# Studies on the Chemical Transformations of Rotenoids. 5 [1]. Synthesis and Cytotoxicity of 1,3-Diazepino[5,6-*b*]benzofuran and Pyridazino[4,5-*b*]benzofurans Fused with Thiazole, Imidazole and Pyrimidine



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Novel benzofuro[2,3-*d*]pyridazinium chlorides fused with thiazole **5a**, imidazole **5b-c** and pyrimidine **5d-f** were prepared starting from 4-chloropyridazino[4,5-*b*]benzofuran **3a**. Treatment of **5b**, **5d** and **5e** with 10% potassium carbonate solution provided the corresponding free bases **6a-c**. Ring closure of methyl rotenononate **1b** with amidines proceeded in the presence of sodium methoxide to give 1,3-diazepino[5,6-*b*]benzofuran-5-ones **7a-c**. Compound **5d** showed cytotoxicity against P388 and L1210 leukemia cells.

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Rotenoids are tropical plant products found principally in the *Leguminosae* species and possess a variety of important pharmacological activities [2-4]. In previous papers we reported the ring transformations of rotenoids into benzofurans and pyridazinobenzofurans fused with five and six-membered nitrogen heterocycles [5-7]. In continuation of our studies on the chemical transformations of rotenoids and evaluation of pharmacologically active rotenoids, we now report the synthesis and cytotoxicity of 1,3-diazepinobenzofurans and pyridazinobenzofurans fused with thiazole, imidazole and pyrimidine.

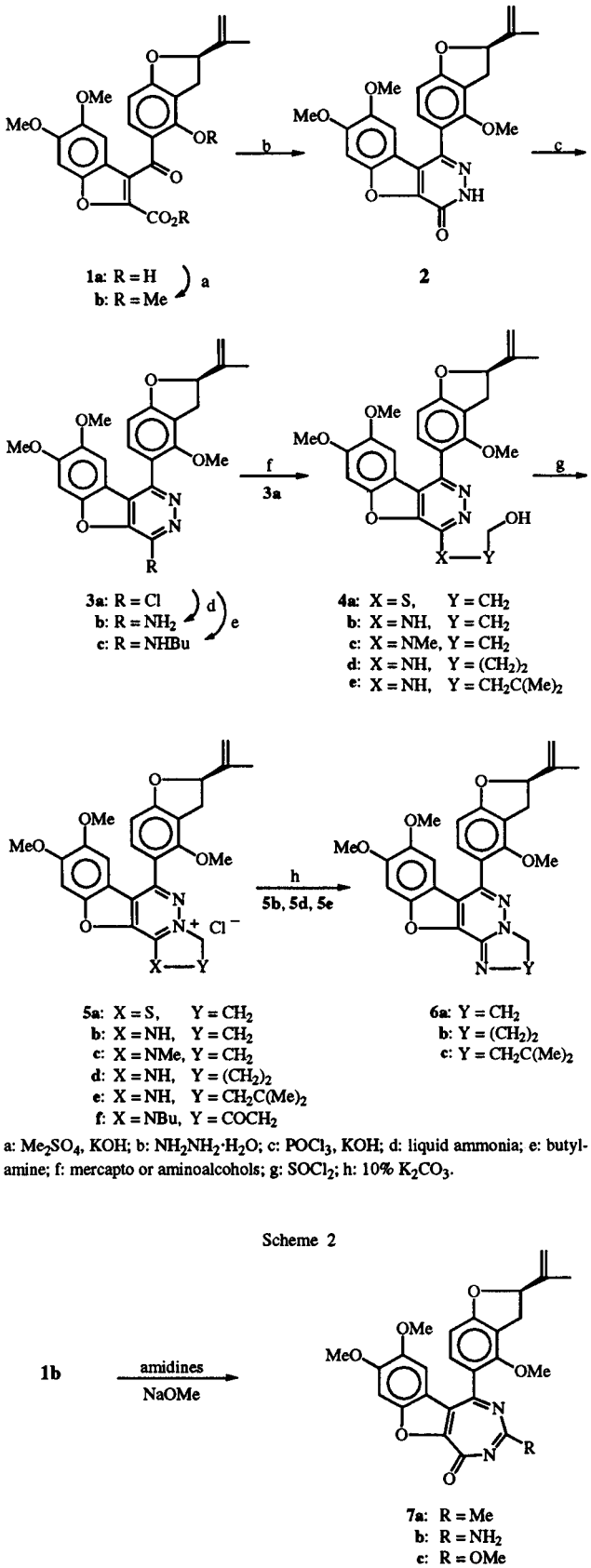
Rotenononic acid **1a** was allowed to react with dimethyl sulfate to give dimethylated benzofuran **1b** in good yield. Compound **1b** is a very useful synthon for constracting the nitrogen heterocycles because it has a difunctional 1,4-dicarbonyl group. Reaction of **1b** with hydrazine hydrate in ethanol resulted in the formation of pyridazine ring to afford pyridazino[4,5-*b*]benzofuran **2** as shown in Scheme 1. Treatment of **2** with phosphorus oxychloride, followed by workup with boiling dioxane-potassium hydroxide solution produced chloro compound **3a**. Nucleophilic substitution of the chlorine atom with liquid ammonia or butylamine proceeded under prolonged heating to give the corresponding 4-amino **3b** and 4-butylaminopyridazine **3c** in 36% and 80% yields. In a similar manner, compound **3a** was reacted with appropriate mercapto or aminoalcohols to yield pyridazinobenzofuranalcohols **4a-e**. Cyclization of **4a-e** with thionyl chloride proceeded in boiling benzene to give novel tetracyclic pyridazinium chlorides **5a-e** as stable crystalline forms. Compound **5f** was alternatively prepared by reaction of **3c** with 3-chloropropionyl chloride. The structures of **5a-f** were established by $^1$H nmr spectra which showed the remarkable downfield shifts of methylene protons adjacent to the quarternally pyridazinium nitrogens. Among pyridazinium chlorides, compounds **5b** and **5d-e** having NH groups in the imidazole or pyrimidine rings, were converted to the corresponding free bases, **6a-c** by treating with 10% potassium carbonate solution.

Compounds in which a seven-membered 1,3-diazepine ring is annelated to benzofuran ring, were obtained from the reaction of **1b** with amidine hydrochlorides as outlined in Scheme 2, although isolated yields were low. Thus compound **1b** was subjected to condensation with acetamidine hydrochloride or guanidine hydrochlorides, followed by purification by silica gel chromatography to give 1,3-diazepinobenzofurans **7a-b**. The appearance of newly formed 3-methyl and 3-amino groups of diazepine ring was confirmed by $^1$H nmr and ir spectra. Similar reaction of **1b** with 2-methyl-2-thiopseudourea sulfate however resulted in the formation of 3-methoxy diazepine **7c** instead of the expected 3-methylthio derivative because of the exchange reaction of the initially formed methylthio group with sodium methoxide anion. The low yields of **7a-c** is probably due to the steric hindrance between two bulky benzofuran rings.

The cytotoxic activity of synthesized compounds **1-7** was tested against L1210 and P388 murine leukemia cells in mice according to the standard protocols [8]. Drug concentration required to inhibit the growth of each leukemia cell by 50% ($IC_{50}$) was measured. The cytotoxic compounds against L1210 were **3c** and **5d**, whose $IC_{50}$ values were 4.4 μg/ml and 4.5 μg/ml respectively. In contrast compounds **5d** and **6b** were active against P388 leukemia and their $IC_{50}$ values were both 2.4 μg/ml.

In conclusion, we have prepared the novel 1,3-diazepino[5,6-*b*]benzofurans and pyridazino[4,5-*b*]benzofurans fused with thiazole, imidazole and pyrimidine. Compound **5d** exhibited cytotoxicity against L1210 and P388 leukemia cells.

Scheme 1




a: $Me_2SO_4$, KOH; b: $NH_2NH_2 \cdot H_2O$; c: $POCl_3$, KOH; d: liquid ammonia; e: butylamine; f: mercapto or aminoalcohols; g: $SOCl_2$; h: 10% $K_2CO_3$.

Scheme 2




## EXPERIMENTAL

All melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were obtained on a JASCO IRA-2 spectrometer. The $^1H$ nmr spectra were recorded with a JEOL EX-270 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 300 spectrometer.

Methyl 3-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-carbonyl)-5,6-dimethoxybenzofuran-2-carboxylate **1b**.

To a stirred solution of 3.6 g (8.5 mmoles) of rotenononic acid **1a** [7] in 30 ml of 10% aqueous potassium hydroxide solution was added dropwise 21 ml of dimethyl sulfate. An additional 80 ml of aqueous potassium hydroxide was added to the reaction mixture during 2 hours. The precipitate was collected, washed with water and recrystallized from ethanol to give colorless needles, mp 146-147°, yield 3.4 g (90%); ir (potassium bromide): 1720 ($CO_2Me$), 1640 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.64, 3.75, 3.88 and 3.98 (four s, 3H each, 4 x OMe); ms: m/z 452 ($M^+$).

*Anal.* Calcd. for $C_{25}H_{24}O_8$: C, 66.37; H, 5.38. Found: C, 66.16; H, 5.30.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3*H*-pyridazino[4,5-*b*]benzofuran-4-one **2**.

A mixture of **1b** (0.42 g, 0.9 mmole) and 20 ml of hydrazine hydrate in 50 ml of ethanol was refluxed for 5 hours and evaporated to dryness. The residue was recrystallized from ethanol to give colorless needles, mp 267-270°, yield 0.36 g (90%); ir (potassium bromide): 3300 (NH), 1670 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 11.44 (s, 1H, NH); ms: m/z 434 ($M^+$).

*Anal.* Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.47; H, 5.07; N, 6.41.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-chloro-7,8-dimethoxypyridazino[4,5-*b*]benzofuran **3a**.

A solution of **2** (0.2 g, 0.46 mmole) in 2 ml of phosphorus oxychloride was refluxed for 0.5 hour and evaporated to dryness. A mixture of the residual powders and 4 ml of 20% aqueous potassium hydroxide solution in 10 ml of dioxane was refluxed for 1 hour. After cooling, the mixture was extracted with chloroform. The solvent was distilled from the extract and the residue was recrystallized from methanol to give colorless needles, mp 177-179.5°, yield 0.15 g (71%); ms: m/z 452 ($M^+$), 454 ($M^+$ +2).

*Anal.* Calcd. for $C_{24}H_{21}ClN_2O_5$; C, 63.65; H, 4.67; N, 6.19. Found: C, 63.48; H, 4.54; N, 5.99.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-amino-7,8-dimethoxypyridazino[4,5-*b*]benzofuran **3b**.

A mixture of **3a** (0.07 g, 0.15 mmole), 4 ml of ethanol and 80 ml of liquid ammonia was heated at 100° for 6 days in a sealed tube. After evaporation of the liquid ammonia, the residue was dissolved in 10 ml of 5% aqueous potassium hydroxide solution and extracted with chloroform. The solvent was distilled from the extract and the residue was recrystallized from isopropyl ether-methanol (10:1) to give a light yellow amorphous powder, mp 213-215°, yield 0.024 g (36%); ir (potassium bromide): 3350, 3200 ($NH_2$) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 5.34 (br s, 2H, $NH_2$); ms: m/z 433 ($M^+$).

*Anal.* Calcd. for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.39; H, 5.43; N, 9.42.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-butylamino-7,8-dimethoxybenzofuro[4,5-*b*]pyridazine **3c**.

A mixture of **3a** (0.14 g, 0.3 mmole), 40 ml of butylamine and 0.5 ml of triethylamine was refluxed for 43 hours and evaporated to dryness. The residue was recrystallized from isopropyl ether-methanol (10:1) to give colorless needles, mp 177-178°, yield 0.12 g (80%); ir (potassium bromide): 3380 (NH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 4.90 (s, 1H, NH); ms: m/z 489 ($M^+$).

*Anal.* Calcd. for $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.38; N, 8.58. Found: C, 68.93; H, 6.20; N, 8.77.

General Procedure for the Preparation of 1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-hydroxyalkylamino(thio)-7,8-dimethoxypyridazino[4,5-*b*]benzofurans **4a-e**.

A mixture of **3a** (0.3 mmole) and mercapto or aminoalkyl alcohols (10 mmoles) in 5 ml of dioxane was refluxed for 20 hours and evaporated to dryness. The residue was recrystallized from isopropyl ether-methanol (10:1) after chromatograpy on silica gel (chloroform).

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-(2-hydroxyethylthio)-7,8-dimethoxypyridazino[4,5-*b*]benzofuran **4a**.

The colorless crystalline powder had mp 155-157°, yield 26%; ir (potassium bromide): 3500 (OH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.70 (t, 2H, J = 7, $SCH_2$), 4.12 (t, 2H, J = 7, $CH_2OH$); ms: m/z 494 ($M^+$).

*Anal.* Calcd. for $C_{26}H_{26}N_2O_6S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.38; H, 5.38; N, 5.47.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-(2-hydroxyethylamino)-7,8-dimethoxypyridazino[4,5-*b*]-benzofuran **4b**.

Colorless needles were obtained, mp 197-199°, yield 81%; ir (potassium bromide): 3300 (NH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.90-4.00 (m, 4H, $CH_2CH_2$), 5.87 (s, 1H, NH); ms: m/z 477 ($M^+$).

*Anal.* Calcd. for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.29; H, 5.90; N, 8.99.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-(*N*-methylhydroxyethylamino)-7,8-dimethoxypyridazino-[4,5-*b*]benzofuran **4c**.

Colorless needles were obtained, mp 172-175°, yield 64%; ir (potassium bromide): 3400 (OH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.60 (s, 3H, NMe), 3.93-4.08 (m, 4H, $CH_2CH_2$): ms: m/z 491 ($M^+$).

*Anal.* Calcd. for $C_{27}H_{29}N_3O_6$: C, 65.98; H, 5.95; N, 8.55. Found: C, 65.80; H, 6.09; N, 8.47.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-(3-hydroxypropylamino)-7,8-dimethoxypyridazino[4,5-*b*]benzofuran **4d**.

Colorless needles were obtained, mp 184-185°, yield 88%, ir (potassium bromide): 3400 (OH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.92 (m, 2H, $CH_2CH_2CH_2$), 5.35 (s, 1H, NH); ms: m/z 473 ($M^+ - H_2O$).

*Anal.* Calcd. for $C_{27}H_{29}N_3O_6$: C, 65.98; H, 5.95; N, 8.55. Found: C, 65.88; H, 6.09; N, 8.42.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-(2,2-dimethy-3-hydroxypropylamino)-7,8-dimethoxypyridazino[4,5-*b*]benzofuran **4e**.

Colorless needles were obtained, mp 119-122°, yield 55%; ir (potassium bromide): 3350 (OH) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 1.05 (s, 6H, 2 x $CH_3$), 3.30 (s, 2H, $CH_2OH$), 3.60 (s, 2H, $NHCH_2$), 5.26 (s, 1H, NH); ms: m/z 519 ($M^+$).

*Anal.* Calcd. for $C_{29}H_{33}N_3O_6$: C, 67.04; H, 6.40; N, 8.09. Found: C, 67.23; H, 6.23; N, 8.20.

General Procedure for the Cyclization of 1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-4-hydroxyalkylamino(thio)-7,8-dimethoxypyridazino[4,5-*b*]benzofurans **4a-e**.

A mixture of **4** (0.3 mmole) and 0.2 ml of thionyl chloride in 30 ml of dry benzene was refluxed for 2 hours and evaporated to dryness. The residue was chromatographed on silica gel column (chloroform) and recrystallized from isopropyl ether-methanol (10:1) to give **5a-e**.

6-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-2,3-dihydrobenzofuro[2,3-*d*]thiazolo-[3,2-*b*]pyridazinium Chloride **5a**.

Colorless crystals were obtained, mp 199-202°, yield 82%; $^1H$ nmr (deuteriochloroform-dimethyl-$d_6$ sulfoxide): δ 4.38 (t, 2H, J = 7, 2-$CH_2$), 5.58 (t, 2H, J = 7, 3-$CH_2$); ms: m/z 476 ($M^+$ -HCl).

*Anal.* Calcd. for $C_{26}H_{25}ClN_2O_5S$: C, 60.87; H, 4.91; N, 5.46. Found: C, 61.04; H, 4.74; N, 5.29.

6-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-2,3-dihydrobenzofuro[2,3-*d*]imidazo[1,2-*b*]-pyridazinium Chloride **5b**.

Colorless needles were obtained, mp 232-235°, yield 76%; $^1H$ nmr (deuteriochloroform): δ 4.43 (t, 2H, J = 8, 2-$CH_2$), 4.92 (t, 2H, J = 8, 3-$CH_2$); ms: m/z 459 (M+ -HCl).

*Anal.* Calcd. for $C_{26}H_{26}ClN_3O_5$: C, 62.97; H, 5.28; N, 8.47. Found: C, 63.25; H, 5.17; N, 8.71.

1-Methyl-6-(2*R*-2-methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-2,3-dihydrobenzofuro[2,3-*d*]imidazo-[1,2-*b*]pyridazinium Chloride **5c**.

Colorless needles were obtained, mp 170-173°, yield 84%; $^1H$ nmr (deuteriochloroform): δ 3.70 (s, 3H, $NCH_3$), 4.64 (t, 2H, J = 8, 2-$CH_2$), 5.12 (t, 2H, J = 8, 3-$CH_2$); ms: m/z 473 ($M^+$ -HCl).

*Anal.* Calcd. for $C_{27}H_{28}ClN_3O_5$: C, 63.59; H, 5.53; N, 8.24. Found: C, 63.40; H, 5.36; N, 8.43.

7-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-1,2,3,4-tetrahydrobenzofuro[2,3-*d*]pyrimido-[1,2-*b*]pyridazinium Chloride **5d**.

Colorless needles were obtained, mp 217-219°, yield 69%; $^1H$ nmr (deuteriochloroform): δ 2.40 (m, 2H, 3-$CH_2$), 3.90 (t, 2H, J = 8, 2-$CH_2$), 4.58 (t, 2H, J = 8, 4-$CH_2$); ms: m/z 473 ($M^+$ -HCl).

*Anal.* Calcd. for $C_{27}H_{28}ClN_3O_5$: C, 63.59; H, 5.53; N, 8.24. Found: C, 63.40; H, 5.36; N, 8.43.

3,3-Dimethyl-7-(2*R*-2-methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-1,2,3,4-tetrahydrobenzofuro[2,3-*d*]pyrimido[1,2-*b*]pyridazinium Chloride **5e**.

Colorless needles were obtained, mp 182-184°, yield 77%; $^1H$ nmr (deuteriochloroform): δ 1.25 (s, 6H, 2 x $CH_3$), 3.60 (s,

2H, 2-$CH_2$), 4.20 (s, 2H, 4-$CH_2$); ms: m/z 501 ($M^+$ -HCl).

*Anal.* Calcd. for $C_{29}H_{32}ClN_3O_5$: C, 64.74; H, 6.00; N, 7.81. Found: C, 64.56; H, 5.80; N, 7.92.

1-Butyl-2-oxo-7-(2*R*-2-methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-1,2,3,4-tetrahydrobenzofuro[2,3-*d*]pyrimido[1,2-*b*]pyridazinium Chloride **5f**.

To a mixture of **3c** (0.1 g, 0.2 mmole) and 0.5 ml of triethylamine in 15 ml of dry chloroform was added dropwise a solution of 0.3 ml of 3-chloropropionyl chloride in 3 ml of dry chloroform at room temperature. After being stirred for 5 minutes, the mixture was worked up with water and extracted with chloroform. The solvent was distilled from the extract and the residue was recrystallized from isopropyl ether-methanol (10:1) to give a light yellow crystalline powder, mp 77-80°, yield 78%; ir (potassium bromide): 1660 (C=O) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.30 (t, 2H, J = 7, 3-$CH_2$), 4.20 (t, 2H, J = 7, 4-$CH_2$); ms: m/z 543 ($M^+$ -HCl).

*Anal.* Calcd. for $C_{31}H_{34}ClN_3O_6$: C, 64.19; H, 5.91; N, 7.24. Found: C, 64.47; H, 5.83; N, 7.00.

General Procedure for the Preparation of Imidazopyridazinobenzofuran **6a** and Pyrimidopyridazinobenzofurans **6b-c** from Pyridazinium Chlorides **5b**, **5d** and **5e**.

Pyridazinium chloride **5b**, **5d** or **5e** (0.1 g, 0.2 mmole) was dissolved in 10 ml of 10% aqueous potassium carbonate solution and extracted with chloroform. The solvent was distilled from the extract and the residue was recrystallized from isopropyl ether-methanol (10:1) to give **6a-c**.

6-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-2,3-dihydroimidazo[1',2':2,3]pyridazino-[4,5-*b*]benzofuran **6a**.

Light yellow crystals were obtained, mp 115-117°, yield 90%; $^1H$ nmr (deuteriochloroform): δ 4.23 and 4.29 (two t, 2H each, J = 8, 2-$CH_2$ and 3-$CH_2$); ms: m/z 459 ($M^+$).

*Anal.* Calcd. for $C_{26}H_{25}N_3O_5$: C, 67.96; H, 5.48; N, 9.14. Found: C, 67.87; H, 5.40; N, 9.32.

7-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-2,3-dihydro-4*H*-pyrimido[1',2':2,3]pyridazino[4,5-*b*]benzofuran **6b**.

Light yellow crystals were obtained, mp 103-105°, yield 85%; $^1H$ nmr (deuteriochloroform): δ 2.19 (m, 2H, 3-$CH_2$), 3.70 (t, 2H, J = 7, 4-$CH_2$), 4.22 (t, 2H, J = 7, 2-$CH_2$); ms: m/z 473 ($M^+$).

*Anal.* Calcd. for $C_{27}H_{27}N_3O_5$: C, 68.49; H, 5.75; N, 8.87. Found: C, 68.60; H, 5.94; N, 8.63.

3,3-Dimethyl-7-(2*R*-2-methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-2,3-dihydro-4*H*-pyrimido[1',2':2,3]pyridazino[4,5-*b*]benzofuran **6c**.

Light yellow crystals were obtained, mp 166-169°, yield 87%; $^1H$ nmr (deuteriochloroform): δ 1.10 (s, 6H, 2 x $CH_3$), 3.38 (s, 2H, 4-$CH_2$), 3.86 (s, 2H, 2-$CH_2$); ms: m/z 501 ($M^+$).

*Anal.* Calcd. for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.17; H, 6.47; N, 8.27.

General Procedure for the Preparation of 3-Substituted 1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-1,3-diazepino[5,6-*b*]benzofuran-5-ones **7a-c**.

To a stirred mixture of **1b** (0.1 g, 0.22 mmole) and amidines (1.1 mmoles) in 30 ml of absolute methanol was added dropwise a sodium methoxide solution prepared from sodium (1.1 mmoles) and 10 ml of absolute methanol. The reaction mixture was refluxed for 5 hours and evaporated to dryness. The residue was diluted with water and extracted with ethyl acetate. The solvent was distilled from the residue and the residue was chromatographed on a silica gel column (chloroform) and recrystallized from isopropyl ether-methanol (10:1) to give **7a-c**.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-3-methyl-8,9-dimethoxy-1,3-diazopino[5,6-*b*]benzofuran-5-one **7a**.

This compound was obtained from **1b** and acetamidine hydrochloride as yellow crystals, mp 203-205°, yield 21%; $^1H$ nmr (deuteriochloroform): δ 2.32 (s, 3H, 3-$CH_3$); ms: m/z 460 ($M^+$).

*Anal.* Calcd. for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 67.90; H, 5.14; N, 6.27.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-3-amino-8,9-dimethoxy-1,3-diazepino[5,6-*b*]benzofuran-5-one **7b**.

This compound was obtained from **1b** and guanidine hydrochloride as yellow crystals, mp >300°, yield 7%; ir (potassium bromide): 3350 and 3180 ($NH_2$) $cm^{-1}$; ms: m/z 461 ($M^+$).

*Anal.* Calcd. for $C_{25}H_{23}N_3O_6$: C, 65.07; H, 5.02; N, 9.11. Found: C, 65.20; H, 5.19; N, 9.01.

1-(2*R*-2-Methylethenyl-4-methoxy-2,3-dihydrobenzofuran-5-yl)-3,8,9-trimethoxy-1,3-diazepino[5,6-*b*]benzofuran-5-one **7c**.

This compound was obtained from **1b** and 2-methyl-2-thiopseudourea sulfate as yellow crystals, mp 133-136°, yield 8%; $^1H$ nmr (deuteriochloroform): δ 3.64 and 3.66 (each s, 6H, 7 and 8-$OCH_3$), 3.87 (s, 3H, 4'-$OCH_3$), 4.09 (s, 3H, 3-$OCH_3$); ms: m/z 476 ($M^+$).

*Anal.* Calcd. for $C_{26}H_{24}N_2O_7$: C, 65.54; H, 5.08; N, 5.88. Found: C, 65.46; H, 4.89; N, 5.99.

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