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Dedicated to Corresponding Member of the Russian Academy of Sciences V.F. Mironov on his 60th anniversary

Synthesis of New 1,2,3,4-Tetrahydroisoquinoline Derivatives. 2-(2,3,3-Trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)anilines

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Abstract—A four-step procedure has been developed for the synthesis of new 2-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)anilines by acylation of 2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)anilines at the amino group with isobutyryl chloride, reduction of the endocyclic C=N bond in *N*-[2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)phenyl]isobutyramides, *N*-alkylation of *N*-[2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl]isobutyramides to *N*-[2-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl]isobutyramides, and acid hydrolysis of the latter.

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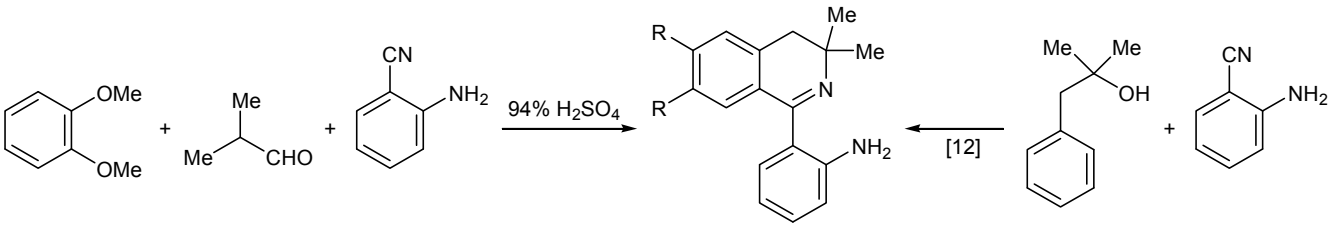
Isoquinoline derivatives of both natural and synthetic origin attract interest primarily due to broad spectrum of their biological activity. Among these compounds, the highest activity has been revealed in 1,2,3,4-tetrahydroisoquinolines [1–10]. Therefore, development of methods for the synthesis of new functionalized 1,2,3,4-tetrahydroisoquinolines suitable for further structural modifications with the goal of creating libraries of biologically active compounds is an important problem.

The present study was aimed at developing a procedure for the synthesis of previously unknown 2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolines containing a 2-aminophenyl substituent on C[1]. Interest in these compounds arises from the fact that some *N*-alkyl-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolines were found to exhibit antiplatelet [9], anticoagulant [10], antiarrhythmic [8, 10], hypotensive [9], and β-adrenergic blocking activities [8]. This makes it reasonable to search for new compounds of that series, especially for those containing groups capable of undergoing further chemical transformations.

We selected 2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)anilines **1a** and **1b** as starting materials for the synthesis of the target structure. 3,4-Dihydroisoquinoline **1a** was synthesized for the first time by one-pot three-component condensation of 1,2-dimethoxybenzene with isobutyraldehyde and 2-aminobenzonitrile in concentrated sulfuric acid, which was developed by us previously [11]. Compound **1b** was

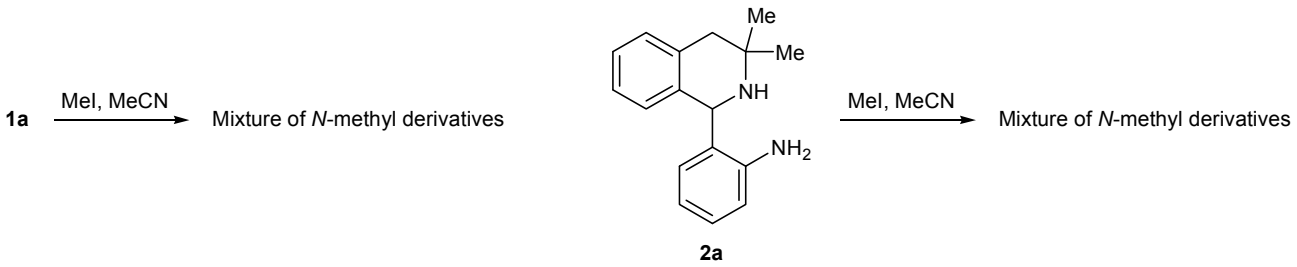
Scheme 1.



1a, **1b**

R = MeO (**a**), H (**b**).

Scheme 2.



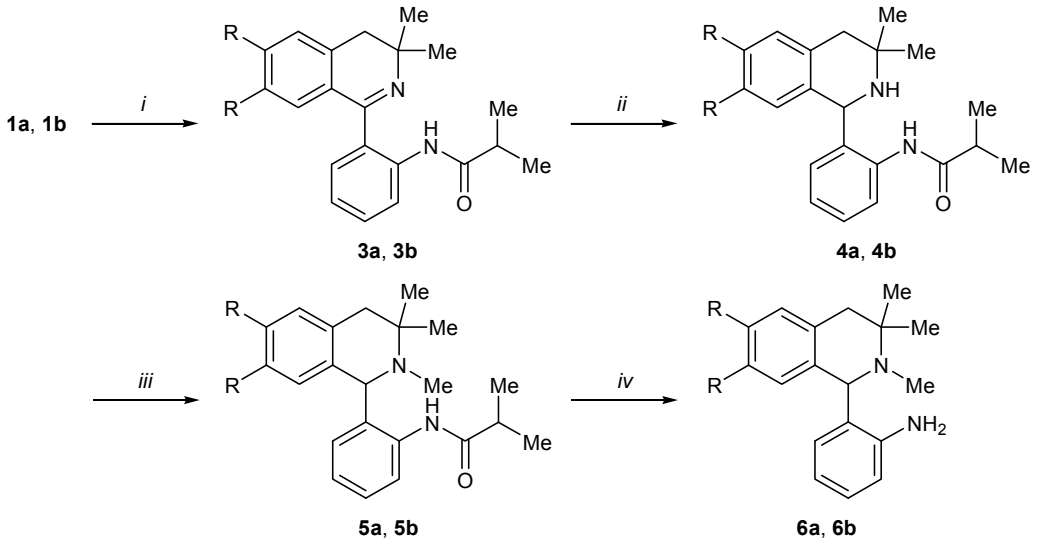
prepared under the classical Ritter conditions from 2-methyl-1-phenylpropan-2-ol and 2-aminobenzonitrile [12] (Scheme 1).

Traditional approaches to *N*-alkyl-1,2,3,4-tetrahydroisoquinolines, which are based on preparation of *N*-alkyl-3,4-dihydroisoquinoline salts and their subsequent reduction or direct *N*-alkylation of 1,2,3,4-tetrahydroisoquinolines, cannot be applied to the synthesis of 2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolines containing a 2-aminophenyl group on C^1. The alkylation of **1a** with methyl iodide in acetonitrile gave a mixture of *N*-methyl derivatives at both endocyclic nitrogen atom and exocyclic amino group (Scheme 2). Analogous pattern was observed in the alkylation under the same conditions of 1,2,3,4-tetrahydroisoquinoline **2a** which was prepared in turn by reduction of 3,4-dihydroisoquinoline **1a** with sodium tetrahydridoborate in methanol.

Therefore, we have developed an experimentally simple four-step procedure for the synthesis of the target compounds from 2-(3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)anilines **1a** and **1b** (Scheme 3). In the first step, the acylation of **1a** and **1b** with isobutyryl chloride gave amides **3a** and **3b** in nearly quantitative yield (97 and 98%, respectively). The endocyclic C^2=N bond in **3a** and **3b** was reduced with sodium tetrahydridoborate in methanol to obtain 1,2,3,4-tetrahydroisoquinolines **4a** and **4b** which were alkylated with methyl iodide in acetonitrile in the presence of potassium carbonate. As a result, *N*-[2-(2,3,3-trimethyl-1,2,3,4-dihydroisoquinolin-1-yl)phenyl]isobutyramides **5a** and **5b** were isolated in good yields. Finally, acid hydrolysis of **5a** and **5b** on heating in 20% aqueous HCl afforded the target 2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolines **6a** and **6b** in 83 and 95% yield, respectively. It should be noted that we failed to accomplish alkaline hydrolysis [13] of **5a** and **5b**; in this case, the initial compounds were recovered from the reaction mixtures.

The structure of all newly synthesized compounds was determined on the basis of their elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra.

Scheme 3.



R = MeO (**a**), H (**b**); Reagents and conditions: *i*: $Me_2CHC(O)Cl$, $ClCH_2CH_2Cl$, 25°C; *ii*: $NaBH_4$, MeOH, 25°C; *iii*: MeI, K_2CO_3, MeCN, 60°C; *iv*: 20% aq. HCl, reflux.

EXPERIMENTAL

The ^{1}H and ^{13}C (DEPT) NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer at 400 and 100 MHz, respectively, using hexamethyldisiloxane as internal standard. The mass spectra were obtained on an Agilent Technologies 6890N/5975B GC/MS system (HP-5ms column, 30 m×0.25 mm, film thickness 0.25 μm; carrier gas helium; electron impact, 70 eV). The melting points were measured on a Stuart SMP40 melting point apparatus and are uncorrected. The IR spectra were recorded on a Bruker IFS-66/S spectrometer with Fourier transform from samples prepared as thin films. The elemental compositions were determined with a Leco CHNS-932 analyzer. Silica gel (0.063–0.200 mm, Alfa Aesar) was used for column chromatography. The progress of reactions was monitored, and the purity of the isolated compounds was checked, by TLC on Sorbfil PTSKh-AF-A-UF plates; spots were visualized under UV light (λ 254 nm).

2-(6,7-Dimethoxy-3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)aniline (1a). A mixture of 2.36 g (20.0 mmol) of powdered 2-aminobenzonitrile and 40 mL of 94% sulfuric acid was stirred for 5 min. A mixture of 2.0 mL (22.0 mmol) of isobutyraldehyde and 2.55 mL (20.0 mmol) of 1,2-dimethoxybenzene was slowly added dropwise on cooling, and the mixture was stirred for 1 h at room temperature. It was then poured into a mixture of 100 g of ice and 120 mL of aqueous ammonia (to pH 7) and extracted with ethyl acetate (4×100 mL). The combined extracts were washed with water and dried over sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography using petroleum ether–ethyl acetate–triethylamine (5:1:0.3) as eluent. Yield 3.72 g (60%), light yellow crystals, R_f 0.29 (petroleum ether–EtOAc–Et_3N, 5:1:0.3), mp 120.8–121.8°C (from acetone–hexane). IR spectrum, ν, cm^{-1}: 3445, 3334, 3021, 2964, 2934, 2866, 2832, 1614, 1574, 1556, 1513, 1493, 1463, 1451, 1348, 1272, 1213, 1170, 1159, 1107, 753, 629. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 s (6H, 3-CH_3), 2.65 s (2H, 4-H), 3.58 s (3H, OCH_3), 3.82 s (3H, OCH_3), 5.82 br.s (2H, NH_2), 6.57 t.d (1H, H_{arom}, J = 7.6, 1.2 Hz), 6.66 s (1H, H_{arom}), 6.76 d (1H, H_{arom}, J = 8.0 Hz), 6.91 s (1H, H_{arom}), 7.03–7.12 m (2H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.62 (2C, CH_3), 37.44 (CH_2), 53.82, 55.54 (OCH_3), 55.60 (OCH_3); 111.70, 111.78, 114.77, 115.89 (CH_{arom}); 120.04, 120.21 (C_{arom}); 129.17, 130.08 (CH_{arom}); 130.92, 146.43, 147.61, 150.74, 162.59 (C_{arom}). Mass spectrum, m/z (I_{rel}, %): 310 (25.3) $[M]^+$, 309 $[M - H]^+$ (100), 294 (10.6), 279 (28.2). Found, %: C 73.43; H 7.11; N 9.05. $C_{19}H_{22}N_2O_2$. Calculated, %: C 73.52; H 7.14; N 9.03. M 310.39.

2-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-aniline (1b) was synthesized according to the procedure described in [12] from 3.75 g (25 mmol) of 2-methyl-1-phenylpropan-2-ol and 2.95 g (25 mmol) of 2-aminobenzonitrile. The product was purified by column chromatography using petroleum ether–ethyl acetate (3:1) as eluent. Yield 3.94 g (63%), light yellow crystals, mp 83.1–84.3°C (from *i*-PrOH) [12]), R_f 0.74 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3451, 3328, 3065, 3024, 2965, 2883, 2825, 1614, 1555, 1493, 1450, 1316, 1304, 1262, 1304, 1262, 1245, 1158, 959, 785, 753, 740. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 s (6H, 3-CH_3), 2.74 s (2H, 4-H), 5.68 br.s (2H, NH_2), 6.57 d.d.d (1H, H_{arom}, J = 7.7, 7.2, 1.2 Hz), 6.77 d.d (1H, H_{arom}, J = 8.1, 1.0 Hz), 7.00 d.d (1H, H_{arom}, J = 7.7, 1.5 Hz), 7.06–7.12 m (2H, H_{arom}), 7.23 d.d (1H, H_{arom}, J = 7.5, 1.3 Hz), 7.25–7.29 m (1H, H_{arom}), 7.39 t.d (1H, H_{arom}, J = 7.4, 1.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 25.71 (2C, CH_3), 37.84 (CH_2), 54.01; 114.86, 115.82 (CH_{arom}); 120.24, 126.39 (CH_{arom}), 127.07 (C_{arom}); 127.52, 128.25, 129.21, 130.05, 130.47 (CH_{arom}); 137.19, 147.50 (C_{arom}); 163.10 (C=N). Mass spectrum, m/z (I_{rel}, %): 250 (26.0) $[M]^+$, 249 (100) $[M - H]^+$, 233 (10.2). Found, %: C 81.64; H 7.21; N 11.23. $C_{17}H_{18}N_2$. Calculated, %: C 81.56; H 7.25; N 11.19. M 250.34.

2-(6,7-Dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)aniline (2a). Compound **1a**, 0.31 g (1 mmol), was dissolved in 5 mL of methanol, and 0.19 g (5 mmol) of $NaBH_4$ was added in small portions over a period 30 min with stirring. The mixture was left for 24 h at room temperature, the solvent was distilled off, and the residue was treated with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated, and the residue (containing more than 97% of **2a**, according to the ^{1}H NMR data), was used in further syntheses without additional purification. Yield 0.292 g (94%), light yellow crystals, mp 106.5–120.7°C (from EtOAc–hexane), R_f 0.21 (petroleum ether–EtOAc–Et_3N, 3:1:0.3). IR spectrum, ν, cm^{-1}: 3424, 3307, 3018, 3004, 2961, 2934, 2909, 2831, 1612, 1513, 1496, 1463, 1302, 1255, 1222, 1116, 1039, 1000, 837, 796, 752. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm:

1.10 s and 1.20 s (3H each, 3-CH_3), 2.21 br.s (1H, NH), 2.48 d and 2.72 d (1H each, 4-H, J = 15.6 Hz), 3.46 s (3H, OCH_3), 3.71 s (3H, OCH_3), 4.98 s (1H, 1-H), 5.12 br.s (2H, NH_2), 6.24 s (1H, H_{arom}), 6.53 d.d (1H, H_{arom}, J = 7.3, 1.2 Hz), 6.57 d.d (1H, H_{arom}, J = 8.1, 1.0 Hz), 6.64 s (1H, H_{arom}), 6.98 d.d.d (1H, H_{arom}, J = 7.9, 7.3, 1.6 Hz), 7.06 d.d (1H, H_{arom}, J = 7.4, 1.5 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 23.41 (CH_3), 31.15 (CH_3), 41.46 (CH_2), 48.83, 55.39 (OCH_3), 55.44 (OCH_3), 57.02 (CH); 110.33, 112.22, 115.44, 115.67 (CH_{arom}); 126.86 (C_{arom}), 127.58 (CH_{arom}), 128.38 (C_{arom}), 130.19 (CH_{arom}); 146.63, 147.15, 147.32 (C_{arom}). Mass spectrum, *m/z* (I_{rel}, %): 312 (100) $[M]^+$, 297 (56.5) $[M - CH_3]^+$, 281 (19.8), 254 (38.7), 239 (25.0), 224 (25.9), 204 (12.7), 180 (9.8), 119 (9.2). Found, %: C 72.93; H 7.81; N 8.90. $C_{19}H_{24}N_2O_2$. Calculated, %: C 73.05; H 7.74; N 8.97. *M* 312.41.

Compounds 3a and 3b (*general procedure*). A solution of 0.11 mL (1.1 mmol) of isobutyryl chloride in 0.6 mL of 1,2-dichloroethane was added with stirring and cooling (10°C) to a solution of 1 mmol of compound **1a** or **1b** in 3 mL of 1,2-dichloroethane. The mixture was stirred for 7 h at room temperature and treated with a saturated aqueous solution of sodium hydrogen carbonate. The organic phase was separated, washed with water, dried over Na_2SO_4, and evaporated. The residue contained more than 99% of **3a** or **3b** (according to the ^{1}H NMR and GC/MS data) and was used without additional purification.

***N*-[2-(6,7-Dimethoxy-3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)phenyl]-2-methylpropanamide (3a).** Yield 0.37 g (97%), light yellow crystals, R_f 0.23 (hexane–EtOAc, 4:1), mp 117.8–119°C. IR spectrum, ν, cm^{-1}: 3203, 3063, 2966, 2933, 1689, 1604, 1581, 1557, 1515, 1464, 1444, 1348, 1292, 1273, 1212, 1168, 1129, 1092, 953, 756. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 d [6H, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 1.30 s (6H, 3-CH_3), 2.47 sept [1H, C**H**$(CH_3)_2$, J = 6.8 Hz], 2.69 s (2H, 4-H), 3.71 s (3H, OCH_3), 3.93 s (3H, OCH_3), 6.71 s (1H, H_{arom}), 6.76 s (1H, H_{arom}), 7.05 t.d (1H, H_{arom}, J = 7.6, 1.2 Hz), 7.33 d.d (1H, H_{arom}, J = 7.6, 1.2 Hz), 7.37 d.d.d (1H, H_{arom}, J = 8.4, 7.2, 1.6 Hz), 8.46 d.d (1H, H_{arom}, J = 8.2, 0.8 Hz), 11.14 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.55 (CH_3), 27.81 (CH_3), 37.15 (CH), 38.41 (CH_2), 54.64, 56.01 (OCH_3), 56.12 (OCH_3); 111.20, 112.18 (CH_{arom}); 120.63; 122.04, 122.12 (CH_{arom}); 125.13; 129.92, 130.49 (CH_{arom}); 131.39, 138.11, 147.11, 151.39 (C_{arom}); 164.26 (C=N), 175.42 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 380 (3.3) $[M]^+$, 337 (100) $[M - CH(CH_3)_2]^+$. Found, %: C 72.68; H 7.36; N 7.39. $C_{23}H_{28}N_2O_3$. Calculated, %: C 72.60; H 7.42; N 7.36. *M* 380.48.

***N*-[2-(3,3-Dimethyl-3,4-dihydroisoquinolin-1-yl)-phenyl]-2-methylpropanamide (3b).** Yield 0.314 g (98%), oily material, R_f 0.44 (petroleum ether–EtOAc, 10:1). IR spectrum, ν, cm^{-1}: 3203, 3101, 3067, 3025, 2967, 2930, 2873, 1693, 1604, 1582, 1561, 1521, 1445, 1315, 1293, 1270, 1160, 962, 786, 762, 743. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 d [6H, CH(C**H**$_3$)$_2$, J = 6.9 Hz], 1.23 s (6H, 3-CH_3), 2.36 sept [1H, C**H**$(CH_3)_2$, J = 6.9 Hz], 2.80 s (2H, 4-H), 7.00 d.d (1H, H_{arom}, J = 7.7, 0.8 Hz), 7.17 t.d (1H, H_{arom}, J = 7.6, 1.1 Hz), 7.22 t.d (1H, H_{arom}, J = 7.6, 1.3 Hz), 7.29 d.d (1H, H_{arom}, J = 7.5, 1.3 Hz), 7.33 d.d (1H, H_{arom}, J = 7.8, 1.5 Hz), 7.36–7.48 m (2H, H_{arom}), 8.03 d (1H, H_{arom}, J = 8.1 Hz), 10.40 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.99 (2C, CH_3), 27.23 (2C, CH_3), 35.29 (CH), 37.67 (CH_2), 54.31; 122.64, 122.99, 126.46, 126.97 (CH_{arom}); 127.24, 127.37 (C_{arom}); 128.19, 129.25, 130.23, 130.82 (CH_{arom}); 137.00, 137.05 (C_{arom}); 163.08 (C=N), 174.25 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 320 (2.5) $[M]^+$, 277 (100) $[M - (CH_3)_2CH]^+$, 249 (5.7) $[M - (CH_3)_2CHC(O)]^+$, 234 (11.4) $[M - (CH_3)_2CHC(O)NH]^+$. Found, %: C 78.84; H 7.53; N 8.70. $C_{21}H_{24}N_2O$. Calculated, %: C 78.71; H 7.55; N 8.74. *M* 320.43.

Compounds 4a and 4b (*general procedure*). Sodium tetrahydridoborate, 0.265 g (7 mmol), was added in small portions over a period of 30 min with stirring to a solution of 1 mmol of compound **3a** or **3b** in 5 mL of methanol. The mixture was stirred for 14 h at room temperature, the solvent was distilled off, and the residue was treated with a saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated, and the residue was recrystallized from ethyl acetate (**4a**) or ethyl acetate–hexane (**4b**). In the synthesis of **4b**, the mother liquor obtained after recrystallization was evaporated, and the residue was purified by chromatography (petroleum ether–acetone, 10:1).

***N*-[2-(6,7-Dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl]-2-methylpropanamide (4a).** Yield 0.306 g (80%), white crystals, R_f 0.17 (hexan–EtOAc, 4:1), mp 138.5–140.5°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3289, 2965, 2934, 2833, 1682, 1610, 1590, 1518, 1466, 1448, 1301, 1256,

1224, 1117, 1075, 758. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.81 d and 1.02 d [3H each, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 1.14 s and 1.27 s (3H each, 3-CH$_3$), 2.21 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8 Hz], 2.59 d and 2.80 d (1H each, 4-H, J = 16.0 Hz), 3.10 br.s (1H, NH), 3.41 s (3H, OCH$_3$), 3.69 s (3H, OCH$_3$), 5.06 s (1H, 1-H), 6.09 s (1H, H$_{arom}$), 6.68 s (1H, H$_{arom}$), 7.08 t.d (1H, H$_{arom}$, J = 7.4, 1.3 Hz), 7.27 t.d (1H, H$_{arom}$, J = 7.8, 1.6 Hz), 7.39 d.d (1H, H$_{arom}$, J = 7.5, 1.4 Hz), 8.04 d (1H, H$_{arom}$, J = 8.0 Hz), 10.78 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 18.90, 19.21, 23.15, 31.11 (CH$_3$); 35.99 (CH), 41.37 (CH$_2$), 48.84, 55.38 (OCH$_3$), 55.50 (OCH$_3$), 57.34 (CH); 110.14, 112.26, 121.29, 122.57 (CH$_{arom}$); 126.14 (C$_{arom}$), 127.59 (CH$_{arom}$), 127.77 (C$_{arom}$), 130.61 (CH$_{arom}$); 131.98, 138.03, 146.79, 147.70 (C$_{arom}$); 173.61 (C=O). Mass spectrum, m/z (I_{rel}, %): 382 (46.2) [M]$^+$, 381 (24.2) [M – H]$^+$, 367 (29.9) [M – CH$_3$]$^+$, 311 (100) [M – (CH$_3$)$_2$CHC(O)]$^+$, 296 (59.2) [M – (CH$_3$)$_2$CHC(O)NH]$^+$, 255 (14.7), 254 (69.5), 239 (12.2), 238 (16.4), 220 (12.8), 219 (10.6), 204 (10.3), 58 (10.8), 43 (20.6). Found, %: C 72.23; H 7.81; N 7.35. $C_{23}H_{30}N_2O_3$. Calculated, %: C 72.22; H 7.91; N 7.32. M 382.50.

***N*-[2-(3,3-Dimethyl-1,2,3,4-dihydroisoquinolin-1-yl)phenyl]-2-methylpropanamide (4b).** Yield 0.297 g (92%), white crystals, mp 125.6–126.8°C (from EtOAc–hexane), R_f 0.23 (petroleum ether–acetone, 10:1). IR spectrum, ν, cm^{-1}: 3285, 3188, 3106, 3018, 2966, 2930, 2873, 1682, 1609, 1590, 1525, 1448, 1382, 1367, 1300, 1197, 1160, 944, 757, 744. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.73 d and 0.98 d [3H each, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 1.15 s and 1.29 s (3H each, 3-CH$_3$), 2.17 sept [1H, C**H**(CH$_3$)$_2$, J = 6.9 Hz], 2.69 d and 2.88 d (1H each, 4-H, J = 16.3 Hz), 3.19 br.s (1H, NH), 5.14 s (1H, 1-H), 6.56 d (1H, H$_{arom}$, J = 7.7 Hz), 6.93–7.00 m (1H, H$_{arom}$), 7.05–7.12 m (3H, H$_{arom}$), 7.26 t.d (1H, H$_{arom}$, J = 7.6, 1.6 Hz), 7.40 d.d (1H, H$_{arom}$, J = 7.5, 1.5 Hz), 8.03 d (1H, H$_{arom}$, J = 8.0 Hz), 10.74 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 18.86 (CH$_3$), 19.12 (CH$_3$), 23.14 (CH$_3$), 31.13 (CH$_3$), 36.00 (CH), 41.81 (CH$_2$), 48.78, 57.65 (CH); 121.33, 122.58, 125.58, 125.92, 126.16, 127.62, 128.80, 130.96 (CH$_{arom}$); 131.87, 133.67, 135.97, 137.96 (C$_{arom}$); 173.52 (C=O). Mass spectrum, m/z (I_{rel}, %): 322 (20.3) [M]$^+$, 307 (24.9) [M – CH$_3$]$^+$, 277 (11.5), 251 (100) [M – (CH$_3$)$_2$CHC(O)]$^+$, 236 (42.3) [M – (CH$_3$)$_2$CHC(O)NH]$^+$, 194 (44.6), 178 (14.9), 144 (17.7), 58 (13), 43 (20.2). Found, %: C 78.15; H 8.17; N 8.62. $C_{21}H_{26}N_2O$. Calculated, %: C 78.22; H 8.13; N 8.69. M 322.44.

Compounds 5a and 5b (*general procedure*). Potassium carbonate, 0.55 g (4 mmol), was added to a solution of 1 mmol of compound **4a** or **4b** in 4 mL of acetonitrile, and 0.19 mL (3 mmol) of methyl iodide was then added dropwise with stirring. The mixture was stirred for 8 h at 60°C, left overnight at room temperature, and heated again for 4 h at 60°C (TLC). The solvent was evaporated, and the residue was treated with water and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The extract was combined with the organic phase, washed with water, dried over Na_2SO_4, and evaporated, and the residue was recrystallized from ethyl acetate (**5a**) or purified by chromatography using petroleum ether–acetone (10:1) as eluent (**5b**).

***N*-[2-(6,7-Dimethoxy-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl]-2-methylpropanamide (5a).** Yield 0.35 g (88%), white crystals, R_f 0.29 (hexane–EtOAc, 4:1), mp 144–146.5°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3179, 3104, 2968, 2934, 2833, 1687, 1611, 1590, 1519, 1466, 1447, 1301, 1260, 1225, 1116, 1012, 757. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 0.96 s (3H, 3-CH$_3$), 1.06 d [3H, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 1.34 s (3H, 3-CH$_3$), 2.14 s (3H, NCH$_3$), 2.27 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8 Hz], 2.66 d and 2.94 d (1H each, 4-H, J = 16.0 Hz), 3.40 s (3H, OCH$_3$), 3.69 s (3H, OCH$_3$), 4.51 s (1H, 1-H), 6.07 s (1H, H$_{arom}$), 6.67 s (1H, H$_{arom}$), 7.10 t.d (1H, H$_{arom}$, J = 7.2, 1.2 Hz), 7.26 t.d (1H, H$_{arom}$, J = 8.0, 1.2 Hz), 7.43 d.d (1H, H$_{arom}$, J = 7.2, 1.2 Hz), 8.12 d (1H, H$_{arom}$, J = 7.8 Hz), 10.67 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 13.92, 18.87, 19.37, 29.62, 33.88 (CH$_3$); 36.01 (CH), 43.33 (CH$_2$), 52.72, 55.22 (OCH$_3$), 55.42 (OCH$_3$), 66.31 (CH); 110.72, 111.41, 120.61, 122.58 (CH$_{arom}$); 125.41, 127.31 (C$_{arom}$); 127.61, 130.92 (CH$_{arom}$); 137.46, 146.71, 147.63 (C$_{arom}$); 173.72 (C=O). Mass spectrum, m/z (I_{rel}, %): 396 (9.3) [M]$^+$, 381 (100) [M – CH$_3$]$^+$, 353 (16.9) [M – CH(CH$_3$)$_2$]$^+$, 311 (17.2), 254 (14.8), 72 (9.2), 43 (9.8). Found, %: C 72.59; H 8.08; N 7.11. $C_{24}H_{32}N_2O_3$. Calculated, %: C 72.70; H 8.13; N 7.06. M 396.52.

***N*-[2-(2,3,3-Trimethyl-1,2,3,4-dihydroisoquinolin-1-yl)phenyl]-2-methylpropanamide (5b).** Yield 0.286 g (85%), white crystals, mp 136.6–138.1°C (from EtOAc), R_f 0.38 (petroleum ether–acetone, 10:1). IR spectrum, ν, cm^{-1}: 3234, 3184, 3106, 3061, 2968, 2930, 2873, 2808, 2792, 1691, 1608, 1590, 1527, 1494, 1469, 1445, 1382, 1367, 1302, 1197, 1161, 1147, 990, 941, 757, 743. ^{1}H NMR spectrum

(DMSO-d_6), δ, ppm: 0.78 d [3H, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 0.97 s (3H, 3-CH$_3$), 1.03 d [3H, CH(C**H**$_3$)$_2$, J = 6.8 Hz], 1.35 s (3H, 3-CH$_3$), 2.14 s (3H, NCH$_3$), 2.23 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8 Hz], 2.77 d and 3.02 d (1H each, 4-H, J = 16.4 Hz), 4.60 s (1H, 1-H), 6.56 d (1H, H$_{arom}$, J = 8.0 Hz), 6.89–7.01 m (1H, H$_{arom}$), 7.05–7.14 m (3H, H$_{arom}$), 7.26 t.d (1H, H$_{arom}$, J = 7.6, 1.6 Hz), 7.44 d.d (1H, H$_{arom}$, J = 7.5, 1.6 Hz), 8.08 d (1H, H$_{arom}$, J = 7.9 Hz), 10.58 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 13.95 (CH$_3$), 18.87 (CH$_3$), 19.30 (CH$_3$), 29.66 (CH$_3$), 33.91 (CH$_3$), 36.04 (CH), 43.76 (CH$_2$), 52.70, 66.50 (CH); 120.73, 122.66, 125.66, 126.22, 126.73, 127.66, 128.17 (CH$_{arom}$); 130.90 (C$_{arom}$), 131.30 (CH$_{arom}$); 133.00, 135.58, 137.39 (C$_{arom}$); 173.66 (C=O). Mass spectrum, m/z (I_{rel}, %): 336 (8.5) $[M]^+$, 321 (100) $[M - CH_3]^+$, 293 (15.4) $[M - (CH_3)_2CH]^+$, 265 (16.4) $[M - (CH_3)_2CHC(O)]^+$, 251 (12.0), 194 (9.8), 158 (15.3), 72 (12.9), 43 (12.9). Found, %: C 78.44; H 8.35; N 8.38. $C_{22}H_{28}N_2O$. Calculated, %: C 78.53; H 8.39; N 8.33. M 336.47.

Compounds 6a and 6b (*general procedure*). A solution of 1 mmol of compound **5a** or **5b** in 15 mL of 20% aqueous HCl was refluxed for 2 h. The mixture was cooled and neutralized to pH 7–8 by adding aqueous ammonia with stirring and cooling. The precipitate was extracted with ethyl acetate, the extract was washed with water, dried over Na_2SO_4, and evaporated, and the residue was purified by chromatography using hexane–acetone (6:1) or petroleum ether–acetone (15:1) as eluent for compounds **6a** and **6b**, respectively.

2-(6,7-Dimethoxy-2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)aniline (6a). Yield 0.271 g (83%), colorless crystals, R_f 0.31 (hexane–EtOAc, 4:1), mp 152.5–153.7°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3423, 3288, 2999, 2965, 2912, 2833, 2782, 1611, 1518, 1496, 1463, 1303, 1260, 1223, 1115, 1013, 752. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 s and 1.26 s (3H each, 3-CH$_3$), 2.10 s (3H, NCH$_3$), 2.37 d and 2.88 d (1H each, 4-H, J = 15.6 Hz), 3.43 s (3H, OCH$_3$), 3.70 s (3H, OCH$_3$), 4.30 s (1H, 1-H), 5.20 s (2H, NH$_2$), 6.19 s (1H, H$_{arom}$), 6.51 d.d (1H, H$_{arom}$, J = 8.0, 0.8 Hz), 6.56 t.d (1H, H$_{arom}$, J = 7.2, 0.8 Hz), 6.61 s (1H, H$_{arom}$), 6.97 t.d (1H, H$_{arom}$, J = 7.6, 1.6 Hz), 7.13 d.d (1H, H$_{arom}$, J = 7.4, 1.6 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 13.63, 29.69, 33.89 (CH$_3$); 43.52 (CH$_2$), 52.39, 55.29 (2C, OCH$_3$), 66.59 (CH); 110.85, 111.26, 115.24, 115.40 (CH$_{arom}$); 126.03, 126.17 (C$_{arom}$); 127.45, 128.29 (CH$_{arom}$); 130.81, 146.48, 147.23 (C$_{arom}$). Mass spectrum, m/z (I_{rel}, %): 326 (20.9) $[M]^+$, 325 (9.9) $[M - H]^+$, 311 (100) $[M - CH_3]^+$, 283 (11.7), 234 (14.1). Found, %: C 73.68; H 8.07; N 8.52. $C_{20}H_{26}N_2O_2$. Calculated, %: C 73.59; H 8.03; N 8.58. M 326.43.

2-(2,3,3-Trimethyl-1,2,3,4-tetrahydroisoquinolin-1-yl)aniline (6b). Yield 0.253 g (95%), white crystals turning yellowish on exposure to air, mp 145.6–147.0°C (from EtOAc), R_f 0.44 (petroleum ether–acetone, 15:1). IR spectrum, ν, cm^{-1}: 3424, 3308, 3018, 3003, 2961, 2934, 2854, 1612, 1512, 1496, 1462, 1302, 1255, 1222, 1116, 1076, 837, 752. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.89 s and 1.27 s (3H each, 3-CH$_3$), 2.10 s (3H, NCH$_3$), 2.60 d and 2.96 d (1H each, 4-H, J = 15.9 Hz), 4.39 s (1H, 1-H), 5.19 br.s (2H, NH$_2$), 6.50 d.d (1H, H$_{arom}$, J = 7.9, 1.1 Hz), 6.55 t.d (1H, H$_{arom}$, J = 7.3, 1.2 Hz), 6.66 d (1H, H$_{arom}$, J = 7.5 Hz), 6.90–6.98 m (2H, H$_{arom}$), 7.00–7.05 m (2H, H$_{arom}$), 7.13 d.d (1H, H$_{arom}$, J = 7.4, 1.5 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 13.66 (CH$_3$), 29.69 (CH$_3$), 33.88 (CH$_3$), 43.98 (CH$_2$), 52.35, 66.71 (CH); 115.34, 115.46, 125.15, 125.50 (CH$_{arom}$); 126.11 (C$_{arom}$); 126.48, 127.48, 127.76, 131.10 (CH$_{arom}$); 133.71, 136.59, 146.50 (C$_{arom}$). Mass spectrum, m/z (I_{rel}, %): 266 (23.1) $[M]^+$, 251 (100) $[M - CH_3]^+$, 220 (16.9), 194 (16.2), 158 (16.1) Found, %: C 81.21; H 8.28; N 10.51. $C_{18}H_{22}N_2$. Calculated, %: C 81.16; H 8.32; N 10.52. M 266.38.

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REFERENCES

1. *Izbrannye metody sinteza i modifikatsii geterotsiklov. Prirodnye izokhinoliny: khimiya i biologicheskaya aktivnost'* (Selected Methods of Synthesis and Modification of Heterocycles. Natural Isoquinolines: Chemistry and Biological Activity), Kartsev, V.G., Moscow: ICSPF, 2011, vol. 8, p. 704.
2. Shah, P. and Singh, I.P., *Expert. Opin. Ther. Pat*., 2017, vol. 27, p. 17.
3. Antkiewicz-Michaluk, L., Wąsik, A., and Michaluk, J., *Neurotoxic. Res*., 2014, vol. 25, p. 1.
4. Krasiński, A., Radić, Z., Manetsch, R., Raushel, J., Taylor, P., Sharpless, K.B., and Kolb, H.C., *J. Am. Chem. Soc*., 2005, vol. 127, p. 6686.
5. Mikhailovskii, A.G., Bubnov, Yu.N., Syropyatov, B.Ya., Dolzhenko, A.V., and Timofeeva, Yu.P., *Pharm. Chem. J*., 1999, vol. 33, p. 128.

6. Boronenkova, E.S., Syropyatov, B.Ya., Gorbunov, A.A., Shklyaev, V.S., and Shklyaev, Yu.V., *Pharm. Chem. J*., 1994, vol. 28, p. 550.
7. Beaumont, D. and Waigh, R.D., *Prog. Med. Chem*., 1981, vol. 18, p. 45.
8. Markaryan, E.A., Airapetyan, G.K., Mikaelyan, A.P., Markaryan, K.Zh., Asatryan, T.O., and Noravyan, O.S., *Pharm. Chem. J*., 1997, vol. 31, p. 71.
9. Mikhailovskii, A.G., Syropyatov, B.Ya., Dolzhenko, A.V., and Vakhrin, M.I., *Pharm. Chem. J*., 2002, vol. 36, p. 374.
10. Shklyaev, Yu.V., Syropyatov, B.Ya., Shklyaev, V.S., Gavrilov, M.S., Boronenkova, E.S., Dautova, R.Z., Aleksandrov, B.B., and Gorbunov, A.A., *Pharm. Chem. J*., 1999, vol. 33, p. 467.
11. Shklyaev, Yu.V. and Nifontov, Yu.V., *Russ. Chem. Bull., Int. Ed*., 2002, vol. 51, p. 844.
12. Seeger, E., Engel, W., Teufel, H., and Machleidt, H., *Chem. Ber*., 1970, vol. 103, p. 1674.
13. Tsuji, K. and Ishikawa, H., *Synth. Commun*., 1994, vol. 24, p. 2943.