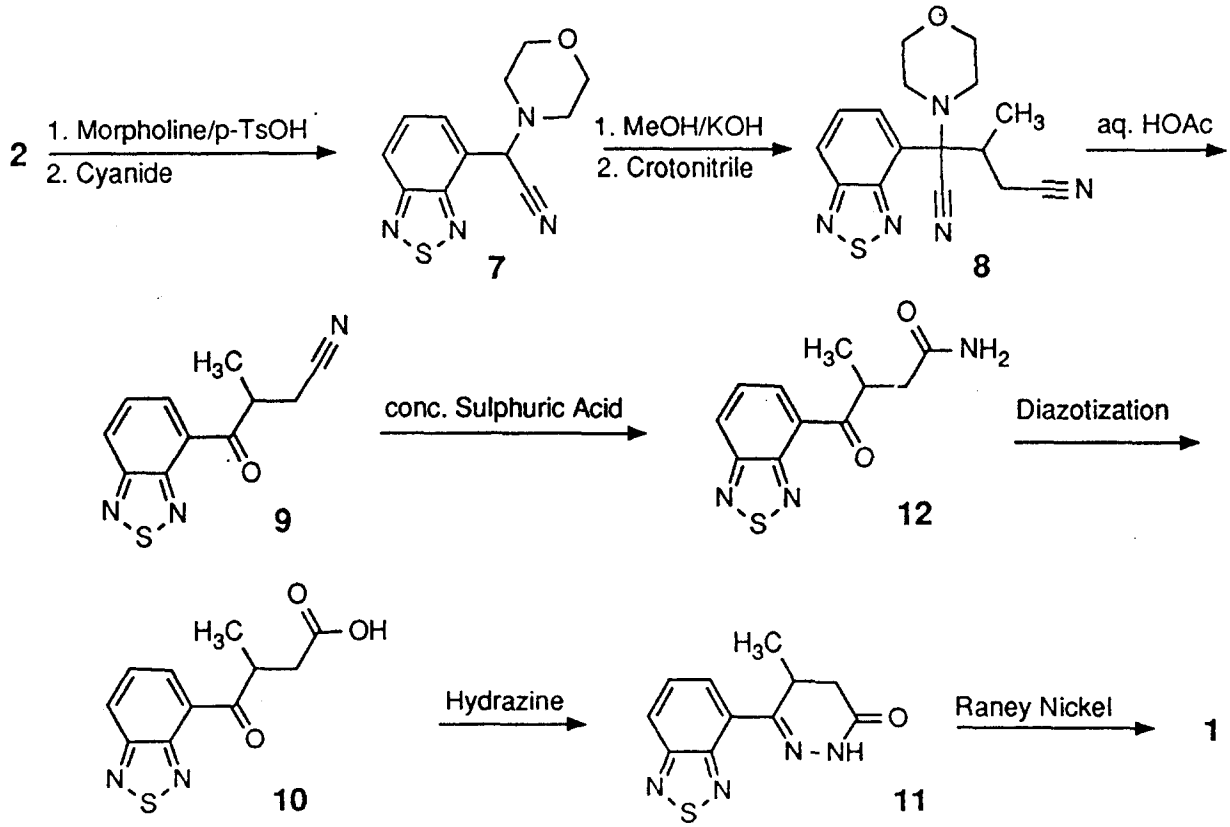


Scheme 2. Synthetic scheme for the preparation of starting 2,1,3-benzothiadiazole-4-carboxaldehyde **2**.



Scheme 3. Attempted Stetter-reaction of aldehyde **2** and 1-cyano-1-propene.

morpholino-acetonitrile **7**. The *Umpolung* of the aldehyde allowed the abstraction of the acidic proton. The carbanion of **7** indeed added to crotononitrile to yield **8** as a mixture of diastereoisomers. After some attempts at optimization, this crucial step could be performed in an acceptable yield of *ca* 40%. Apparently the bulk of the activating group together with the steric hindrance of the methyl group of the crotononitrile inhibited the addition. This explanation is supported by the fact that the addition of **7** to acrylonitrile gave much better results (scheme 4). The subsequent removal of the activating morpholino-nitrile group could be achieved smoothly by heating **8** in 75% aqueous acetic acid. In order to finish the construction of the pyridazinone ring, the liberated keto-nitrile **9** only had to be converted into keto-acid **10** and cyclized with hydrazine to give **11**. Due to the base sensitivity of the thiadiazole masking group, the nitrile had to be hydrolyzed under acidic conditions. In order to apply the mildest possible conditions, the



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

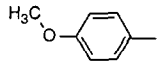
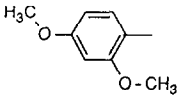
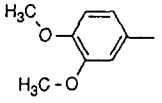
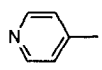
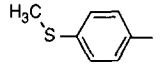
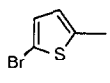
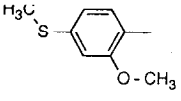
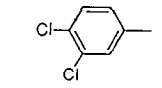
nitrile was converted into its amide **12** using concentrated sulfuric acid at room temperature. After diazotization, it finally gave the desired acid **10**. Cyclization with hydrazine subsequently made available the masked pyridazinone **11** from which by hydrogenation in the presence of Raney nickel, the diamine **1** was liberated [2]. This molecule finally served as the synthon for a variety of new heterocyclic pyridazino-benzimidazoles which are listed in table I.

The necessary condensations were carried out in close analogy to the method described in the foregoing paper [1]. The aldehydes used were either commercial reagents or prepared according to known procedures.

NMR spectra

The proton signals of the pyridazinone ring displayed a characteristic pattern in the aliphatic region. Generally, the methyl group appeared as a sharp doublet at *ca* 1.2 ppm. One of the geminal methylene protons absorbed at about 2.4 and the other at about 2.8 ppm. The vicinal methine proton was normally situated at about 3.5 ppm. The two principal protonation sites of the benzimidazole should give rise to two different tautomers. In contrast to the 'normal' meribendan series in the foregoing paper, in the 'bent' series the NMR spectra in the region of the pyridazinone ring protons showed additional signals when deuterated dimethylsulfoxide was used as the solvent. Very often, but not always, an extra methyl signal appeared close to the parent signal. More strikingly, in almost every case, an extra signal at about 4.5 ppm was observed. This signal appeared as a multiplet and its intensity added together with the parent signal to 1H. We explain these extra signals by the existence of two diastereoisomeric forms due to restricted rotation around the single bond which connects the aromatic ring to the pyridazinone ring. The calculation using the computer program MOPAC* clearly indicated a sterically forbidden area for one of the two possible tautomers **A** and **B** (fig 2). The energy difference between the two extrema was calculated to be 15 kcal/mol. The restricted rotation of **A** is apparently increased by the hydrogen-bonding solvent dimethylsulphoxide compared to chloroform which is not supposed to be capable of forming hydrogen bonds (fig 3).

Table I. Residues of new 'bent' benzimidazolo-pyridazinones.

No	*Residue*	*No*	*Residue*	*No*	*Residue*
13		19		25	
14		20		26	
15		21		27	
16		22		28	
17		23			
18		24			

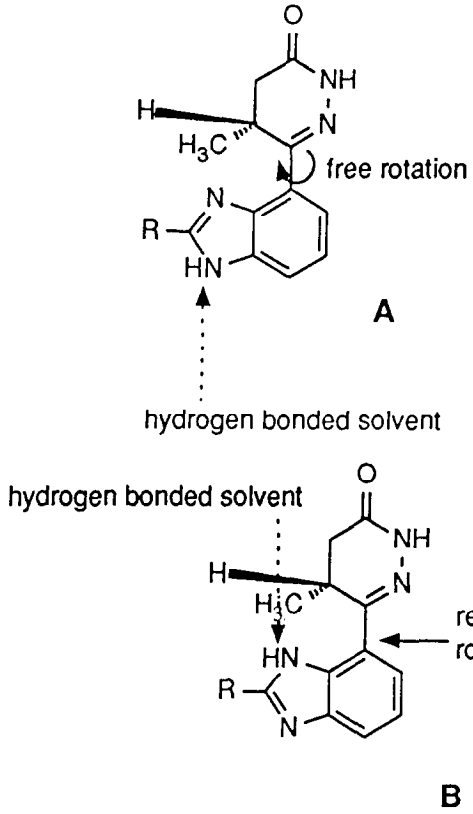


Fig 2. Possible explanation for the observation of diastereoisomers in the NMR spectra.

*Courtesy of M Krug, E Merck, Drug Design.

Biological results

All new 'bent' heterocyclo-benzimidazolo-pyridazinones had a fairly uniform inhibitory effect on the isolated phosphodiesterase isoform III with an $IC_{50} \approx 10^{-7}$ M and they were almost without any effect on the isoform I [11].

Of utmost importance for us was the Ca^{2+}-sensitivity. In the relevant skinned muscle preparation, all tested substances had no effect [12].

Regarding positive inotropy, the situation is not clear-cut. Some of the compounds were effective, although in an order of magnitude which does not make them eligible for any further testing or development. Other compounds showed no effect or were even inotropically negative [13]. This wide variety of effects on isolated guinea pig papillary muscle was paralleled by the uniformly strong inhibition of phosphodiesterase III.

In summary, it can be stated that the effort in synthesizing 'bent' pyridazinones has not paid off in finding new positive inotropic compounds.

Experimental protocols

All analytical data were obtained from the Central Analytical Department of E Merck. 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 employed 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.

2,1,3-Benzothiadiazole-4-carboxaldehyde **2**

A mixture of 4-methyl-2,1,3-benzothiadiazole (19.6 g, 130 mmol) and *N*-bromosuccinimide (23.3 g, 130 mmol) in carbon tetrachloride (200 ml) was refluxed for 5 h under irradiation with a 300 W sunlamp. After cooling with ice, the succinimide was filtered off and the filtrate was washed with water. After drying with magnesium sulfate, the solvent was evaporated and the remaining solid collected to afford pure 4-bromomethyl-2,1,3-benzothiadiazole **3** (24.3 g, 81.6%), mp: 83°C.

4-Bromomethyl-2,1,3-benzothiadiazole **3** (2.29 g, 10 mmol) was heated under reflux in methanol (100 ml) containing anhydrous sodium acetate (1.64 g, 20 mmol). After 5 h (thin–layer chromatography (TLC) control), the solvent was evaporated; the remaining residue was then taken up in dichloromethane and washed with water. Evaporation of the dried solution, after chromatography over silica using a 1/9 mixture of ether/petrol, gave the desired 4-acetoxymethyl-2,1,3-benzothiadiazole **5** (1.2 g, 57.7%) as a waxy solid, mp: 47°C.

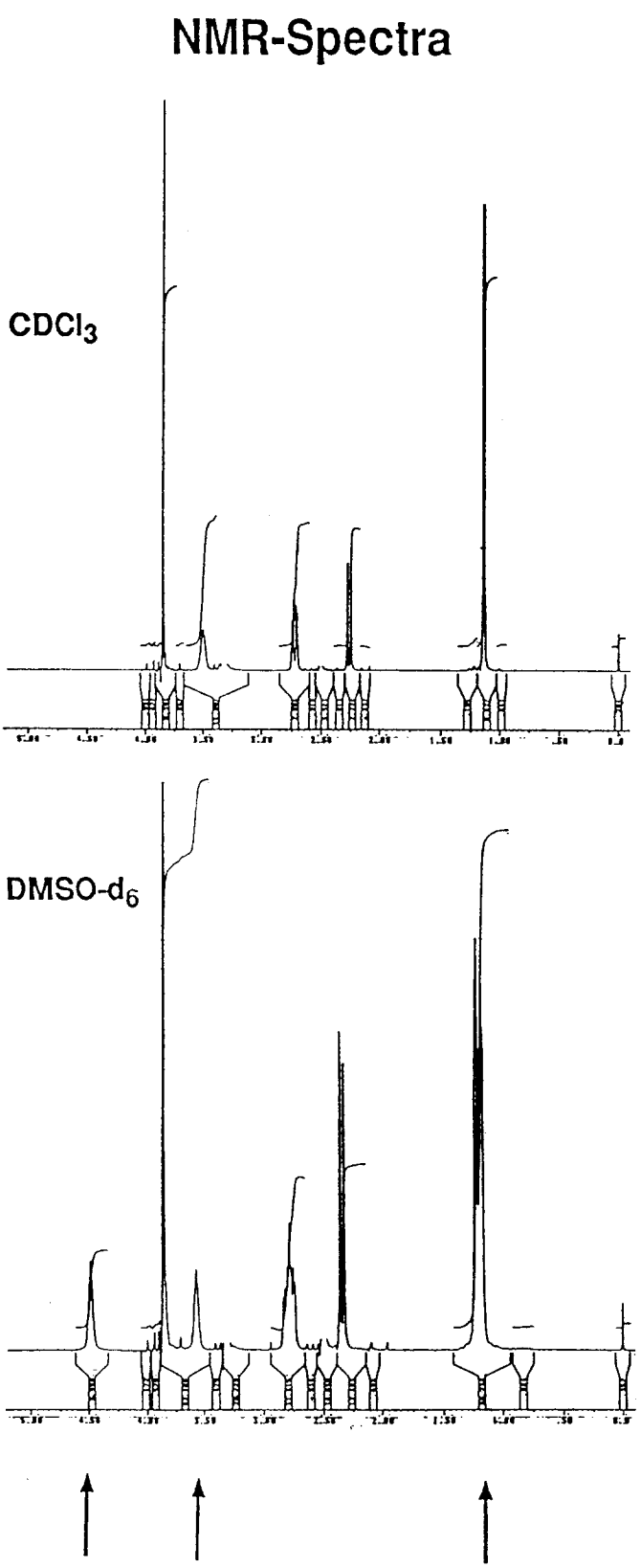


Fig 3. Characteristic NMR spectra in deuterated chloroform and dimethylsulfoxide.

A mixture of acetate **5** (1.2 g, 6 mmol) and sodium hydroxide (0.6 g, 15 mmol) in methanol (30 ml) was heated under reflux. After 30 min the solvent was evaporated and the residue was passed over a bed of silica using ether as the solvent. After evaporation, 4-hydroxymethyl-2,1,3-benzothiadiazole was obtained as a solid (1 g, quant), mp: 70°C.

The alcohol **4** (3.32 g, 20 mmol) was stirred in dichloromethane (150 ml) with manganese dioxide (20 g, 230 mmol) at ambient temperature. After 3 h (TLC control), the inorganic material was removed by filtration and the filtrate was evaporated to yield solid 2,1,3-benzothiadiazole-4-carboxaldehyde **2** (3 g, 91.5%), mp: 99°C.

Alternatively, 4-methyl-2,1,3-benzothiadiazole was treated with 2 equivalents of *N*-bromosuccinimide in the same manner as described above to give the desired benzal bromide **6** with mp: 132°C.

4-Dibromomethyl-2,1,3-benzothiadiazole **6** (163.3 g, 0.53 mol) was refluxed in 85% formic acid (1 000 ml). After 3 h, the formic acid was distilled off and the residue was taken up in dichloromethane. Residual traces of acid were removed by washing with saturated bicarbonate solution. After drying over sodium sulfate, the solvent was removed and the residue was chromatographed over silica using a 1/1 mixture of ether/petrol as the solvent to yield solid aldehyde **2** with mp: 101°C (87 g, quant).

2-[4-(2,1,3-Benzothiadiazolo)]-morpholino-acetonitrile 7
To a stirred solution of *p*-toluene sulfonic acid (8 g, 42 mmol) in tetrahydrofuran (400 ml) was added dropwise morpholine (7.4 ml, 84 mmol) keeping the temperature below 40°C. Then the aldehyde **2** (6.6 g, 40 mmol) was added and the resulting mixture was heated under reflux for 2 h. After cooling to 30°C, a solution of potassium cyanide (3.28 g, 48 mmol) in water (5 ml) was added and the mixture was heated for another hour under reflux. After stirring overnight at room temperature, the solvent was evaporated and the residue was taken up in dichloromethane. After washing with water followed by evaporation of the solvent, the residue was chromatographed over silica using dichloromethane as the solvent to give the desired morpholino-acetonitrile **7**, which was obtained after crystallisation from ethyl acetate/ether (8.4 g, 81%) mp: 126°C.

3-Methyl-[4-(2,1,3-benzothiadiazolo)]-4-morpholino-4-cyano-butyronitrile **8**
The morpholino-acetonitrile **7** (38 g, 146 mmol) in tetrahydrofuran (1 000 ml) was treated with 30% ethanolic potassium hydroxide (3.5 ml). After cooling to 10°C, 1-cyano-1-propene (15 g, 220 mmol) was added dropwise. After 2 h of stirring at ambient temperature, more 30% ethanolic potassium hydroxide (3.5 ml) and 1-cyano-1-propene (15 g, 220 mmol) were added. After a total of 4 h, the solvent was evaporated and the residue was taken up in dichloromethane. Washing with water was followed by drying over magnesium sulfate and evaporation. The remaining crude product was chromatographed over silica using ether/petrol (1/1) as solvent to give a pale solid (35.6 g, 74.5%) mp: 137°C. ^{1}H-NMR ($CDCl_3$) δ = 1.13 (3H, CH_3), 2.3–2.8 (6H, m, CH_2), 3.24 (1H, dd, CH), 3.74 (4H, t, CH_2), 7.6–8.2 (3H, m, aromatic-H).

3-Methyl-[4-(2,1,3-benzothiadiazolo)]-4-oxobutyronitrile ***9***
The product **9** (1.8 g, 5.5 mmol) of the foregoing reaction was dissolved in 75% aqueous acetic acid (20 ml) and stirred for 1 h at 100°C. Then the acetic acid was removed by distillation and the residue was taken up in dichloromethane. Traces of remaining acid were removed by washing with saturated sodium bicarbonate solution. After drying with magnesium sulfate the solution was passed over silica gel. After evaporation of the solvent, a pale solid, mp: 81°C (1.15 g, 91%) was obtained. ^{1}H-NMR ($CDCl_3$): δ = 1.4l (3H, d, CH_3), 2.82 (2H, dt, CH_2), 4.78 (1H, m, CH), 7.77 (1H, m) and 8.33 (2H, m, aromatic-H).

3-Methyl-[4-(2,1,3-benzothiadiazolo)]-4-oxobutyric amide ***12***
The keto-nitrile **9** (81 g, 351 mmol) was carefully added to conc sulfuric acid (350 ml). During this process, the temperature was kept between 20 and 25°C.After stirring for 2 h the reaction mixture was carefully poured onto chipped ice and the product was extracted with dichloromethane. After evaporation, a solid melting at 127°C (83.7 g, 96%) was obtained. IR: 3510, 3170, 1670, 1525, 1405, 1245, 750 cm^{-1}.

3-Methyl-[4-(2,1,3-benzothiadiazolo)]-4-oxobutyric acid ***10***
A stirred homogeneous solution of the crude amide **12** (83 g, 333 mmol) in dilute sulfuric acid (from 185 ml sulfuric acid and 1800 ml water) and acetonitrile (2500 ml) was treated with a solution of sodium nitrite (170 g, 2.5 mmol) in water (500 ml) maintaining the reaction temperature at 20°C. The reaction mixture was subsequently stirred for another 4 h at 50°C. The bulk of the acetonitrile was distilled off at reduced pressure. After cooling, the reaction mixture was neutralized with sodium bicarbonate and unreacted amide was extracted with dichloromethane. The aqueous phase was then acidified and extracted with ethyl acetate to yield crude acid (70.3 g, 84%) melting at 108°C.

6-[4-(2,1,3-Benzothiadiazolo)]-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one **11**
Crude keto-acid **10** (69 g, 280 mmol) in ethanol (600 ml) was treated with hydrazine hydrate (21.5 g, 430 mmol) under reflux. After 2 h, the solvent was removed by distillation and the residue was chromatographed over silica using dichloromethane/methanol (97/3) as the solvent. The desired product was obtained from the main fraction as a pale solid (59.8 g, 85%), mp: 150°C. Microanalysis: (C, H, N, S) $C_{11}H_9N_4OS \cdot 0.25CH_3OH$. IR: 3307, 1686, 1359, 1319, 1186, 753 cm^{-1}. MS (MG 245.3): 246(100) M$^+$, 231(28), 217(30), 202(61). ^{1}H-NMR ($CDCl_3$): δ = 1.31 (3H, CH_3), 2.58 (1H, dd) and 2.92 (1H, dd, CH_2), 4.03 (1H, m, CH), 7.74 (1H, d), 7.90 (1H) and 8.02 (1H, s, aromatic-H), 9.4 (1H, s, NH).

6-(2,3-Diaminophenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one ***1***
Benzothiadiazolo-pyridazinone **11** (60 g, 244 mmol) was hydrogenated at ambient temperature in methanol (6000 ml) over Raney nickel (360 g) as the catalyst. When the hydrogen uptake had ceased, the catalyst was removed by filtration. After evaporation of the solvent, the residue was triturated with ether to give the diamino compound (42.6 g, 80%) melting at 186°C. An analytical specimen was recrystallized from dichloromethane/ether and melted at 199°C. Microanalysis: (C, H, N) $C_{11}H_{14}N_4O \cdot 0.25H_2O$. MS (MG 218): 218(100) M$^+$, 174(31), 160(18), 145(6),133(17). ^{1}H-NMR (DMSO–d_6): δ = 1.08 (3H, CH_3), 2.20 (1H, dd) and 2.68 (1H, dd, CH_3), 3.39 (1H, m, CH), 5.45 (4H, broad, NH_2), 6.46 (1H, t), 6.63 and 6.85 (each 1H, d, aromatic-H).

Condensation of ***1*** *with aldehydes as in the preceding paper [1]*

5-Methyl-6-[2-(4-methoxyphenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***13***
Yield: 57%, mp: 242°C (from acetone). IR: 3372, 1694, 1665, 1611, 1481, 1427, 1364, 1319, 1254 cm^{-1}. MS (MG 334):

334(100) M^+, 319(9), 305(5), 290(10). ^{1}H-NMR (tautomeric mixture) (DMSO–d_6): δ = 1.20 (3H, 2d, CH_3), 2.35 (1H, d) and 2.80 (1H, 2dd, CH_2), 3.58–4.51 (1H, m, CH), 3.89 (3H, s, OCH_3), 7.06–7.39, 7.47–7.82 and 8.10–8.25 (7H, m, aromatic-H).

5-Methyl-6-[2-(2,4-dimethoxyphenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***14***
Yield: 71%, mp: 274°C. Microanalysis: (C, H, N) $C_{20}H_{20}N_4O_3$. IR: 3434, 1671, 1613, 1474, 1432, 1283, 1255, 1213, 1027 cm^{-1}. MS (MG = 364): 364(100) M^+, 333(18), 320(39), 306(31), 278(46). ^{1}H-NMR (DMSO–d_6): δ = 1.21 (3H, CH_3), 2.35 (1H, d) and 2.84 (1H, dd, CH_2), 3.64 (1H, m, CH), 3.85 and 4.18 (each 3H, s, O–CH_3), 6.4–8.4 (6H, m, aromatic-H).

5-Methyl-6-[2-(3,4-dimethoxyphenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***15***
Yield: 69%, mp: 274°C. Microanalysis: (C, H, N) $C_{20}H_{20}N_4O_3$. IR: 3434, 1671, 1613, 1474, 1432, 1283, 1255, 1213, 1027 cm.$^{-1}$. MS (MG 364): 364(100) M^+, 333(18), 320(39), 306(31), 278(46). ^{1}H-NMR (DMSO–d_6): δ = 1.23 (3H, d, CH_3), 2.34 (1H, d) and 2.80 (1H, dd, CH_2), 3.86 and 3.91 (each 3H, s, CH_3), 7.1–7.9 (6H, m, aromatic-H).

5-Methyl-6-[2-(4-methylthiophenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***16***
Yield: 63%, mp: 232°C. Microanalysis: (C, H, N) $C_{19}H_{18}N_4OS \cdot 0.25H_2O$. IR: 1694, 1662, 1472, 1419, 1364, 1285, 1198 cm^{-1}. MS (MG 350): 350(100) M^+, 335(10), 321(5), 306(10). ^{1}H-NMR (DMSO–d_6): δ = 1.23 (3H, d, CH_3), 2.36 (1H, d) and 2.79 (1H, dd, CH_2), 2.59 (3H, s, S–CH_3), 3.57 and 4.47 (1H, m, tautomers, CH), 7.0–8.5 (7H, m, aromatic-H).

5-Methyl-6-[2-(2-methoxy-4-methylthiophenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***17***
With 2-methoxy-4-methylthiobenzaldehyde [14]. Yield: 74%, mp: 268°C. Microanalysis: (C, H, N) $C_{20}H_{20}N_4O_2S \cdot 0.25H_2O$. IR: 3441, 3201, 1678, 1595, 1563, 1463, 1416, 1285, 1232, 1198, 1029 cm^{-1}. MS (MG 380): 380(100) M^+, 349(14), 336(34), 322(25), 284(38). ^{1}H-NMR (DMSO–d_6): δ = 1.20 (3H, d, CH_3), 2.35 (1H, d) and 2.84 (1H, dd, CH_3), 2.61 (3H, s, S–CH_3), 3.65 (1H, m, CH), 7.0–8.5 (6H, m, aromatic-H).

5-Methyl-6-[2-(3,4-dichlorophenyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***18***
Yield: 43%, mp: 250°C. Microanalysis: (C, H, N) $C_{18}H_{14}Cl_2N_4O \cdot 0.25CH_3OH$). IR: 3381, 3296, 1691, 1658, 1455, 1421, 1371, 1350, 1288 cm^{-1}. MS (MG 373): 372(100) M^+, 357(10), 343(8), 328(10), 287(13). ^{1}H-NMR (DMSO–d_6): δ = 1.24 (3H, d, CH_3), 2.40 (1H, d) and 2.83 (1H, dd, CH_2), 3.68 (1H, m, CH), 7.2–8.5 (6H, m, aromatic-H).

5-Methyl-6-[2-(2-pyridyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***19***
Yield: 56%, mp: 217°C. Microanalysis: (C, H, N) $C_{17}H_{15}N_5O$. IR: 3423, 1683, 1597, 1447, 1365, 1281 cm^{-1}. MS (MG 305): 305(100) M^+, 290(17), 276(14), 261(65), 221(29), 195(20). ^{1}H-NMR (DMSO–d_6): δ = 1.22 (3H, d, CH_3), 2.45 (1H, d) and 2.84 (1H, dd, CH_2), 3.64 and 4.48 (1H, m, CH), 7.2–8.8 (7H, m, aromatic-H).

5-Methyl-6-[2-(3-pyridyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***20***
Yield: 49%, mp: 172°C. Microanalysis: (C, H, N) $C_{17}H_{15}N_5O$. IR: 3360, 1660, 1419, 1365, 1285, 1029 cm^{-1}. MS (MG 305): 305(100) M^+, 290(5), 276(4), 261(7), 181(25), 153(43), 125(43). ^{1}H-NMR (DMSO–d_6): δ = 1.22 (3H, d, CH_3), 2 35 (1H, d) and 2.85 (1H, dd, CH_2), 3.64 and 4.48 (1H, m, CH), 7.2–7.9 and 8.5–8.8 (7H, m, aromatic-H).

5-Methyl-6-[2-(4-pyridyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***21***
Yield: 52%, mp: 260°C. Microanalysis: (C, H, N) $C_{17}H_{15}N_5O \cdot 0.25H_2O$. IR: 3397, 2898, 1610, 1428, 1365, 1283, 1225, 1189, 1170, 1069, 1028 cm^{-1}. MS (MG 305): 305(100) M^+, 290(12), 276(6), 261(10), 220(11). ^{1}H-NMR (DMSO–d_6): δ = 1.24 (3H, d, CH_3), 2.37 (1H, d) and 2.83 (1H, dd, CH_2),3.60 and 4.45 (1H, m, CH), 7.38 (1H, t) and 7.55–7.95 (3H, m), 8.15 and 8.82 (each 2H, d, pyridine-H).

5-Methyl-6-[2-(2-pyrazinyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***22***
With pyrazine-2-carboxaldehyde [15]. Yield: 33%, mp: 294–295°C. Microanalysis: (C, H, N) $C_{16}H_{14}N_6O \cdot 0.25H_2O$. IR: 3412, 3207, 2926, 1691, 1445, 1361, 1284, 1218, 1195, 1157, 1030, 1015 cm^{-1}. MS (MG 306): 306(100) M^+, 291(17), 277(14), 262(61), 222(25), 196(19). ^{1}H-NMR (DMSO–d_6): δ = 1.24 (3H, dd, CH_3), 2.36 (1H, d) and 2.84 (1H, dd, CH_2), 3.64 and 4.46 (1H, m, CH), 7.25–7.96 (3H, m, aromatic-H), 8.81 (2H, s) and 9.54 (1H, s, pyrazine-H).

5-Methyl-6-[2-(3-pyrazolyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***23***
With pyrazole-3-carboxaldehyde [1]. Yield: 54%, mp: 261°C. Microanalysis: (C, H, N) $C_{15}H_{14}N_6O \cdot 0.25CH_3OH$. IR: 3435, 1675, 1366, 1342, 1298 cm^{-1}. MS (MG 294): 294(100) M^+, 279(15), 265(11), 250(51), 210(21), 184(16). ^{1}H-NMR (DMSO–d_6): δ = 1.15 (3H, d, CH_3), 2.33 (1H, d) and 2.71 (1H, dd, CH_2), 3.62 and 4.4 (1H, broad, CH), 6.94 and 7.99 (each 1H, s, pyrazole-H), 7.2–7.8 (3H, m, aromatic-H).

5-Methyl-6-[2-(2-imidazolyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***24***
Yield: 61%, mp: 310°C. Microanalysis: (C, H, N) $C_{15}H_{14}N_6O \cdot 0.25CH_3OH$. IR: 3449, 1671, 1509, 1497, 1404, 1376, 1340, 1295, 1285 cm^{-1}. MS (MG 294): 294(100) M^+, 279(17), 265(16), 250(81), 210(33),184(20). ^{1}H-NMR (DMSO–d_6): δ = 1.20 (3H, d, CH_3), 2.35 (1H, d) and 2.83 (1H, dd, CH_2), 3.63 (1H, m, CH), 7.2–7.9 (5H, m, aromatic-H and imidazole-H).

5-Methyl-6-[2-(4-methyl-5-imidazolyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***25***
With 4-methyl-imidazole-5-carboxaldehyde [16]. Yield: 55%, mp: 242°C. Microanalysis: (C, H, N) $C_{16}H_{16}N_6O \cdot 1CH_3OH$. IR: 3427, 3348, 1672, 1618, 1540, 1366, 1348, 1286, 1237, 1197, 1158, 1023 cm^{-1}. MS (MG 308): 308(100) M^+, 293(20), 279(16), 264(64), 250(11), 237(14), 224(30), 198(20). ^{1}H-NMR (DMSO–d_6): δ = 1.22 (3H, dd, CH_3), 2.32 (1H, d) and 2.82 (1H, dd, CH_2), 3.19 (3H, d, imidazole–CH_3), 3.62 and 4.47 (1H, m, CH), 7.1–7.6 (4H, m, aromatic-H and imidazole-H).

5-Methyl-6-[2-(1-methyl-5-imidazolyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***26***
With 1-methyl-imidazole-5-carboxaldehyde [17]. Yield: 62%, mp: 259°C. Microanalysis: (C, H, N) $C_{16}H_{16}N_6O \cdot 0.5H_2O$. IR: 1661, 1619, 1610, 1409, 1366, 1338, 1287, 1229, 1200, 1129, 1033 cm^{-1}. MS (MG 308): 308(100) M^+, 293(6), 279(5), 264(17), 222(10). ^{1}H-NMR (DMSO–d_6): δ = 1.23 (3H, dd, CH_3), 2.33 (1H, d) and 2.84 (1H, dd, CH_2), 3.52 and 4.78 (1H, m, CH), 3.32 and 4.08 (3H, s, N-CH_3), 7.2–7.4 and 7.5–7.9 (5H, m, aromatic-H and imidazole-H).

5-Methyl-6-[2-(2-thienyl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***27***
Yield: 48%, mp: 275°C. Microanalysis: (C, H, N) $C_{16}H_{14}N_4OS \cdot 0.25H_2O$. IR: 3225, 1683, 1661, 1561, 1481, 1453, 1368, 1288, 1193 cm^{-1}. MS (MG 310): 310(100) M^+, 295(10), 281(7), 266(11), 225(12). ^{1}H-NMR (DMSO-d_6): δ = 1.22 (3H, d, CH_3), 2.36 (1H, d) and 2.80 (1H, dd, CH_2), 3.56 and 4.35 (1H, m, CH), 7.3–8.1 (6H, m, aromatic-H and thiophene-H).

5-Methyl-6-[2-(5-bromothien-2-yl)-4-benzimidazoyl]-2,3,4,5-tetrahydro-pyridazin-3-one ***28***
Yield: 33%, mp: 232°C. Microanalysis: (C, H, N) $C_{16}H_{13}BrN_4OS$. IR: 3390, 3297, 1692, 1656, 1566, 1484, 1424, 1366, 1307, 1195 cm^{-1}. MS (MG 389): 390(100) M^+, 373(9), 361(7), 344(15), 224(21). ^{1}H-NMR (DMSO-d_6): δ = 1.21 (3H, d, CH_3), 2.33 (1H, d) and 2.78 (1H, dd, CH_2), 3.55 (1H, m, CH), 7.31 (1H, t) and 7.5–8.0 (thiophene-H and aromatic-H), 7.41 (1H, d, thiophene-H).

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