ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 10, pp. 1556–1563. © Pleiades Publishing, Ltd., 2011.
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Synthesis of New Amides of the *N*-Methylpiperazine Series

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Received February 10, 2011

Abstract—New carboxylic acid amides containing an *N*-methylpiperazine fragment were synthesized by reactions of 1-methylpiperazine or 3- and 4-(4-methylpiperazin-1-ylmethyl)aniline with 4-chlorobenzoyl chloride and of 4-methyl-3-nitroaniline with 4-(4-methylpiperazin-1-ylmethyl)benzoyl chloride or benzotriazol-1-yl 4-(4-methylpiperazin-1-ylmethyl)benzoate. 4-Chloro-*N*-[4-(4-methylpiperazin-1-ylmethyl)phenyl]benzamide reacted with imidazole, quinolin-5-amine, and 2-methylquinolin-5-amine to give substituted 4-amino-*N*-[4-(4-methylpiperazin-1-ylmethyl)phenyl]benzamides. 4-Methyl-3-nitrophenyl-4-methylpiperazin-1-yl-substituted benzamides were reduced with hydrazine hydrate over Raney nickel to obtain *N*-(3-amino-4-methylphenyl)-4-(4-methylpiperazin-1-ylmethyl)benzamide as key intermediate in the synthesis of antileukemic agent imatinib and its isomer with alternative position of the amide group, 4-[(3-amino-4-methylphenylamino)methyl]phenyl-(4-methylpiperazin-1-yl)}methanone.

DOI: 10.1134/S1070428011100198

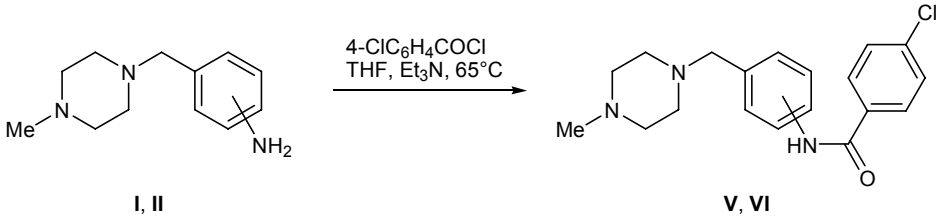
Piperazine derivatives constitute a widespread and well studied group of organic compounds. Diversity of pharmacological properties and selectivity of biological action indicate strong potential of compounds containing a benzylpiperazine or piperazinecarboxamide fragment. Some benzylpiperazine derivatives were found to act as serotonin (5-HT_{1A}), dopamine (D_2, D_3), and α_{1A}-adrenergic receptor antagonists and inhibitors of phosphodiesterase, HIV reverse transcriptase, HIV-1 protease, tyrosine kinase, and other physiologically important enzymes [1–7]. Aryl- and hetarylpiperazine fragments are pharmacophoric units in many medicines, including such widely known drugs as antihelminthic agent benzylpiperazine, antileukemic agent imatinib, antihistaminic drugs meclizine and cyclizine, antidepressants befuraline and piberaline, antihypoxic agent trimetazidine, and nootropic agent fipexide.

In the present work we synthesized new functionalized amides on the basis of benzylpiperazine derivatives and substituted benzoic acids. Such potential biologically active benzylpiperazines are promising from the viewpoint of further design of medical agents in the piperazine series.

Initial compounds **I**–**III** containing a benzylpiperazine fragment were synthesized by reductive amination of 3-nitro-, 4-nitro-, and 4-carboxybenzaldehydes with 1-methylpiperazine (**IV**) according to Leuckart–Wallach or using sodium triacetoxyhydridoborate generated *in situ* from sodium tetrahydridoborate and acetic acid [8, 9]. The subsequent reduction of nitrobenzylpiperazines with hydrazine hydrate over Raney nickel gave aminobenzylpiperazines **I** and **II** [8, 10].

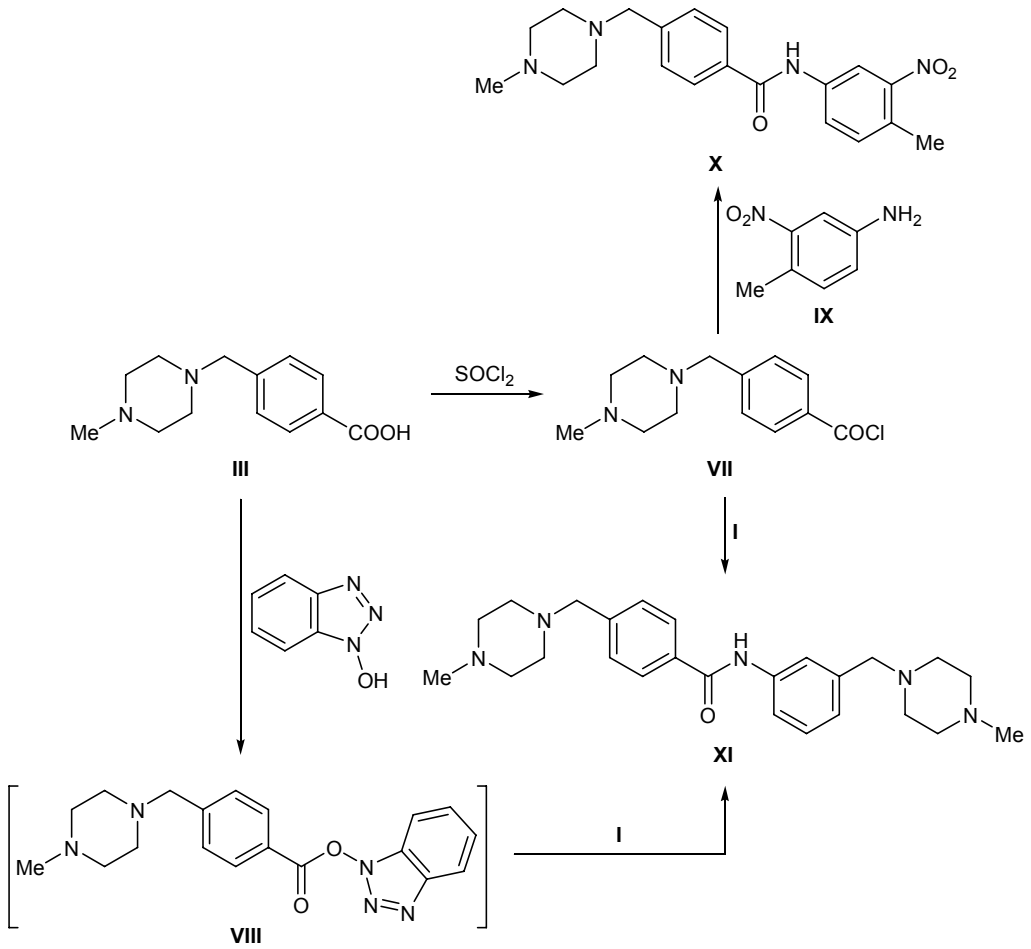
Substituted benzoic acids were subjected to amidation with 1-methylpiperazine (**IV**) and 3- and

Scheme 1.



I, **II** **V**, **VI**

Scheme 2.

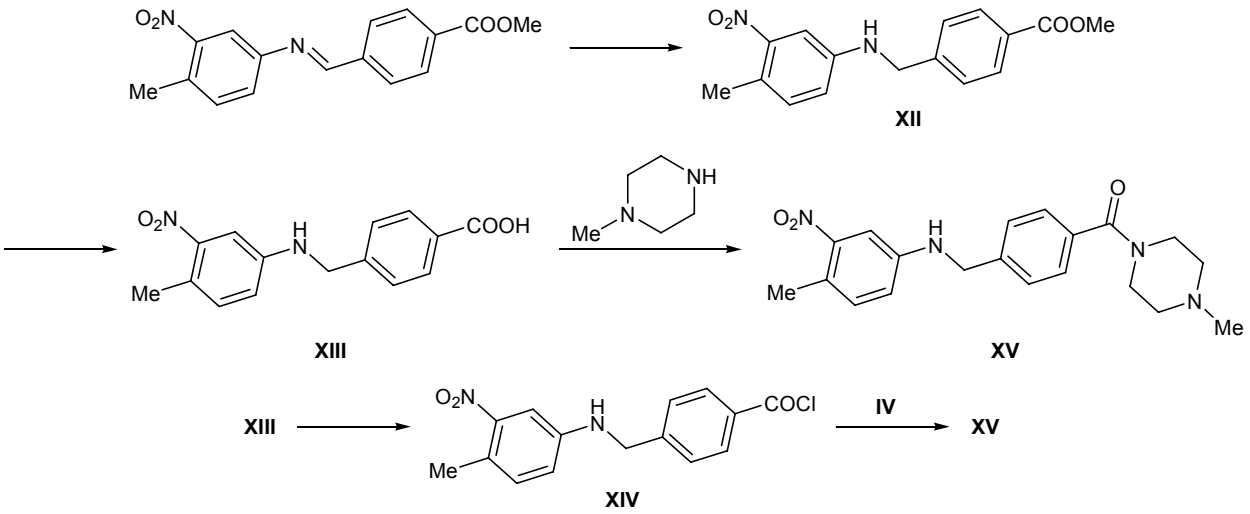


4-(4-methylpiperazin-1-ylmethyl)anilines **I** and **II** under various conditions according to known procedures for building up amide bond [11, 12]. By heating compounds **I** and **II** with *p*-chlorobenzoyl chloride in tetrahydrofuran (THF) in the presence of triethylamine as hydrogen chloride acceptor we obtained 4-chloro-*N*-[3-(4-methylpiperazin-1-ylmethyl)phenyl]benzamide (**V**) and 4-chloro-*N*-[4-(4-methylpiperazin-1-ylmethyl)-phenyl]benzamide (**VI**) in 53 and 58% yield, respectively (Scheme 1).

4-(4-Methylpiperazin-1-ylmethyl)benzoic acid (**III**) was initially converted into acid chloride **VII** or benzotriazolyl ester **VIII**. Acylation of 4-methyl-3-nitroaniline (**IX**) and amine **I** with acid chloride **VII** under analogous conditions gave *N*-(4-methyl-3-nitrophenyl)-4-(4-methylpiperazin-1-ylmethyl)benzamide (**X**) and 4-(4-methylpiperazin-1-ylmethyl)-*N*-[3-(4-methylpiperazin-1-ylmethyl)phenyl]benzamide (**XI**). The latter was also synthesized by successive esterification of acid **III** with 1-hydroxybenzotriazole in methylene chloride in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and aminolysis of ester **VIII** with amine **I** in the presence of 4-dimethylaminopyridine (DMAP). Despite lability of the hydroxytriazole moiety, which allows the aminolysis to occur at room temperature, the yield of amide **XI** from ester **VIII** was lower (42%) than in the reaction of amine **I** with benzoyl chloride **VII** (55%; Scheme 2).

The ester group in the molecule of methyl 4-(4-methyl-3-nitrophenylaminomethyl)benzoate (**XII**) obtained by reduction of methyl 4-(4-methyl-3-nitrophenyliminomethyl)benzoate is inactive in the reaction with 1-methylpiperazine (**IV**). Therefore, ester **XII** was subjected to hydrolysis, the resulting acid **XIII** was converted into chloride **XIV**, and 1-methylpiperazine (**IV**) reacted with both acid **XIII** and chloride **XIV** to produce the desired amide **XV** in 35 and 42% yield, respectively (Scheme 3). The reaction of 1-methylpiperazine (**IV**) with 4-formylbenzoic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide selectively afforded 4-(4-methylpiperazine-1-carbonyl)benzaldehyde (**XVI**) (Scheme 4).

Scheme 3.



The presence of functional substituents in molecules **V**, **VI**, **X**, **XIII**, and **XVI** makes it possible to involve them in further transformations and obtain a number of derivatives which exhibit diverse biological activity and are precursors of a large number of medicines. For example, 4-formylbenzamide **XVI** can be used to synthesize amides **XXIII** via condensation with various secondary heterocyclic and primary heteroaromatic amines and subsequent reduction of Schiff bases thus formed (Scheme 4).

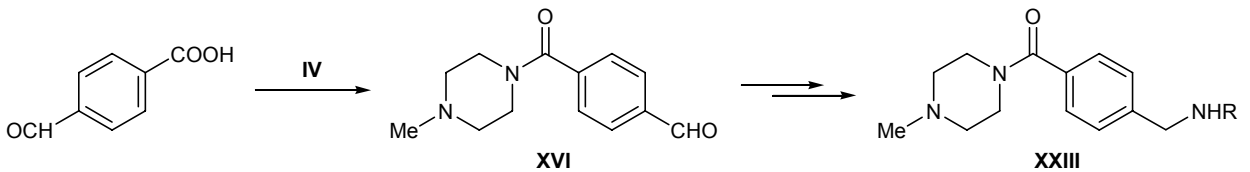
The reactions of 4-chloro-*N*-[4-(4-methylpiperazin-1-ylmethyl)phenyl]benzamide (**VI**) with imidazole, quinolin-5-amine, and 2-methylquinolin-5-amine gave new hetaryl-substituted amides **XVII**–**XIX** (Scheme 5). Despite electron-withdrawing effect of the amide carbonyl group in **VI**, which should facilitate nucleophilic replacement of the chlorine atom, the above reactions required fairly severe conditions, prolonged (30 h) heating of the reactants in dioxane at 100°C.

4-Methyl-3-nitrophenyl-substituted benzamides **X** and **XV** were reduced with hydrazine hydrate in the presence of Raney nickel to obtain *N*-(3-amino-4-methylphenyl)-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (**XX**) as key intermediate in the synthesis of antileukemic drug imatinib (**XXI**) and an isomer of **XX** with alternative position of the amide group, 4-(3-amino-4-methylphenylaminomethyl)phenyl-(4-methylpiperazin-1-yl)methanone (**XXII**) (Scheme 5).

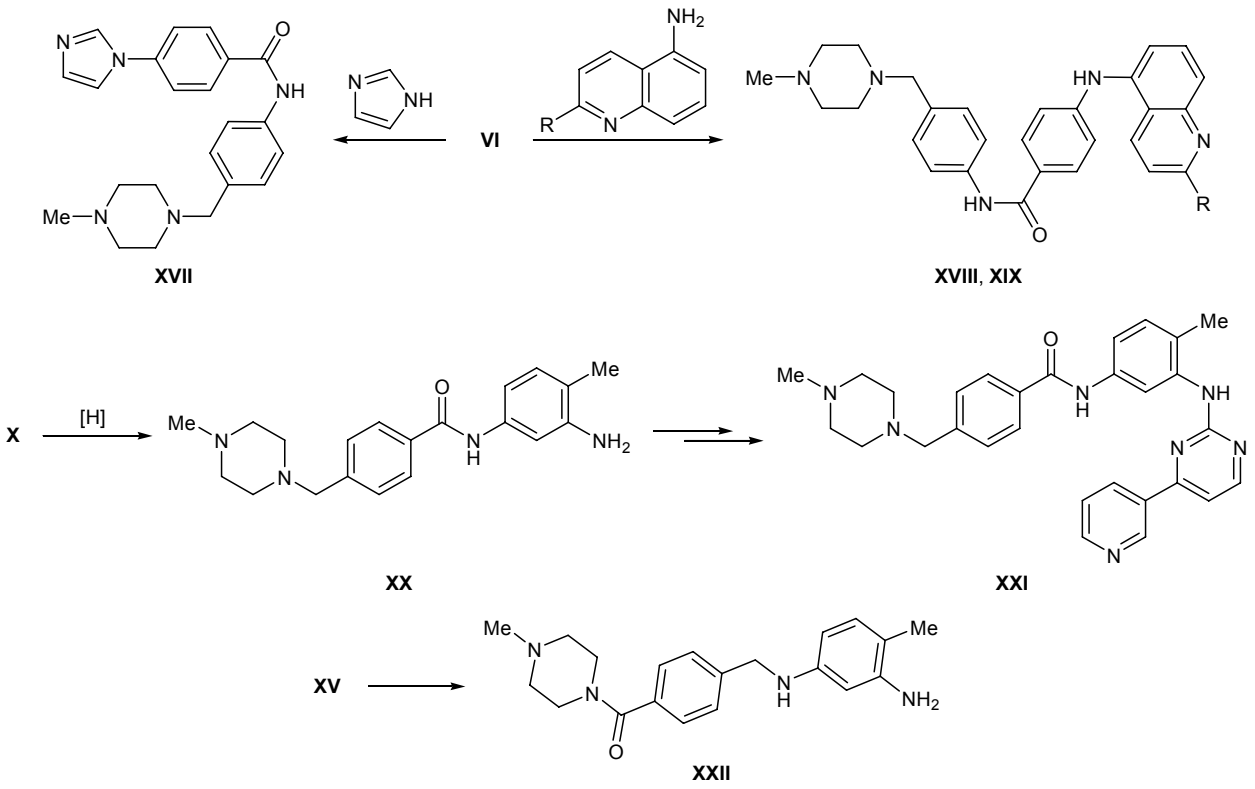
The structure of the newly synthesized amides was confirmed by their elemental analyses and ^{1}H and ^{13}C NMR, IR, and mass spectra. In the IR spectra of **V**, **VI**, **X**, **XI**, **XV**–**XX**, and **XXII** stretching vibrations of the amide group appeared at 1685–1665 (C=O) and 3440–3265 cm^{-1} (NH). In the spectra of amino amides **XV**, **XVIII**–**XX**, and **XXII**, the latter region also contained absorption bands due to stretching vibrations of primary and secondary amino groups. The aldehyde carbonyl group in compound **XVI** gave rise to absorption at 1720 cm^{-1}. Stretching vibration bands of the nitro group in the spectra of **X** and **XII**–**XV** were observed at 1555–1535 and 1375–1335 cm^{-1}. In the mass spectra of the isolated compounds the molecular ion peak $[M]^+$ had an intensity of 2–39%. The base peak in the mass spectra of most compounds was that with *m*/*z* 99 which corresponds to $[MeN(CH_2)_4N]^+$; also, $[M - Me]^+$ (I_{rel} 10–18%) and $[M - Me - NO_2]^+$ ion peaks (I_{rel} 9–11%; in the spectra of nitro amides **X** and **XV**) were observed.

The amide NH proton resonated in the ^{1}H NMR spectra at δ 7.21–8.60 ppm; signals from protons in aromatic and heteroaromatic rings were observed in the same region. Signals from protons in the piperazine

Scheme 4.



Scheme 5.



XVIII, R = H; **XIX**, R = Me.

ring were located at δ 2.35–3.82 ppm. Signals from benzylic protons in the ArC**H**$_2$N(CH$_2$)$_4$NMe fragment appeared at δ 3.45–3.58 ppm, and those in the ArC**H**$_2$NHAr fragment (**XV**, **XXII**), at 4.47–4.63 ppm. Proton in the secondary amino group (**XV**, **XVIII**, **XIX**, **XXII**) resonated at δ 4.26–4.55 ppm, while protons in the primary amino group (**XX**, **XXII**) gave signals at δ 3.55–3.77 ppm. The singlet at δ 2.24–2.35 ppm was assigned to the NMe group. The ^{1}H NMR spectra of **X**, **XII**–**XV**, **XIX**, **XX**, and **XXII** also contained a singlet from the ArMe group at δ 2.11–2.72 ppm, and compound **XVI** displayed a signal from the aldehyde proton at δ 10.04 ppm. In the ^{13}C NMR spectra, aromatic and carbonyl carbon signals were observed in the region δ_C 104–171 ppm, the aldehyde carbon atom in the spectrum of **XVI** resonated at δ_C 191 ppm, and carbon nuclei in the piperazine ring and methyl groups were characterized by chemical shifts ranging from 16 to 63 ppm.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-500 spectrometer at 500 and 100 MHz, respectively, using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on an Agilent Technologies 6850/5973 GC–MS system. Thin-layer chromatography was performed on Merck DC-Plasticfolien Kieselgel 60 F_{254} plates using chloroform–methanol (85 : 15) and butan-1-ol–ethanol–aqueous ammonia (8 : 1 : 1) as eluents. The melting points were determined on a Kofler hot stage.

3- and 4-(4-Methylpiperazin-1-ylmethyl)anilines **I** and **II** were synthesized as reported in [8, 10], and 4-(4-methylpiperazin-1-yl-methyl)benzoic acid (**III**) was prepared according to [9].

4-Chloro-*N*-[3- and 4-(4-methylpiperazin-1-yl-methyl)phenyl]benzamides V and VI (*general procedure***).** A solution of 1.03 g (5 mmol) of amine **I** or **II** and 0.6 g (6 mmol) of triethylamine in 20 ml of tetrahydrofuran was heated for 30 min at 55–60°C, 1.05 g (6 mmol) of *p*-chlorobenzoyl chloride was added in one portion, and the mixture was stirred for 9–10 h at 60–65°C. When the reaction was complete, the solvent was distilled off, the residue was treated with 30 ml of water, acidified with 10% hydrochloric acid to pH 2, and extracted with ethyl acetate (3×40 ml). The extract

contained by-products and was discarded. The aqueous phase was treated with 20% aqueous sodium hydroxide to pH 9 and extracted with chloroform (3×40 ml), the extract was dried over $MgSO_4$, and evaporated under reduced pressure, and the solid residue was recrystallized from chloroform–hexane.

Compound **V**. Yield 53%, mp 167–168°C. IR spectrum (KBr), ν, cm^{-1}: 3310 (NH), 1685 (C=O), 1580 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.24 (3H, MeN), 2.49 br.s [8H, $N(CH_2)_4N$], 3.45 s (2H, CH_2), 7.21 s (1H, NHCO); 7.30 s, 7.44 d, 7.51 d, 7.58 d (8H, H_{arom}, ^3J = 8.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 164.78, 137.92, 136.33, 134.47, 132.95, 129.90, 129.52, 129.31, 128.67, 128.04, 127.88, 120.11, 119.73, 62.00, 54.71, 52.49, 45.46. Mass spectrum, *m*/*z* (I_{rel}, %): 343 (36) $[M]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 66.15; H 6.22; Cl 10.10; N 12.17. $C_{19}H_{22}ClN_3O$. Calculated, %: C 66.38; H 6.40; Cl 10.33; N 12.33.

Compound **VI**. Yield 58%, mp 160–161°C. IR spectrum (KBr), ν, cm^{-1}: 3300 (NH), 1670 (C=O), 1590 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.27 (3H, MeN), 2.45 br.s [8H, $N(CH_2)_4N$], 3.47 s (2H, CH_2), 7.24 s (1H, NHCO); 7.31 d, 7.45 d, 7.55 d, 7.81 d (8H, H_{arom}, ^3J = 7.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 164.34, 137.86, 136.31, 134.40, 133.04, 130.13, 129.65, 129.42, 128.78, 128.19, 128.08, 120.16, 119.87, 62.03, 54.68, 52.56, 45.59. Mass spectrum, *m*/*z* (I_{rel}, %): 343 (24) $[M]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 66.21; H 6.33; Cl 10.19; N 12.03. $C_{19}H_{22}ClN_3O$. Calculated, %: C 66.38; H 6.40; Cl 10.33; N 12.33.

4-(4-Methylpiperazin-1-ylmethyl)benzoyl chloride dihydrochloride (VII). A solution of 0.66 g (3 mmol) of acid **III** in 10 ml of toluene was cooled to 0°C, 2.2 ml (30 mmol) of thionyl chloride and 2.4 g (30 mmol) of pyridine were added, and the mixture was stirred for 1 h on cooling and then for 12 h at 60°C. The solvent and pyridine were distilled off under reduced pressure, and the residue was washed with diethyl ether (3×30 ml). Yield 92%, colorless crystals, mp 300°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3480, 2970, 2454 (NH^+), 1784, 1680, 1460, 1430, 1214. Found, %: C 47.99; H 5.96; Cl 32.58; N 8.45. $C_{13}H_{17}ClN_2O \cdot 2HCl$. Calculated, %: C 47.93; H 5.84; Cl 32.72; N 8.60.

***N*-(4-Methyl-3-nitrophenyl)-4-(4-methylpiperazin-1-ylmethyl)benzamide (X).** Triethylamine, 0.6 g (6 mmol), was added under stirring at room temperature to a solution of 0.5 g (3 mmol) of 4-methyl-3-nitroaniline (**IX**) in 10 ml of THF. The solution was cooled to 0°C, 1.15 g (3.5 mmol) of dihydrochloride **VII** was added, and the mixture was stirred for 1 h at 0°C and then for 16 h at 50°C. The mixture was evaporated, the residue was treated with 10 ml of 10% aqueous sodium hydroxide and extracted with ethyl acetate (3×20 ml), and the extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized from chloroform–diethyl ether. Yield 48%, colorless crystals, mp 140–141°C. IR spectrum (KBr), ν, cm^{-1}: 3360 (NH); 1680 (C=O); 1580 (δNH); 1545, 1375 (NO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.29 s (3H, MeN), 2.48 br.s [8H, $N(CH_2)_4N$], 2.58 s (3H, Me), 3.57 s (2H, CH_2); 7.33 d, 7.89 d.d, 7.46 d, 7.81 d (7H, H_{arom}, ^3J = 8.3, ^4J = 2.2 Hz); 7.95 br.s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.97, 46.01, 53.14, 55.09, 62.45, 115.98, 124.7, 127.03, 129.25, 129.45, 133.29, 136.84, 143.38, 149.11, 165.63. Mass spectrum, *m*/*z* (I_{rel}, %): 368 (25) $[M]^+$, 353 (13) $[M - Me]^+$, 307 (9) $[M - Me - NO_2]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 64.95; H 6.38; N 15.04. $C_{20}H_{24}N_4O_3$. Calculated, %: C 65.22; H 6.52; N 15.22.

4-(4-Methylpiperazin-1-ylmethyl)-*N*-[3-(4-methylpiperazin-1-ylmethyl)phenyl]benzamide (XI). *a*. Compound **XI** was synthesized as described above for amide **X** from dihydrochloride **VII** and 1-(3-aminobenzyl)-4-methylpiperazine (**I**).

b. *N*,*N*′-Dicyclohexylcarbodiimide, 0.3 g (1.5 mmol), was added to a solution of 0.24 g (1 mmol) of 4-(4-methylpiperazin-1-ylmethyl)benzoic acid (**III**) in 10 ml of methylene chloride. The mixture was stirred for 10 min at room temperature, 0.24 g (1.8 mmol) of 1-hydroxybenzotriazole was added, and the mixture was stirred for 16 h. The precipitate of *N*,*N*′-dicyclohexylurea was filtered off and washed with methylene chloride (3×20 ml), the filtrate was combined with the washings, 0.2 g (1 mmol) of compound **I** and 0.1 g (catalytic amount) of 4-dimethylaminopyridine were added, and the mixture was stirred for 30 h at 18–25°C. When the reaction was complete (TLC), the mixture was treated with 10 ml of water and 2 ml of 25% aqueous ammonia and extracted with methylene chloride (3×20 ml). The extract was dried over Na_2SO_4 and evaporated under reduced pressure. Yield 55% (*a*), 42% (*b*); yellow oily substance. IR spectrum (film), ν, cm^{-1}: 3360 (NH), 1665 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.24 s (3H, MeN), 2.29 s (3H, MeN), 2.48–2.56 m [16H, $N(CH_2)_4N$], 3.51 s (2H, CH_2), 3.58 s (2H, CH_2); 7.10 d, 7.32 m, 7.45 d, 7.60 d, 7.83 d (8H, H_{arom}, ^3J =

8.2 Hz); 7.97 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.23, 50.93, 53.32, 55.28, 62.74, 63.09, 119.27, 120.95, 125.59, 127.24, 129.18, 129.60, 133.96, 138.23, 139.49, 142.86, 165.81. Mass spectrum, *m*/*z* (I_{rel}, %): 421 (19) $[M]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 70.95; H 8.09; N 16.31. $C_{25}H_{35}N_5O$. Calculated, %: C 71.26; H 8.31; N 16.63.

Methyl 4-[(4-methyl-3-nitrophenylamino)methyl]benzoate (XII). A solution of 1.5 g (5 mmol) of methyl 4-[(4-methyl-3-nitrophenylimino)methyl]benzoate in 20 ml of benzene was added under stirring to a mixture of 10 mmol of sodium tetrahydridoborate, 5 ml of benzene, and 30 mmol of glacial acetic acid, cooled to 0°C. The mixture was stirred for 2 h without cooling and was left to stand for 20 h at room temperature. It was then treated with 40–50 ml of a 20% aqueous solution of sodium hydroxide, the organic phase was separated, washed with water, and dried over $MgSO_4$, the solvent was distilled off, and the solid residue was recrystallized from ethanol. Yield 90%, yellow crystals, mp 107–108°C. IR spectrum (KBr), ν, cm^{-1}: 3440 (NH); 1740 (C=O); 1540, 1360 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (3H, Me), 3.91 s (3H, CO_2Me), 4.36 br.s (1H, NH), 4.42 s (2H, CH_2); 6.70 d.d, 7.08 d, 7.20 d, 7.41 d, 8.01 d (7H, H_{arom}, ^3J = 7.4, ^4J = 2.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.69, 48.11, 52.33, 108.21, 118.04, 122.34, 127.36, 129.74, 130.35, 133.59, 143.92, 146.73, 150.03, 167.02. Mass spectrum: *m*/*z* 300 $[M]^+$. Found, %: C 63.78; H 5.07; N 9.45. $C_{16}H_{16}N_2O_4$. Calculated, %: C 64.00; H 5.33; N 9.33.

4-(4-Methyl-3-nitrophenylaminomethyl)benzoic acid (XIII). An aqueous solution of 0.04 g (1 mmol) of sodium hydroxide was added under stirring to a solution of 0.29 g (1 mmol) of compound **XII** in 10 ml of methanol, and the mixture was heated for 12 h under reflux. When the reaction was complete (TLC), the mixture was treated with 10% hydrochloric acid to pH 1 and evaporated, and the residue was dried over a period of 1 h at 60°C under reduced pressure. Yield 98%, yellow crystals, mp 216–218°C. IR spectrum (KBr), ν, cm^{-1}: 3500 (OH); 3410 (NH); 1710 (C=O); 1545, 1335 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.47 s (3H, Me), 4.20 t (1H, NH, ^3J = 5.5 Hz). 4.52 d (2H, CH_2, ^3J = 5.5 Hz); 7.91 d.d, 7.18 d, 7.32 d, 7.43 d, 8.01 d (7H, H_{arom}, ^3J = 8.1, ^4J = 1.9 Hz); 10.98 br.s (1H, COOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.53, 51.85, 103.71, 112.21, 127.02, 129.10, 129.26, 129.40, 130.22, 130.81, 142.89, 144.93, 147.38, 166.47. Mass spectrum: *m*/*z* 286 $[M]^+$. Found, %: C 62.80; H 4.62; N 9.75. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.94; H 4.90; N 9.79.

4-(4-Methyl-3-nitrophenylaminomethyl)benzoyl chloride hydrochloride (XIV) was obtained by reaction of acid **XIII** with thionyl chloride according to the procedure described above for the synthesis of compound **VII**. Yield 88%, colorless crystals, mp 289–290°C. IR spectrum (KBr), ν, cm^{-1}: 3460 (NH); 2450 (NH_2^+); 1760 (C=O); 1555, 1340 (NO_2). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.40 s (3H, Me), 4.32 t (1H, NH, ^3J = 5.6 Hz), 4.57 d (2H, CH_2, ^3J = 5.7 Hz); 7.38 d, 7.49 d, 7.57 s, 8.12 d (7H, H_{arom}, ^3J = 8.2 Hz). Found, %: C 52.54; H 3.95; Cl 20.59; N 8.02. $C_{15}H_{13}ClN_2O_3\cdot$ HCl. Calculated, %: C 52.79; H 4.11; Cl 20.82; N 8.21.

4-(4-Methyl-3-nitrophenylaminomethyl)phenyl (4-methylpiperazin-1-yl)methanone (XV). *a*. A solution of 0.2 g (0.5 mmol) of acid **XIII** and 0.05 g (0.5 mmol) of 1-methylpiperazine (**IV**) in 10 ml of THF was cooled to 0°C, and 0.11 g (0.6 mmol) of DCC was added under stirring. After 1.5 h, the precipitate of *N*,*N*′-dicyclohexylurea was added and washed with THF (3×20 ml), the filtrate was combined with the washings and evaporated, and the residue was treated with 10 ml of 10% aqueous sodium hydroxide and extracted with ethyl acetate (3×20 ml). The extract was dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was recrystallized from ethyl acetate–diethyl ether.

b. Amide **XV** was synthesized from 1-methylpiperazine (**IV**) and hydrochloride **XIV** according to the procedure described above for the synthesis of benzamide **X**. Yield 35% (*a*), 42% (*b*); yellow crystals, mp 185–186°C. IR spectrum (KBr), ν, cm^{-1}: 3440 (NH); 1680 (C=O); 1535, 1375 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.31 s (3H, NMe), 2.50 s (3H, Me), 2.90 br.s [8H, $N(CH_2)_4N$], 4.26 t (1H, NH, ^3J = 5.8 Hz), 4.47 d (2H, CH_2, ^3J = 5.8 Hz); 7.36 d, 7.45 d, 7.82 d, 8.01 s, 8.19 d (7H, H_{arom}, ^3J = 7.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.36, 45.78, 53.01, 54.73, 62.20, 116.03, 124.80, 126.89, 129.01, 129.15, 133.12, 136.62, 143.11, 148.97, 165.42. Mass spectrum, *m*/*z* (I_{rel}, %): 368 (39) $[M]^+$, 353 (10) $[M - Me]^+$, 307 (11) $[M - Me - NO_2]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 65.01; H 6.40; N 14.97. $C_{20}H_{24}N_4O_3$. Calculated, %: C 65.22; H 6.52; N 15.22.

4-(4-Methylpiperazin-1-ylcarbonyl)benzaldehyde (XVI). A solution of 0.2 g (1.3 mmol) of 4-formylbenzoic acid, 0.13 g (1.3 mmol) of 1-methylpiperazine (**IV**), and 2 ml of pyridine in 10 ml of tetrahydrofuran was stirred for 10 min at 50°C, 0.28 g

(1.5 mmol) of DCC was added, and the mixture was stirred for 20 h. The product was isolated as described above for amide **XV** (including evaporation of ethyl acetate). Yield 80%, yellow liquid. IR spectrum (film), ν, cm^{-1}: 1720 (C=O), 1680 (CHO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.32 s (3H, NMe); 2.35 br.s, 2.61 br.s, 2.94 br.s, 3.82 br.s [8H, $N(CH_2)_4N$]; 7.56 d, 7.93 d (4H, H_{arom}, ^3J = 7.9 Hz); 10.04 s (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 41.91, 45.87, 54.46, 55.06, 62.53, 127.67, 129.82, 136.79, 141.38, 168.79, 191.41. Mass spectrum, *m*/*z* (I_{rel}, %): 232 (2) $[M]^+$, 105 (23) $[C_6H_4CHO]^+$, 133 (30%) $[M - MeN(CH_2)_4N]^+$, 99 (28) $[MeN(CH_2)_4N]^+$, 70 (90). Found, %: C 66.95; H 6.72; N 11.88. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.24; H 6.90; N 12.07.

4-(1*H*-Imidazol-1-yl)-*N*-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]benzamide (XVII). A solution of 0.17 g (0.5 mmol) of benzamide **VI** in 10 ml of dioxane was heated to 80°C, 0.035 g (0.5 mmol) of imidazole was added under stirring, and the mixture was heated for 6 h at 100°C. After cooling, the precipitate was filtered off and washed with dioxane and diethyl ether (3×20 ml). Yield 50%, mp 189–190°C. IR spectrum (KBr), ν, cm^{-1}: 3410 (NH), 1685 (C=O), 1580 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 s (3H, NMe), 2.56 br.s [8H, $N(CH_2)_4N$], 3.59 s (3H, CH_2); 6.28 d, 7.24 d, 7.49 d, 7.73 d, 8.11 d, 8.36 s, 8.81 d (11H, H_{arom}, ^3J = 8.1 Hz), 8.24 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.15, 46.01, 54.39, 62.47, 116.60, 119.41, 120.82, 126.13, 129.52, 129.70, 129.85, 140.74, 141.23, 143.14, 166.13. Mass spectrum, *m*/*z* (I_{rel}, %): 375 (18) $[M]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 70.24; H 6.43; N 18.50. $C_{22}H_{25}N_5O$. Calculated, %: C 70.38; H 6.71; N 18.65.

***N*-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]-4-[(quinolin-5-yl- and 2-methylquinolin-5-yl)amino]-benzamides XVIII and XIX (*general procedure*).** A solution of equimolar amounts (0.5 mmol) of benzamide **VI** and quinolin-5-amine or 2-methylquinolin-5-amine in 10 ml of dioxane was stirred for 30 h at 100°C. The precipitate was filtered off, washed with dioxane and diethyl ether (3×20 ml), and recrystallized from chloroform–hexane.

Compound **XVIII**. Yield 37%, mp 198–199°C. IR spectrum (KBr), ν, cm^{-1}: 3430, 3285 (NH), 1685 (C=O), 1590 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.33 s (3H, NMe), 2.49 br.s [8H, $N(CH_2)_4N$], 3.53 s (3H, CH_2), 4.39 s (1H, NH); 6.50 d, 6.79 d, 7.08 m, 7.21 d, 7.28 d, 7.41 d, 7.56 d, 8.22 d, 8.68 d.d (14H, H_{arom}, ^3J = 8.2, ^4J = 4.0 Hz); 8.53 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.31, 46.19, 52.89, 55.17, 62.10, 105.02, 115.24, 117.10, 119.01, 120.51, 127.39, 127.47, 130.19, 130.31, 130.59, 136.30, 141.86, 143.19, 148.92, 154.51, 156.83, 158.90, 169.11, 170.93. Mass spectrum, *m*/*z* (I_{rel}, %): 451 (35) $[M]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 74.41; H 6.28; N 15.30. $C_{28}H_{29}N_5O$. Calculated, %: C 74.50; H 6.43; N 15.52.

Compound **XIX**. Yield 40%, mp 173–174°C. IR spectrum (KBr), ν, cm^{-1}: 3410, 3280 (NH), 1695 (C=O), 1580 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, NMe), 2.48–2.54 m [8H, $N(CH_2)_4N$], 2.72 s (3H, Me), 3.48 s (3H, CH_2), 4.55 br.s (1H, NH); 6.48 d, 6.80 d, 7.12 m, 7.23 d, 7.42 d, 7.45 m, 7.54 d, 8.10 d, 8.68 d.d (13H, H_{arom}, ^3J = 8.0 Hz); 8.60 s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.37, 43.17, 46.17, 53.16, 55.22, 62.46, 104.94, 115.12, 116.75, 118.66, 120.56, 127.46, 127.67, 129.01, 130.30, 130.38, 130.68, 136.35, 142.07, 143.15, 149.04, 154.49, 156.99, 158.86, 169.04, 171.19. Mass spectrum, *m*/*z* (I_{rel}, %): 465 (29) $[M]^+$, 450 (10) $[M - Me]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 74.60; H 6.52; N 14.79. $C_{29}H_{31}N_5O$. Calculated, %: C 74.84; H 6.67; N 15.05.

***N*-(3-Amino-4-methylphenyl)-4-(4-methylpiperazin-1-ylmethyl)benzamide (XX).** Amide **X**, 1.69 g (5 mmol), was dissolved in 10 ml of methanol, 5 mmol of skeletal Raney nickel was added, and 10 mmol of 80% hydrazine hydrate was then added. The mixture foamed up and turned colorless. It was stirred for 45 min at 50–60°C and for 1 h at room temperature and filtered through a layer of celite, and the filtrate was evaporated. Yield 84%, colorless oily substance. IR spectrum (film), ν, cm^{-1}: 3400–3350 (NH, NH_2), 1685 (C=O), 1600 (δNH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.14 (3H, Me), 2.29 s (3H, MeN), 2.47 br.s [8H, $N(CH_2)_4N$], 3.55 s (2H, CH_2), 3.68 s (2H, NH_2); 6.73 d.d, 6.99 d, 7.42 d, 7.88 d, 7.46 d, 7.92 s (7H, H_{arom}, ^3J = 8.2, ^4J = 2.0 Hz); 7.29 br.s (1H, NHCO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.85, 45.93, 53.01, 55.03, 62.47, 106.84, 110.08, 118.58, 126.92, 129.27, 130.59, 133.96, 136.89, 142.41, 145.12, 165.43. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (27) $[M]^+$, 323 (18) $[M - Me]^+$, 307 (15) $[M - Me - NH_2]^+$, 240 (30) $[M - MeN(CH_2)_4N + 1]^+$, 118 (8) $[COC_6H_4CH_2]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 70.71; H 7.55; N 16.39. $C_{20}H_{26}N_4O$. Calculated, %: C 70.98; H 7.74; N 16.55.

[4-(3-Amino-4-methylphenyaminomethyl)-phenyl](4-methylpiperazin-1-yl)methanone (XXII) was synthesized from nitro amide **XV** according to the procedure described above for amide **XX**. Yield 77%,

oily substance. IR spectrum (film), ν, cm^{-1}: 3420–3360 (NH, NH_2), 1685 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.11 (3H, Me), 2.31 s (3H, MeN); 2.39 br.s, 2.63 br.s, 2.98 br.s, 3.67 br.s [8H, $N(CH_2)_4N$]; 3.77 s (2H, NH_2), 4.29 s (1H, NH), 4.63 s (2H, CH_2); 6.44 d, 6.85 d, 7.42 d, 7.56 d, 7.62 s (7H, H_{arom}, ^3J = 8.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.89, 46.01, 52.93, 54.85, 62.22, 107.02, 109.78, 118.46, 127.04, 129.19, 130.62, 133.96, 137.01, 142.24, 144.99, 165.17. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (34) $[M]^+$, 323 (14) $[M - Me]^+$, 99 (100) $[MeN(CH_2)_4N]^+$. Found, %: C 70.82; H 7.50; N 16.44. $C_{20}H_{26}N_4O$. Calculated, %: C 70.98; H 7.74; N 16.55.

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