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Synthesis of *p*-Aminobenzoic Acid Diamides Based on 4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic Acid and [4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methylamine

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Abstract—Reaction of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxyl chloride with anesthesin followed by hydrolysis of the formed ester has afforded 4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonylamino]benzoic acid. The acid chloride has been used for acylation of various amines to yield the corresponding diamides. Reaction of [4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methylamine with chlorides of *N*-substituted *p*-aminobenzoic acids has led to formation of diamides.

Keywords: *p*-aminobenzoic acid, diamide, acylation

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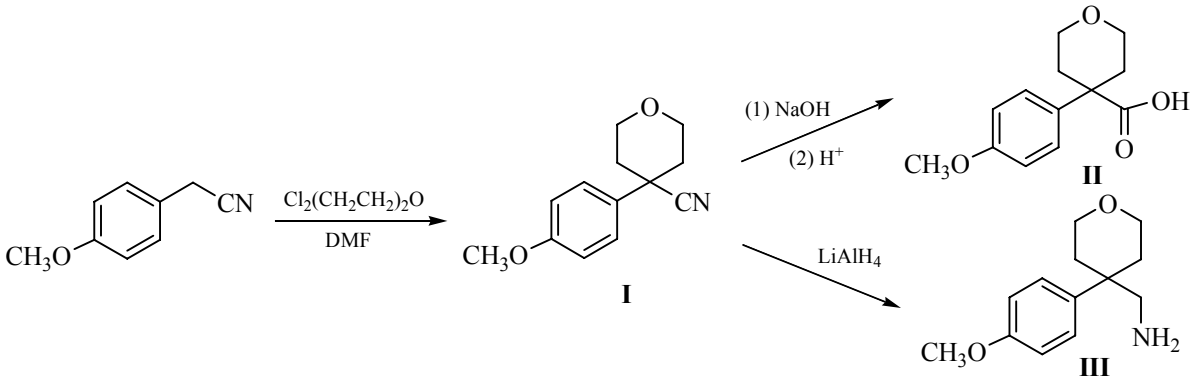
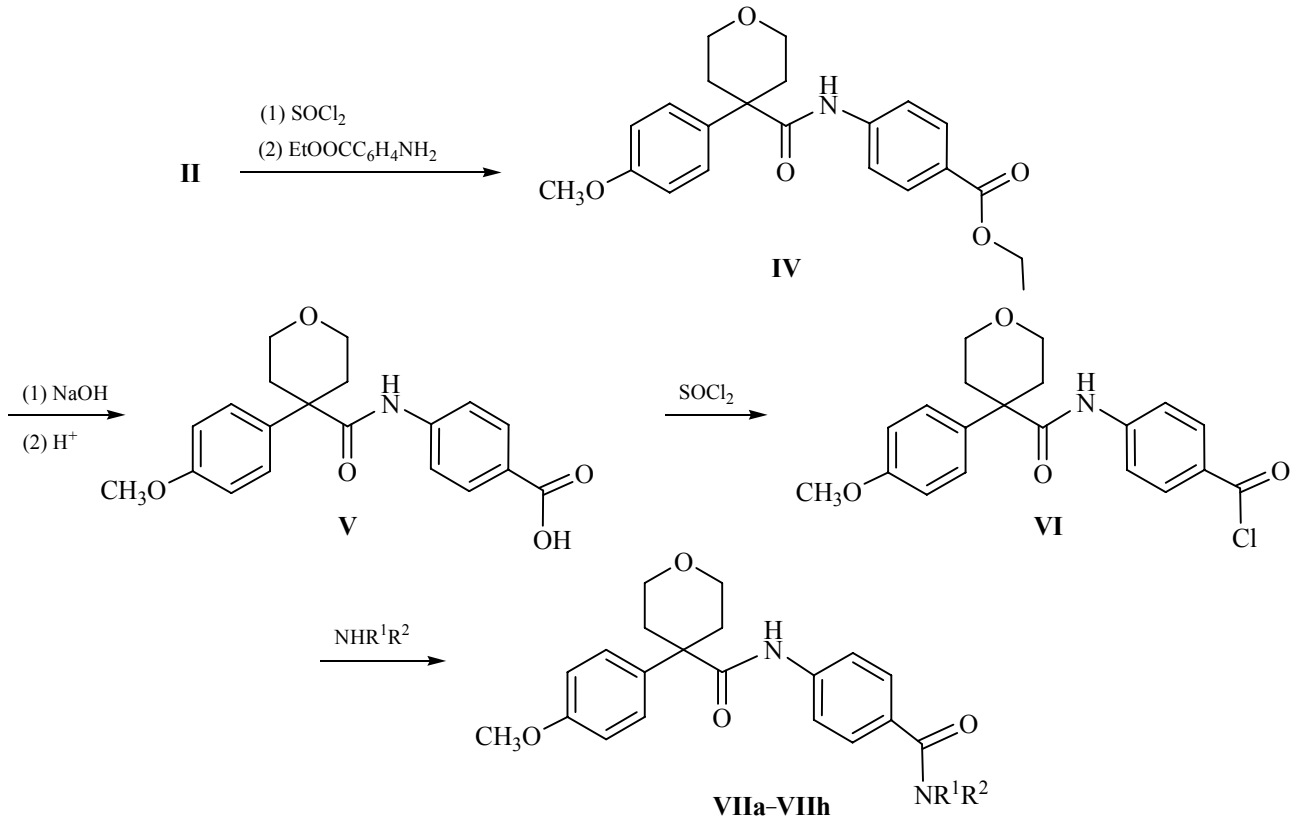
p-Aminobenzoic acid plays an important part in biochemical processes, and the presence of this pharmacophore fragment causes the utilitarian properties of a number of drugs [1–3]. Recent studies have identified compound with a broad range of biological activity among phenyltetrahydropyran derivatives [4, 5].

In order to prepare novel biologically active compounds of this series, we performed synthesis of *p*-aminobenzoic acid diamides containing 4-(4-methoxyphenyl)-tetrahydro-2*H*-pyran moiety. Nitrile of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid **I** was used as starting compound. The nitrile preparation via condensation of 4-metoxyphenylacetonitrile with dichloroethyl ether in the presence of sodium hydride under nitrogen atmosphere has been described elsewhere [5]. We prepared that nitrile in yield of 65–70% via condensation in DMF in the presence of sodium hydroxide. Alkaline hydrolysis of nitrile **I** followed by acidification yielded 4-(4-methoxyphenyl) tetrahydro-2*H*-pyran-4-carboxylic acid **II**, and reduction of compound **I** with lithium aluminum hydride afforded [4-(4-methoxyphenyl)tetrahydro- 2*H*-pyran-4-yl]methylamine **III**. The resulting compounds

Scheme 1.



Scheme 2.



NR^1R^2 = $N(CH_2)_5$ (**a**), $N(CH_2CH_2)_2O$ (**b**); R^1 = H, R^2 = $(CH_2)_2N(CH_2CH_2)_2O$ (**c**), furan-2-ylmethyl (**d**), pyridin-2-yl (**e**), 1,3,4-thiadiazol-2-yl (**f**), 3-$CF_3C_6H_4$ (**g**), 2-OCH_3-5-$CH_3C_6H_3$ (**h**).

were used to obtain diamides of *p*-aminobenzoic acid (Scheme 1).

4-Amido substituted benzoic acids could be obtained via reaction of *p*-aminobenzoic acid with the corresponding acid chlorides [6]. In particular, we used chlorides of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic, benzoic, 4-methoxy- and 4-bromobenzoic, phenoxyacetic, diphenylacetic, and 2-furoic acids.

We revealed that the reaction of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonyl chloride with *p*-aminobenzoic acid was accompanied with resin formation. Therefore, we developed another approach towards synthesis of the amido acid through the acid ester. Condensation of chloride **II** with *p*-aminobenzoic acid (anesthesin) yielded amido ester **IV**; alkaline hydrolysis of the latter followed by acidification led to formation of amido acid **V**. Interaction of chloride **VI** with various amines such as piperidine, morpholine, 2-(morpholin-4-yl)ethylamine, furfurylamine, pyridin-2-ylamine thiadiazol-2-ylamine, and substituted aniline in anhydrous dioxane in the presence of triethylamine gave diamides **VIIa**–**VIIh** with yields of 70–75% (Scheme 2).

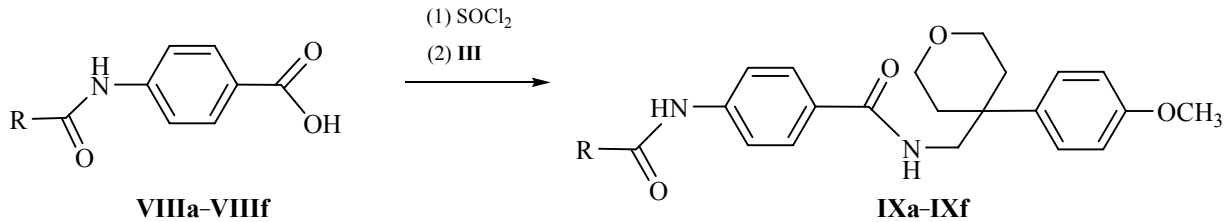
In addition, we synthesized diamides **IXa**–**IXf** via reaction of [4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methylamine **III** with chlorides of 4-acylaminobenzoic acids **VIIIa**–**VIIIf** prepared by interacting the corresponding acid chloride with *p*-aminobenzoic acid (Scheme 3).

Structures and purity of the products were confirmed by physico-chemical methods and TLC analysis.

EXPERIMENTAL

IR spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer (suspension in Vaseline oil). ^{1}H NMR spectra were registered using a Varian Mercury-300 spectrometer (solution in DMSO-d_6) relative to TMS as internal reference. Melting points were

Scheme 3.



VIIIa–VIIIf **IXa–IXf**

R = C_6H_5 (**a**), 4-$CH_3OC_6H_4$ (**b**), 4-BrC_6H_4 (**c**), $CH_2OC_6H_5$ (**d**), $CH(C_6H_5)_2$ (**e**), furan-2-yl (**f**).

determined using a Boetius apparatus. The reaction progress was monitored by TLC on Silufol UV-254 plates, eluting with a benzene–acetone mixture (4 : 1) and detecting with iodine vapor.

[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]-methylamine **III** was prepared according to [5].

4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonitrile (I). 24 g (0.6 mol) of finely powdered NaOH was added to a solution of 29.5 g (0.2 mol) of 4-methoxyphenylacetonitrile in 50 mL of anhydrous dimethylformamide, and the reaction mixture was stirred during 0.5 h. 29 g (0.2 mol) of 2,2-dichlorodiethyl ether was then added dropwise to the mixture, maintaining the temperature at 80–90°C, and the mixture was stirred at 100°C during 5 h. After cooling, 300 mL of water was added, and the reaction product was extracted with benzene (3 × 100 mL). The extract was dried over Na_2SO_4 and evaporated. The residue was distilled. Yield 30 g (69%), bp 180–184°C (3 mmHg), mp 85–87°C (methanol), R_f 0.65 (benzene–ether, 8 : 1). IR spectrum, ν, cm^{-1}: 2210 (CN), 1606 (arom). ^1H NMR spectrum, δ, ppm: 1.97–2.11 m (4H, CH_2C), 3.71–3.80 m (2H, OCH_2), 3.80 s (OCH_3), 3.97–4.03 m (2H, OCH_2), 6.89–6.94 m and 7.36–7.41 m (4H, C_6H_4).

4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid (II). A mixture of 21.7 g (0.1 mol) of nitrile **II** and 14 g (0.25 mol) of KOH in 150 mL of ethylene glycol was refluxed during 10 h. After cooling, 100 mL of water was added. The mixture was acidified with diluted HCl (1 : 1). The formed crystals were filtered off. Yield 21 g (89%), mp 162–164°C (ethanol), R_f 0.43 (benzene–acetone, 1 : 1). ^1H NMR spectrum, δ, ppm: 1.73–1.83 m (2H, CH_2C), 2.38–3.41 m (2H, CH_2C), 3.71–3.80 m (2H, OCH_2), 3.77 s (OCH_3), 3.80–3.86 m (2H, OCH_2), 4.66 br.s (1H, OH), 6.78–6.83 m and 7.26–7.31 m (4H, C_6H_4). Found, %: C 66.21; H 6.72. $C_{13}H_{16}O_4$. Calculated, %: C 66.09; H 6.83.

Ethyl [4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonylamino]benzoate (IV). A mixture of 18.9 g (0.08 mol) of 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid **II** and 11.9 g (0.1 mol) of thionyl chloride in 80 mL of benzene was refluxed during 6 h. The solvent was distilled off, 20 mL of benzene was added, and the solvent was distilled off to dryness. The residue was dissolved in 100 mL of toluene, and the resulting solution was added dropwise to a mixture of 15.3 g (0.08 mol) anesthesin and 8 g (0.08 mol) of triethylamine in 100 mL of toluene. The mixture was refluxed during 4 h. Triethylamine hydrochloride was filtered off; the filtrate was sequentially washed with diluted hydrochloric acid, water, 10% sodium hydroxide and water, dried over Na_2SO_4, and evaporated. Yield 24 g (78.4%), mp 145–146°C (benzene), R_f 0.65. IR spectrum, ν, cm^{-1}: 3310 (NH), 1706 (Ar, C=O), 1680 (NC=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.38 t (3H, CH_3, *J* 7.1), 1.90–2.02 m and 2.53–2.62 m (4H, CH_2), 3.53–3.63 m and 3.74–3.81 m (4H, OCH_2), 3.77 s (OCH_3), 4.29 q (2H, $C\underline{H}_2CH_3$, *J* 7.1), 6.82–6.88 m and 7.30–7.35 m (4H, $C_6\underline{H}_4OMe$), 7.70–7.75 m and 7.82–7.87 m (4H,$C_6\underline{H}_4NH$), 9.14 br.s (1H, NH). Found, %: C 68.70; H 6.69; N 3.78. $C_{22}H_{25}NO_5$. Calculated, %: C 68.91; H 6.57; N 3.65.

4-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonylamino]benzoic acid (V). A mixture of 15.3 g (0.04 mol) of ester amide **IV** and 60 mL of 20% NaOH in 50 mL of methanol was refluxed during 2 h. The solution was cooled, diluted with 100 mL of water, and acidified with diluted hydrochloric acid (1 : 1). The formed crystals were filtered off and recrystallized from ethanol. Yield 12.0 g (85%), mp 195–196°C, R_f 0.49 (benzene–acetone, 1 : 1). IR spectrum, ν, cm^{-1}: 3340 (NH), 2700–2550 (COOH), 1690 (Ar, C=O), 1660 (NC=O). ^1H NMR spectrum, δ, ppm: 1.90–2.01 m and 2.53–2.61 m (4H, CH_2), 3.53–3.62 m and 3.73–3.81 m (4H, OCH_2), 3.76 s (OCH_3), 6.82–6.87 m and 7.30–7.35 m (4H, $C_6\underline{H}_4OMe$), 7.67–7.72 m and 7.81–7.86 m (4H,$C_6\underline{H}_4NH$), 9.10 s (1H, NH), 12.19 br.s

(1H,COOH). Found, %: C 67.85; H 5.78; N 3.79. $C_{20}H_{21}NO_5$. Calculated, %: C 67.59; H 5.96; N 3.94.

4-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-carbonylamino]benzoyl chloride (VI). A solution of 17.7 g (0.05 mol) of acid **V** and 7.2 g (0.06 mol) of thionyl chloride in 100 mL of anhydrous toluene was refluxed until complete dissolution (10–12 h). After removal of the solvent, 30 mL of anhydrous diethyl ether was added, and acid chloride was filtered off. Yield 14.5 g (77%), mp 132°C. IR spectrum, ν, cm^{-1}: 1730 (C=O), 1610 (Ar). The resulting acid chloride was used without further purification.

Diamides VIIa–VIIh. A mixture of 0.05 mol of chloride **VI** and 20 mL of anhydrous dioxane was added dropwise to a solution of 0.05 mol of the amine and 0.05 mol of triethylamine in 50 mL of anhydrous dioxane. The reaction mixture was refluxed during 5 h, cooled, and poured into 100–150 mL of water. The formed crystals were filtered off, washed sequentially with diluted hydrochloric acid (1 : 3), water, 5% sodium hydroxide solution, and water, dried, and recrystallized.

4-(4-Methoxyphenyl)-*N*-[4-(piperidin-1-carbonyl)-phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIa). Yield 72%, mp 156–158°C (ethanol), R_f 0.42. ^{1}H NMR spectrum, δ, ppm: 1.49–1.61 m (4H, β,β'-CH_2), 1.63–1.73 m (2H, γ-CH_2, piperidine), 1.88–2.00 m and 2.53–2.62 m (4H, CH_2C), 3.39–3.51 m (4H, α,α'-CH_2, piperidine), 3.53–3.62 m and 3.73–3.81 m (4H, OCH_2), 3.77 s (3H, OCH_3), 6.82–6.87 m (2H, C_6H_4OMe), 7.19–7.24 m and 7.29–7.35 m (4H, C_6H_4N), 7.63–7.68 m (2H, C_6H_4O), 9.04 br.s (1H, NH). Found, %: C 71.31; H 7.02; N 6.50. $C_{25}H_{30}N_2O_4$. Calculated, %: C 71.07; H 7.16; N 6.63.

4-(4-Methoxyphenyl)-*N*-[4-(morpholin-4-ylcarbonyl)-phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIb). Yield 71%, mp 171–173°C (toluene), R_f 0.46. ^{1}H NMR spectrum, δ, ppm: 1.90–2.02 m and 2.54–2.62 m (4H, CH_2), 3.49 m and 3.54 m (8H, C_4H_8NO), 3.59–3.66 m and 3.70–3.79 m (4H, OCH_2), 3.77 s (3H, OCH_3), 6.83–6.88 m (2H, $C_6\underline{H}_4OMe$), 7.21–7.26 m and 7.30–7.37 m (4H, C_6H_4N), 7.65–7.70 m (2H, C_6H_4O), 9.06 br.s (1H, NH). Found, %: C 67.69; H 6.78; N 6.81. $C_{24}H_{28}N_2O_5$. Calculated, %: C 67.91; H 6.65; N 6.60.

4-(4-Methoxyphenyl)-*N*-{4-[2-(morpholin-4-yl)-ethylcarbamoyl]phenyl}tetrahydro-2*H*-pyran-4-carboxamide (VIIc). Yield 70%, mp 140–142°C (toluene), R_f 0.40. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.90–2.02 m (2H, CH_2), 2.43–2.52 m [6H, $CH_2N(CH_2)_2$], 2.54–2.62 m (2H, CH_2), 3.38 t. d (2H, $C\underline{H}_2NH$, *J* 6.5, 5.4), 3.54–3.63 m and 3.73–3.81 m (8H, OCH_2), 3.77 s (3H, OCH_3), 6.82–6.88 m and 7.30–7.36 m (4H, C_6H_4O), 7.61–7.74 m (4H, C_6H_4N), 7.88 br.t (1H, $CH_2\underline{NH}$, *J* 5.4), 9.06 s (1H, NH). Found, %: C 66.57; H 7.24; N 8.71. $C_{26}H_{33}N_3O_5$. Calculated, %: C 66.79; H 7.11; N 8.99.

4-(4-Methoxyphenyl)-*N*-[4-(furan-2-ylmethylcarbamoyl)phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIId). Yield 73%, mp 170–172°C (ethanol), R_f 0.49. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.90–2.01 m and 2.53–2.61 m (4H, CH_2), 3.53–3.62 m and 3.72–3.81 m (4H, OCH_2), 3.76 s (OCH_3), 4.45 d (2H, NCH_2, *J* 5.7), 6.20 d.d (1H, H^3 furan, *J* 3.2, 0.9), 6.30 d.d (1H, H^4, furan, *J* 3.2, 1.9), 6.82–6.87 m and 7.30–7.35 m (4H, C_6H_4O), 7.38 d.d (1H, H^5, furan, *J* 1.9, 0.9), 7.60–7.65 m and 7.75–7.80 m (4H, C_6H_4N), 8.52 br.t (1H, $\underline{NH}CH_2$, *J* 5.7), 9.07 br.s (1H, NH). Found, %: C 69.35; H 5.94; N 6.36. $C_{25}H_{26}N_2O_5$. Calculated, %: C 69.11; H 6.03; N 6.45.

4-(4-Methoxyphenyl)-*N*-[4-(pyridin-2-ylcarbamoyl)-phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIe). Yield 70%, mp 153–155°C (ethanol), R_f 0.48. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.91–2.03 m and 2.54–2.64 m (4H, CH_2), 3.54–3.65 m and 3.74–3.82 m (4H, OCH_2), 3.77 s (OCH_3), 6.83–6.88 m (2H, C_6H_4O), 7.02 d.d. d (1H, H^5, pyridine, *J* 7.2, 4.9, 0.9), 7.31–7.36 m (2H, C_6H_4O), 7.68–7.75 m (3H, C_6H_4N, H^4, pyridine), 7.93–7.99 m (2H, C_6H_4N), 8.26–8.30 m (2H, $H^{3,6}$, pyridine), 9.12 br.s (1H, NH), 10.13 br.s (1H, NHPy). Found, %: C 69.83; H 5.71; N 9.68. $C_{25}H_{25}N_3O_4$. Calculated, %: C 69.59; H 5.84; N 9.74.

4-(4-Methoxyphenyl)-*N*-[4-(1,3,4-thiadiazol-2-ylcarbamoyl)phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIf). Yield 75%, mp 246–248°C (ethanol), R_f 0.51. ^{1}H NMR spectrum, δ, ppm: 1.91–2.03 m and 2.53–2.63 m (4H, CH_2), 3.54–3.63 m and 3.74–3.82 m (4H, OCH_2), 3.77 s (3H, OCH_3), 6.82–6.87 m and 7.30–7.36 m (4H, C_6H_4O), 7.73–7.79 m and 8.04–8.10 m (4H, C_6H_4N), 8.90 s (1H, N=CH), 9.17 br.s (1H, NH), 12.74 br.s (1H, NH, thiazole). Found, %: C 60.43; H 5.20; N 12.56. $C_{22}H_{22}N_4O_4S$. Calculated, %: C 60.26; H 5.06; N 12.78.

4-(4-Methoxyphenyl)-*N*-[4-(3-trifluoromethylphenylcarbamoyl)phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIg). Yield 75%, mp 178–180°C (ethanol), R_f 0.53. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92–2.03 m and 2.54–2.63 m (4H, CH_2), 3.54–3.64 m and 3.74–3.82 m (4H, OCH_2), 3.77 s (3H, OCH_3),

6.83–6.89 m (2H, C_6H_4O), 7.28 br.d (1H, H^4, $C_6H_4CF_3$, *J* 7.7), 7.31–7.37 m (2H, C_6H_4O), 7.45 br.t (1H, H^5, $C_6H_4CF_3$, *J* 8.0), 7.71–7.76 m and 7.88–7.93 m (4H, C_6H_4N), 8.08 br.d (1H, H^6, $C_6H_4CF_3$, *J* 8.2), 8.19 br.t (1H, H^2, $C_6H_4CF_3$, *J* 1.9), 9.17 br.s (1H, N<u>H</u>C_6H_4), 9.04 br.s (1H, N<u>H</u>$C_6H_4CF_3$). Found, %: C 65.31; H 4.93; N 5.49. $C_{27}H_{25}F_3N_2O_4$. Calculated, %: C 65.05; H 5.05; N 5.62.

4-(4-Methoxyphenyl)-*N*-[4-(2-methoxy-5-methylphenylcarbamoyl)phenyl]tetrahydro-2*H*-pyran-4-carboxamide (VIIh). Yield 73%, mp 210–212°C (ethanol), R_f 0.49. ^{1}H NMR spectrum, δ, ppm: 1.91–2.03 m (2H, CH_2), 2.33 s (3H, CH_3), 2.54–2.63 m (2H, CH_2), 3.53–3.63 m and 3.74–3.82 m (4H, OCH_2), 3.77 s (3H, OCH_3), 3.89 s (3H, C<u>H</u>$_3$OC_6H_3), 6.81–6.83 m (2H, $H^{3,4}$, C_6H_3), 6.83–6.88 m and 7.30–7.36 m (4H, C_6H_4O), 7.73–7.81 m (4H, C_6H_4N), 8.03 br.s (1H, H^6, C_6H_3), 8.65 br.s (1H, <u>NH</u>C_6H_3), 9.16 br.s (1H, NH). Found, %: C 70.59; H 6.51; N 5.79. $C_{28}H_{30}N_2O_5$. Calculated, %: C 70.87; H 6.37; N 5.90.

Amic acids VIIIa–VIIIf were obtained according to procedure described in Refs. [7, 8].

Diamides IXa–IXf. A mixture of 0.01 mol of acid **VIII** and 0.015 mol of thionyl chloride in anhydrous toluene was refluxed during 8–10 h. After the solvent removal, the residue was dissolved in 30 mL of anhydrous dioxane. The obtained mixture was added dropwise at 15–18°C to a solution of 0.01 mol of [4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methylamine **III** and 0.01 mol of triethylamine in 50 mL of anhydrous dioxane. The reaction mixture was refluxed during 5 h, cooled, and poured into 100–150 mL of water. The formed crystals were filtered off, washed sequentially with dilute hydrochloric acid (1 : 3), water, 5% sodium hydroxide solution, and water, dried, and recrystallized from ethanol.

***N*-{4-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-ylmethylcarbamoyl]phenyl}benzamide (IXa).** Yield 79%, mp 195–197°C, R_f 0.53. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81–1.92 m and 1.99–2.08 m (4H, CH_2C), 3.39 d (2H, NCH_2, *J* 6.1), 3.41–3.46 m and 3.68–3.76 m (4H, CH_2O), 3.79 s (3H, OCH_3), 6.83 m and 7.23 m (4H, C_6H_4O), 7.43 m (3H, C_6H_5), 7.46 br.t (1H, N<u>H</u>CH_2, *J* 6.1), 7.68 m (2H, C_6H_5), 7.81 m and 7.98 m (4H, C_6H_4N), 10.19 s (1H, NH). Found, %: C 72.67; H 6.51; N 6.18. $C_{27}H_{28}N_2O_4$. Calculated, %: C 72.95; H 6.35; N 6.30.

4-Methoxy-*N*-{4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-ylmethylcarbamoyl]phenyl}benzamide (IXb). Yield 75%, mp 202–204°C, R_f 0.50. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83–1.95 m and 2.00–2.10 m (4H, CH_2C), 3.40 d (2H, NCH_2, *J* 6.1), 3.42–3.47 m and 3.68–3.76 m (4H, CH_2O), 3.79 s and 3.87 s (6H, OCH_3), 6.82 m and 6.97 m (4H, C_6H_4O), 7.27 m and 7.68 m (4H, C_6H_4CO), 7.47 br.t (1H, <u>NH</u>CH_2, *J* 6.1), 7.83 m and 7.98 m (4H, C_6H_4N), 10.02 s (1H, NH). Found, %: C 70.67; H 6.52; N 6.02. $C_{28}H_{30}N_2O_5$. Calculated, %: C 70.87; H 6.37; N 5.90.

4-Bromo-*N*-{4-[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-ylmethylcarbamoyl]phenyl}benzamide (IXc). Yield 72%, mp 208–210°C, R_f 0.54. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.85–1.95 m and 1.98–2.05 m (4H, CH_2C), 3.39 d (2H, NCH_2, *J* 6.1), 3.42–3.48 m and 3.68–3.76 m (4H, CH_2O), 3.79 s (3H, OCH_3), 6.83 m and 7.23 m (4H, C_6H_4O), 7.48 br.t (1H, <u>NH</u>CH_2, *J* 6.1), 7.63 m and 7.83 m (4H, C_6H_4Br), 7.79 m and 7.98 m (4H, C_6H_4N), 10.12 s (1H, NH). Found, %: C 61.73; H 5.32; N 5.51. $C_{27}H_{27}BrN_2O_4$. Calculated, %: C 61.96; H 5.20; N 5.35.

***N*-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-ylmethyl]-4-(2-phenoxyacetylamino)benzamide (IXd).** Yield 75%, mp 172–174°C, R_f 0.56. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.85–1.95 m and 1.98–2.07 m (4H, CH_2C), 3.39 d (2H, NCH_2, *J* 6.1), 3.42–3.48 m and 3.70–3.77 m (4H, CH_2OCH_2), 3.79 s (3H, OCH_3), 4.61 s (2H, OCH_2), 6.82–6.91 m and 6.95–7.00 m (5H, C_6H_5), 7.24–7.32 m (4H, C_6H_4O), 7.53 br.t (1H, N<u>H</u>CH_2, *J* 6.1), 7.69 s (4H, C_6H_4), 9.98 s (1H, NH). Found, %: C 70.66; H 6.52; N 5.77. $C_{28}H_{30}N_2O_5$. Calculated, %: C 70.87; H 6.37; N 5.90.

4-(2,2-Diphenylacetylamino)-*N*-[4-(4-methoxyphenyl)-tetrahydro-2*H*-pyran-4-ylmethyl]benzamide (IXe). Yield 76%, mp 165–167°C, R_f 0.59. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84–1.94 m and 1.97–2.06 m (4H, CH_2C), 3.38 d (2H, NCH_2, *J* 6.1), 3.40–3.46 m and 3.68–3.76 m (4H, CH_2OCH_2), 3.78 s (3H, OCH_3), 5.14 s (1H, $CHPh_2$), 6.82–6.87 m (2H, C_6H_4O), 7.17–7.31 m and 7.34–7.38 m (12H, Ph, C_6H_4O), 7.46 br.t (1H, <u>NH</u>CH_2, *J* 6.1), 7.65 s (4H, C_6H_4N), 10.30 s (1H, NH). Found, %: C 76.68; H 6.29; N 5.15. $C_{34}H_{34}N_2O_4$. Calculated, %: C 76.38; H 6.41; N 5.24.

***N*-{4-[4-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-4-ylmethylcarbamoyl]phenyl}furan-2-carboxamide (IXf).** Yield 69%, mp 153–155°C, R_f 0.55. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.82–1.92 m and 1.99–2.08 m (4H, CH_2C), 3.39 d (2H, NCH_2, *J* 6.1), 3.41–3.47 m and 3.68–3.75 m (4H, CH_2O), 3.79 s (3H, OCH_3), 6.59 d.d (1H, H^4, furan, *J* 3.5, 1.7), 6.86 m and 7.25 m (5H,

C_6H_4O, H^3, furan), 7.55 br.t (1H, N<u>H</u>CH_2, *J* 6.1), 7.71 d (1H, H^5, furan, *J* 1.7), 7.63 m and 7.80 m (4H, C_6H_4N), 10.05 s (1H, NH). Found, %: C 69.38; H 6.19; N 6.27. $C_{25}H_{26}N_2O_5$. Calculated, %: C 69.11; H 6.03; N 6.45.

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