ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 7, pp. 972–976. © Pleiades Publishing, Ltd., 2012.
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Synthesis of Diamides from 1,4-Benzodioxane-2- and Isochroman-1-carboxylic Acids

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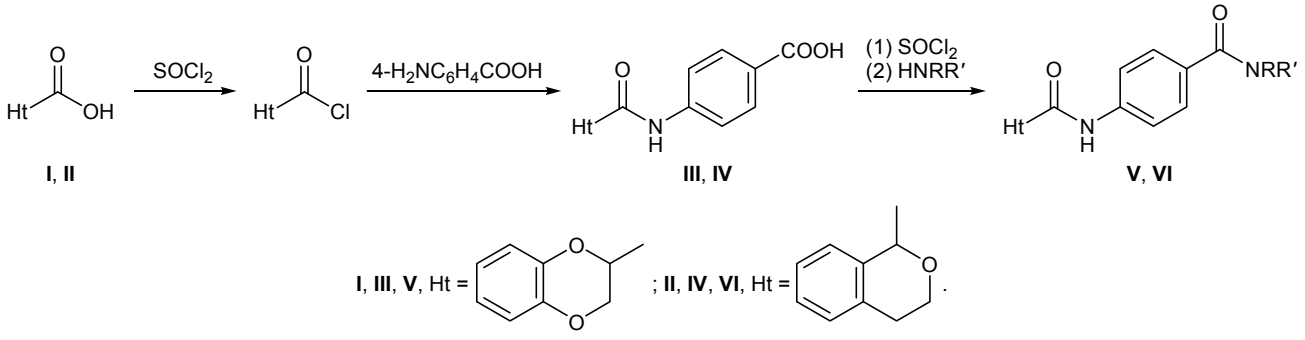
Received January 16, 2012

Abstract—1,4-Benzodioxane-2-carboxylic acid and isochroman-1-carboxylic acid were treated with thionyl chloride, and the resulting acid chlorides reacted with *p*-aminobenzoic acid in dioxane in the presence of pyridine to produce the corresponding amido acids. The latter were converted into acid chlorides which were brought into reaction with various amines to obtain a number of new diamides.

DOI: 10.1134/S1070428012070147

Interest in derivatives of oxygen-containing heterocycles, 1,4-benzodioxane and isochroman, is determined by their high and diverse pharmacological activity. With a view to reveal effective biologically active substances in this series, over a number of years we performed studies on the synthesis of new amines, amino alcohols, amino amides, and diamides possessing adrenolytic, sympatholytic, antiarrhythmic, and antihypoxic properties [1]. While continuing studies in this line we tried to synthesize new diamides containing both heterocyclic 1,4-benzodioxane or isochroman fragment and pharmacophoric N-substituted *p*-aminobenzoic acid fragment. The latter is present in molecules of a number of drugs and is probably responsible for their pharmacological properties. We proposed the following scheme for the synthesis of such compounds. 1,4-Benzodioxane-2-carboxylic acid (**I**) or isochroman-1-carboxylic acid (**II**) was initially treated with thionyl chloride to obtain the corresponding acid chloride which then reacted with *p*-aminobenzoic acid to afford key amido acids **III** and **IV**. When the reaction was carried out in toluene at 105–110°C (reaction time 6–8 h), insoluble dimeric products were formed. Desired amido acids **III** and **IV** were obtained in 75–80% yield by heating in dioxane at 65–70°C for 4–5 h. Acids **III** and **IV** were then converted into acid chlorides, and reactions of the latter with various amines gave diamides **Va**–**Vh** and **VIa**–**VIi** (Scheme 1). The best yields (55–70%) were obtained in anhydrous dioxane in the presence of pyridine. As amine compo-

Scheme 1.



V, R = H, R′ = *i*-Bu (**a**), 4-EtOC(O)C_6H_4 (**b**), 1,4-benzodioxan-2-ylmethyl (**c**), 1-phenylcyclopentylmethyl (**d**), 1-(1,4-benzodioxan-2-yl)ethyl (**e**), 3-(morpholin-4-yl)propyl (**f**), 1,3,4-thiadiazol-2-yl (**g**); RR′N = morpholin-4-yl (**h**); **VI**, R = H, R′ = *s*-Bu (**a**), 4-EtOC(O)C_6H_4 (**b**), 1,4-benzodioxan-2-ylmethyl (**c**), 1-phenylcyclopentylmethyl (**d**), 3-Cl-4-MeC_6H_3 (**e**), 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (**f**), isochroman-1-ylmethyl (**g**), pyridin-2-yl (**h**); RR′N = piperidin-1-yl (**i**).

nent we used alkyl-, aralkyl-, hetaryl-, and hetaryl-alkyl-amines, cyclic amines, and substituted anilines with a view to reveal the most efficient pharmacophoric fragment in the molecules of the final products.

The structure and purity of the synthesized compounds were confirmed by physicochemical methods and thin-layer chromatography. Compounds **Vb**–**Vd**, **Vf**, and **VIc** were tested for their activity against calcium chloride-induced arrhythmia; however, no pronounced antiarrhythmic effect was observed. Study on pharmacological properties of the synthesized compounds will be continued.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-300 instrument from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra were run on an MKh-1321A mass spectrometer with direct sample admission into the ion source. The melting points were determined on a Boetius hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene–acetone (3 : 1) as eluent; development with iodine vapor.

1,4-Benzodioxane-2-carboxylic acid (**I**) and its chloride were synthesized according to the procedure reported in [2], and isochroman-1-carboxylic acid (**II**) and its chloride were prepared as described in [3].

4-(1,4-Benzodioxan-2-ylcarbonylamino)benzoic acid (III). Pyridine, 3.2 g (40 mmol), was added to a solution of 6.7 g (50 mmol) of *p*-aminobenzoic acid in 80 ml of anhydrous dioxane, a solution of 12.0 g (40 mmol) of 1,4-benzodioxane-2-carbonyl chloride in 50 ml of anhydrous dioxane was then slowly added, the mixture was heated for 4–5 h at 70°C, cooled, and poured into 200 ml of water, and the precipitate was filtered off, washed with hot water, and dried in air. Yield 9.2 g (78%), mp 259–260°C (from EtOH), R_f 0.54. IR spectrum, ν, cm^{-1}: 3391 (NH), 2730–2550 (OH), 1683 (C=O, acid), 1610, 1593 (C=O, amide). Found, %: C 64.00; H 4.50; N 4.58. $C_{16}H_{13}NO_5$. Calculated, %: C 64.21; H 4.35; N 4.68.

4-(Isochroman-1-ylcarbonylamino)benzoic acid (IV) was synthesized in a similar way. Yield 75%, light brown crystals, mp 243–244°C (EtOH), R_f 0.61. ^{1}H NMR spectrum, δ, ppm: 2.79 d.t (1H, CH_2, J = 16.3, 4.4 Hz), 3.10 d.d.d (1H, CH_2, J = 16.3, 8.5, 5.0 Hz), 3.92 d.d.d (1H, OCH_2, J = 11.1, 8.5, 4.0 Hz), 4.30 d.t (1H, OCH_2, J = 11.1, 4.9 Hz), 5.25 s (1H, OCH), 7.10–7.20 m (3H) and 7.44 m (1H) (isochroman), 7.77 m and 7.88 m (2H each, C_6H_4), 9.75 s (1H, NH); 12.21 m (1H, OH). Found, %: C 57.00; H 4.81; N 4.48. $C_{17}H_{15}NO_4$. Calculated, %: C 57.28; H 5.05; N 4.78.

Acid III and IV chlorides were synthesized by heating a solution of 50 mmol of acid **III** or **IV** and 7.2 g (60.5 mmol) of thionyl chloride in 50 ml of anhydrous toluene for 10 h at 80–85°C. The mixture was cooled, the unreacted acid was filtered off, the filtrate was evaporated under reduced pressure, 30 ml of anhydrous toluene was added to the residue, and the mixture was evaporated to dryness. Yield 78–80%. The products were brought into reaction with amines without additional purification.

Diamides Va–Vh and VIa–VIi (*general procedure***).** A mixture of 40 mmol of acid **III** or **IV** chloride, 40 mmol of the corresponding amine, and 3.2 g (40 mmol) of pyridine in 50–70 ml of anhydrous dioxane was heated for 10–12 h at 70–75°C. The mixture was filtered, the filtrate was poured into 150–200 ml of water, the mixture was left overnight, and the precipitate was filtered off, washed with dilute hydrochloric acid (1 : 3), water, a 5% solution of NaOH, and water again, dried in air, and recrystallized from alcohol.

***N*-(4-Isobutylcarbamoylphenyl)-1,4-benzodioxane-2-carboxamide (Va).** Yield 74%, white crystals, mp 164–165°C, R_f 0.35. ^{1}H NMR spectrum, δ, ppm: 0.94 d (6H, CH_3, J = 6.7 Hz), 1.88 d [1H, C**H**$(CH_3)_2$, J = 6.7 Hz], 3.08 d.d (2H, CH_2, J = 6.7, 6.0 Hz), 4.28 d.d (1H, OCH_2, J = 11.4, 6.9 Hz), 4.47 d.d (1H, OCH_2, J = 11.4, 2.7 Hz), 4.83 d.d (1H, OCH, J = 6.9, 2.7 Hz), 6.78–6.88 m (3H) and 7.00 m (1H) (benzodioxane), 7.70 m and 7.79 m (2H each, C_6H_4), 8.04 t (1H, N**H**CH_2, 6.0 Hz), 9.98 s (1H, NH). Found, %: C 67.68; H 6.45; N 7.71. $C_{20}H_{22}N_2O_4$. Calculated, %: C 67.80; H 6.21; N 7.91.

Ethyl 4-[4-(1,4-benzodioxan-2-ylcarbonylamino)-benzoylamino]benzoate (Vb). Yield 75%, white crystals, mp 212–213°C, R_f 0.37. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, J = 7.1 Hz), 4.31 q (2H, O**H**$_2$CH$_3$, J = 7.1 Hz), 4.31 d.d (1H, OCH_2, J = 11.4, 6.7 Hz), 4.48 d.d (1H, OCH_2, J = 11.4, 2.7 Hz), 4.86 d.d (1H, OCH, J = 6.7, 2.7 Hz), 6.79–6.89 m (3H) and 7.01 m (1H) (benzodioxane), 7.81 m and 7.97 m (2H each, NC_6H_4CON), 7.92 s (4H, NC_6H_4COO),

10.12 s (1H, NH), 10.19 s (1H, NH). Found, %: C 67.46; H 4.71; N 6.00. $C_{25}H_{22}N_2O_6$. Calculated, %: C 67.26; H 4.93; N 6.28.

***N*-[4-(1,4-Benzodioxan-2-ylmethylcarbamoyl)-phenyl]-1,4-benzodioxane-2-carboxamide (Vc).** Yield 74%, light gray crystals, mp 160–161°C, R_f 0.41. ^{1}H NMR spectrum, δ, ppm: 3.51 d.t (1H, CH_2, J = 13.7, 6.2 Hz), 3.63 d.t (1H, CH_2, J = 13.7, 5.4 Hz), 3.96 d.d (1H, OCH_2, J = 11.8, 7.6 Hz), 4.29 d.d (1H, OCH_2, J = 11.5, 6.9 Hz), 4.29–4.36 m (2H, OCH_2, OCH), 4.46 d.d (1H, OCH_2, J = 11.5, 2.7 Hz), 4.84 d.d (1H, OCH, J = 6.9, 2.7 Hz), 6.72–6.88 m (7H) and 7.00 m (1H) (benzodioxane), 7.73 m and 7.84 m (2H each, C_6H_4), 8.46 d.d (1H, N**H**CH_2, J = 6.2, 5.4 Hz), 10.02 s (1H, NHCO). Found, %: C 67.00; H 4.65; N 6.00. $C_{25}H_{22}N_2O_6$. Calculated, %: C 67.26; H 4.93; N 6.28.

***N*-[4-(1-Phenylcyclopentylmethylcarbamoyl)-phenyl]-1,4-benzodioxane-2-carboxamide (Vd).** Yield 78%, white crystals, mp 120–121°C, R_f 0.42. ^{1}H NMR spectrum, δ, ppm: 1.67 m (2H), 1.81–1.93 m (4H), and 1.99–2.10 m (2H, C_5H_8); 3.46 d (2H, NCH_2, J = 6.2 Hz), 4.28 d.d (1H, OCH_2, J = 11.4, 6.9 Hz), 4.46 d.d (1H, OCH_2, J = 11.4, 2.7 Hz), 4.82 d.d (1H, OCH, J = 6.9, 2.7 Hz), 6.78–6.88 m (3H) and 7.00 m (1H) (benzodioxane), 7.14 m (1H) and 7.24–7.33 m (4H) (Ph), 7.33 t (1H, N**H**CH_2, J = 6.2 Hz), 7.62–7.70 m (4H, C_6H_4), 9.98 s (1H, NH). Found, %: C 73.22; H 6.34; N 5.87. $C_{28}H_{28}N_2O_4$. Calculated, %: C 73.68; H 6.14; N 6.14.

***N*-{4-[1-(1,4-Benzodioxan-2-yl)ethylcarbamoyl]-phenyl}-1,4-benzodioxane-2-carboxamide (Ve).** Yield 67%, light brown crystals, mp 138–140°C, R_f 0.38. ^{1}H NMR spectrum, δ, ppm: 1.38 d (3H, CH_3, J = 6.6 Hz), 3.95 d.d (1H, OCH_2, J = 11.3, 7.4 Hz), 4.10 m (1H, OCH_2), 4.17–4.33 m (4H, OCH_2, OCH), 4.47 d.d (1H, OCH_2, J = 11.3, 2.2 Hz), 4.84 d.d (1H, OCH, J = 6.8, 2.4 Hz), 6.71–6.88 m (7H) and 7.00 m (1H) (benzodioxane), 7.73 m and 7.84 m (2H each, C_6H_4), 8.16 d (1H, N**H**CH, J = 8.3 Hz), 10.03 s (1H, NH). Found, %: C 67.54; H 5.43; N 5.82. $C_{26}H_{24}N_2O_6$. Calculated, %: C 67.83; H 5.22; N 6.09.

***N*-{4-[3-(Morpholin-4-yl)propylcarbamoyl]-phenyl}-1,4-benzodioxane-2-carboxamide (Vf).** Yield 72%, white crystals, mp 166–167°C, R_f 0.52. ^{1}H NMR spectrum, δ, ppm: 1.71 q (2H, $NHCH_2C\mathbf{H}_2$, J = 6.9 Hz), 2.38 t (2H, NCH_2, J = 6.9 Hz), 2.39 m (4H, $NC\mathbf{H}_2CH_2O$), 3.31 t.d (2H, $NHC\mathbf{H}_2$, J = 6.9, 5.7 Hz), 3.59 m (4H, $OC\mathbf{H}_2CH_2N$), 4.28 d.d (1H, OCH_2, J = 11.5, 6.9 Hz), 4.46 d.d (1H, OCH_2, J = 11.5, 2.8 Hz), 4.83 d.d (1H, OCH, J = 6.9, 2.8 Hz), 6.77–6.89 m (3H) and 7.00 m (1H) (benzodioxane), 7.71 m and 7.78 m (2H each, C_6H_4), 8.13 t (1H, N**H**CH_2, J = 5.7 Hz), 10.01 s (1H, NH). Found, %: C 64.63; H 6.12; N 9.49. $C_{23}H_{27}N_3O_5$. Calculated, %: C 64.94; H 6.35; N 9.88.

***N*-[4-(1,3,4-Thiadiazol-2-ylcarbamoyl)phenyl]-1,4-benzodioxane-2-carboxamide (Vg).** Yield 61%, white crystals, mp 167–168°C, R_f 0.40. ^{1}H NMR spectrum, δ, ppm: 4.31 d.d (1H, OCH_2, J = 11.4, 6.7 Hz), 4.47 d.d (1H, OCH_2, J = 11.4, 2.7 Hz), 4.86 d.d (1H, OCH, J = 6.7, 2.7 Hz), 6.79–6.89 m (3H) and 7.01 m (1H) (benzodioxane), 7.83 m and 8.14 m (2H each, C_6H_4), 8.93 s (1H, CHS), 10.15 s (1H, NH), 12.81 br (1H, NH). Found, %: C 56.17; H 3.34; N 14.25. $C_{18}H_{14}N_4O_4S$. Calculated, %: C 56.54; H 3.66; N 14.66.

***N*-[4-(Morpholin-4-ylcarbonyl)phenyl]-1,4-benzodioxane-2-carboxamide (Vh).** Yield 75%, white crystals, mp 214–216°C, R_f 0.55. ^{1}H NMR spectrum, δ, ppm: 3.50–3.57 m (4H) and 3.59–3.64 m (4H) (OCH_2CH_2N), 4.29 d.d (1H, OCH_2, J = 11.4, 6.8 Hz), 4.46 d.d (1H, OCH_2, J = 11.4, 2.7 Hz), 4.84 d.d (1H, OCH, J = 6.8, 2.7 Hz), 6.78–6.89 m (3H) and 7.01 m (1H) (benzodioxane), 7.33 m and 7.74 m (2H each, C_6H_4), 10.01 s (1H, NH). Found, %: C 65.44; H 5.73; N 7.33. $C_{20}H_{20}N_2O_5$. Calculated, %: C 65.21; H 5.43; N 7.61.

***N*-[4-(Butan-2-ylcarbamoyl)phenyl]isochroman-1-carboxamide (VIa).** Yield 67%, light brown crystals, mp 162–163°C, R_f 0.30. Found, %: C 71.12; H 6.51; N 7.55. *m*/*z* 352 $[M]^+$. $C_{21}H_{24}N_2O_3$. Calculated, %: C 71.59; H 6.82; N 7.95. *M* 352.43.

Ethyl 4-[4-(isochroman-1-ylcarbonylamino)benzoylamino]benzoate (VIb). Yield 67%, light brown crystals, mp 172–173°C, R_f 0.28. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, J = 7.1 Hz), 2.84 m and 3.10 m (1H each, CH_2), 3.93 d.d.d (1H, OCH_2, J = 11.2, 8.2, 3.8 Hz), 4.31 q (2H, $OC\mathbf{H}_2CH_3$, J = 7.1 Hz), 4.31 m (1H, OCH_2), 5.27 s (1H, OCH), 7.11–7.20 m (3H) and 7.46 m (1H) (isochroman), 7.82 m and 7.95 m (2H each, NC_6H_4CON), 7.91 s (4H, NC_6H_4-COO), 9.82 s (1H, NH), 10.16 s (1H, NH), Found, %: C 70.75; H 5.33; N 6.12. $C_{26}H_{24}N_2O_5$. Calculated, %: C 70.27; H 5.41; N 6.31.

***N*-[4-(1,4-Benzodioxan-2-ylmethylcarbamoyl)-phenyl]isochroman-1-carboxamide (VIc).** Yield 64%, white crystals, mp 157–158°C, R_f 0.35. ^{1}H NMR

spectrum, δ, ppm: 2.79 d.t (1H, CH_2, J = 16.2, 4.4 Hz), 3.10 d.d.d (1H, CH_2, J = 8.2, 8.6, 5.1 Hz), 3.51 d.t (1H, NCH_2, J = 13.8, 6.3 Hz), 3.63 d.t (1H, NCH_2, J = 13.8, 5.4 Hz), 3.92 d.d.d (1H, OCH_2, J = 11.2, 8.6, 4.0 Hz), 3.96 d.d (1H, OCH_2, J = 11.9, 7.7 Hz), 4.27–4.37 m (3H, OCH_2, OCH), 5.26 s [1H, OCHC(O)], 6.71–6.85 m (4H, benzodioxane), 7.10–7.21 m (3H) and 7.47 m (1H) (isochroman), 7.75 m and 7.83 m (2H each, C_6H_4), 8.43 t (1H, N**H**CH_2, J = 5.9 Hz), 9.69 s (1H, NH). Found, %: C 69.92; H 5.12; N 6.00. $C_{26}H_{24}N_2O_5$. Calculated, %: C 70.27; H 5.41; N 6.31.

***N*-[4-(1-Phenylcyclopentylmethylcarbamoyl)-phenyl]isochroman-1-carboxamide (VId).** Yield 68%, light brown crystals, mp 139–140°C, R_f 0.37. ^{1}H NMR spectrum, δ, ppm: 1.60–1.75 m (2H), 1.77–1.94 m (4H), and 1.97–2.10 m (2H) (C_5H_8); 2.78 d.t (1H, CH_2, J = 16.3, 4.4 Hz), 3.09 d.d.d (1H, CH_2, J = 16.3, 8.6, 5.0 Hz), 3.45 d (2H, NHC**H**$_2$, J = 6.3 Hz), 3.91 d.d.d (1H, OCH_2, J = 11.1, 8.6, 4.0 Hz), 4.30 d.t (1H, OCH_2, J = 11.1, 5.0 Hz), 5.24 s (1H, OCH), 7.10–7.20 m (3H) and 7.44 m (1H) (isochroman), 7.15 t (1H, N**H**CH_2, J = 6.3 Hz), 7.23–7.33 m (5H, Ph), 7.61 m and 7.69 m (2H each, C_6H_4), 9.68 s (1H, NH). Found, %: C 76.45; H 6.28; N 5.92. $C_{29}H_{30}N_2O_3$. Calculated, %: C 76.65; H 6.61; N 6.17.

***N*-[4-(3-Chloro-4-methylphenylcarbamoyl)-phenyl]isochroman-1-carboxamide (VIe).** Yield 63%, gray crystals, mp 171–172°C, R_f 0.41. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 2.80 d.t (1H, CH_2, J = 16.3, 4.4 Hz), 3.11 d.d.d (1H, CH_2, J = 16.3, 8.5, 5.1 Hz), 3.93 d.d.d (1H, OCH_2, J = 11.1, 8.5, 4.0 Hz), 4.31 d.t (1H, OCH_2, J = 11.1, 5.1 Hz), 5.27 s (1H, OCH), 7.11–7.22 m (3H) and 7.47 m (1H) (isochroman), 7.16 d (1H, 5-H in C_6H_3, J = 8.3 Hz), 7.61 d.d (1H, 6-H in C_6H_3, J = 8.3, 2.2 Hz), 7.90 d (1H, 2-H in C_6H_3, J = 2.2 Hz), 7.81 m and 7.92 m (2H each, C_6H_4), 9.79 s (1H, NH), 9.94 s (1H, NH). Found, %: C 68.01; H 4.68; N 6.17. $C_{24}H_{21}ClN_2O_3$. Calculated, %: C 68.49; H 4.99; N 6.66.

***N*-{4-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-phenyl}isochroman-1-carboxamide (VIf).** Yield 67%, light brown crystals, mp 97–98°C, R_f 0.33. ^{1}H NMR spectrum, δ, ppm: 2.78 t (2H, C_6H_3C**H**$_2$, J = 7.3 Hz), 2.78 m (1H, CH_2), 3.10 d.d.d (1H, CH_2, J = 16.0, 8.6, 5.0 Hz), 3.46 t.d (2H, NCH_2, J = 7.3, 5.7 Hz), 3.75 s (3H, OCH_3), 3.76 s (3H, OCH_3), 3.91 d.d.d (1H, OCH_2, J = 11.1, 8.4, 4.0 Hz), 4.30 d.t (1H, OCH_2, J = 11.1, 4.9 Hz), 5.25 s (1H, OCH), 6.69–6.77 m (3H, C_6H_3), 7.10–7.20 m (3H) and 7.45 m (1H) (isochroman), 7.72 m and 7.76 m (2H each, C_6H_4), 8.09 t (1H, N**H**CH_2, J = 5.7 Hz), 9.69 s (1H, NH). Found, %: C 70.82; H 6.33; N 6.00. $C_{27}H_{28}N_2O_5$. Calculated, %: C 70.43; H 6.09; N 6.09.

***N*-[4-(Isochroman-1-ylmethylcarbamoyl)phenyl]-isochroman-1-carboxamide (VIg).** Yield 73%, light yellow crystals, mp 169–170°C, R_f 0.45. ^{1}H NMR spectrum, δ, ppm: 2.71–2.96 m (3H, CH_2), 3.10 m (1H, CH_2), 3.43 d.d.d (1H, NCH_2, J = 13.6, 9.1, 5.4 Hz), 3.75 d.d.d (1H, OCH_2, J = 11.3, 7.7, 4.2 Hz), 3.87 d.d.d (1H, NCH_2, J = 13.6, 5.7, 3.0 Hz), 3.92 m (1H, OCH_2), 4.12 d.t (1H, OCH_2, J = 11.4, 5.0 Hz), 4.31 d.t (1H, OCH_2, J = 11.1, 5.0 Hz), 4.88 d.d (1H, OC**H**CH_2, J = 9.1, 3.0 Hz), 5.25 s (1H, OCH); 7.06–7.19 m (6H), 7.26 m (1H), and 7.46 m (1H) (isochroman); 7.73 m and 7.82 m (2H each, C_6H_4), 8.13 t (1H, N**H**CH_2, J = 5.7 Hz), 9.70 s (1H, NH). Found, %: C 73.55; H 5.89; N 6.18. $C_{27}H_{26}N_2O_4$. Calculated, %: C 73.30; H 5.88; N 6.33.

***N*-[4-(Pyridin-2-ylcarbamoyl)phenyl]isochroman-1-carboxamide (VIh).** Yield 71%, gray crystals, mp 183–184°C, R_f 0.51. ^{1}H NMR spectrum, δ, ppm: 2.79 d.t (1H, CH_2, J = 16.4, 4.4 Hz), 3.11 m (1H, CH_2), 3.92 d.d.d (1H, OCH_2, J = 11.2, 8.5, 4.0 Hz), 4.31 d.t (1H, OCH_2, J = 11.2, 5.0 Hz), 5.27 s (1H, OCH), 7.03 m (1H, Py), 7.11–7.21 m (3H) and 7.46 m (1H) (isochroman), 7.72 m (1H, Py), 7.80 m and 8.00 m (2H each, C_6H_4), 8.26–8.31 m (2H, Py), 9.76 s (1H, NH), 10.18 s (1H, NH). Found, %: C 70.54; H 5.27; N 11.42. $C_{22}H_{19}N_3O_3$. Calculated, %: C 70.78; H 5.09; N 11.26.

***N*-[4-(Piperidin-1-ylcarbonyl)phenyl]isochroman-1-carboxamide (VIi).** Yield 71%, light brown crystals, mp 134–135°C, R_f 0.47. ^{1}H NMR spectrum, δ, ppm: 1.51–1.73 m (6H, 3-H, 4-H, 5-H, piperidine), 2.79 d.t (1H, CH_2, J = 16.3, 4.4 Hz), 3.10 d.d.d (1H, CH_2, J = 16.3, 8.7, 5.1 Hz), 3.47 m (4H, NCH_2, piperidine), 3.91 d.d.d (1H, OCH_2, J = 11.1, 8.7, 4.1 Hz), 4.31 d.t (1H, OCH_2, J = 11.1, 4.9 Hz), 5.24 s (1H, OCH), 7.10–7.20 m (3H) and 7.44 m (1H) (isochroman), 7.26 m and 7.74 m (2H each, C_6H_4), 9.67 s (1H, NH). Found, %: C 72.32; H 6.19; N 7.42. m/z 364 $[M]^+$. $C_{22}H_{24}N_2O_3$. Calculated, %: C 72.53; H 6.59; N 7.69. M 364.44.

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