ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 10, pp. 1449–1452. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © Zh.V. Ignatovich, Yu.V. Sinyutich, K.N. Gusak, E.V. Koroleva, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 10, pp. 1479–1482.

Synthesis of *N*-[2(3,4)-Aminophenyl]-4-({4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)benzamides

Zh. V. Ignatovich, Yu. V. Sinyutich, K. N. Gusak, and E. V. Koroleva

Institute of New Materials Chemistry, National Academy of Sciences of Belarus,
ul. F. Skoriny 36, Minsk, 220141 Belarus
e-mail: evk@ichnm.basnet.by

Received March 30, 2015

Abstract—New *N*-[2(3,4)-aminophenyl]benzamides containing a pharmacophoric 2-(arylamino)pyrimidine fragment have been synthesized from the corresponding substituted benzoic acid.

DOI: 10.1134/S1070428015100164

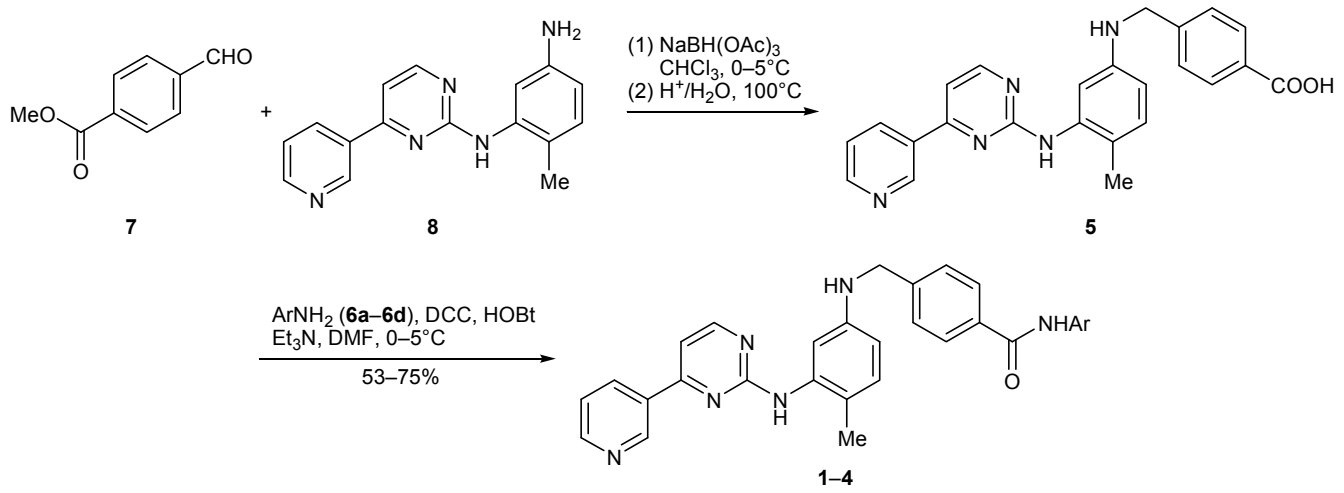
Advances of molecular biology in the determination of mechanisms of inhibition of tumor growth by small molecules gave rise to a radically new approach to the design of drugs for targeted antitumor therapy. A relevant synthetic strategy implies combination in a single molecule of pharmacophoric fragments of known compounds inhibiting different stages of tumor genesis and growth. A number of biologically active compounds were synthesized by combining structural fragments of tyrosine kinase and histone deacetylase inhibitors in a single relatively small molecule. The resulting structures showed additive and synergistic effects compared to the precursors. They displayed a broader spectrum of tyrosine kinase inhibition while remaining histone deacetylase inhibitors; in particular, they inhibited $AblT^{315}I$ Imatinib-resistant mutant [1, 2]. *N*-(2-Aminophenyl)-4-{[4-(pyridin-3-yl)-3-(pyrimidin-2-ylamino)phenyl]aminomethyl}benzamide is a structural analog (with respect to the arylaminopyrimidine fragment) of Imatinib, which is the known tyrosine kinase inhibitor and antileukemic drug [3]. It has recently been shown that this compound also inhibits hystone deacetylase *in vitro* [1].

We have developed a rational synthesis of *N*-[2(3,4)-aminophenyl]-4-({3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)benzamides **1**–**4** according to a convergent scheme. The amide bond was built up in the final step from acid **5** and isomeric phenylenediamines **6a**–**6d**. Substituted benzoic acid **5** was synthesized in 85% yield by direct reductive amination of methyl 4-formylbenzoate (**7**) with amine **8**, following a procedure developed previously. Acid **5** was used as hydrochloride without purification at the step of synthesis of its benzotriazolyl ester [4, 5].

Amides **1**–**4** were synthesized in 54–75% yield by aminolysis of activated benzotriazolyl ester derived from acid **5** with benzenediamines **6a**–**6d** (Scheme 1). Amides **1**–**4** are structural analogs of compounds acting as specific histone deacetylase inhibitors. In all cases, the aminolysis selectively afforded the corresponding monoamide. In the reaction with 4-methylbenzene-1,3-diamine (**6d**), only the more sterically accessible amino group in the *para* position with respect to the methyl group was involved. The aminolysis of acid **5** benzotriazolyl ester with nitroanilines was characterized by a lower yield, whereas no desired amide was obtained from *o*-nitroaniline, presumably due to electron-withdrawing effect of the nitro group [6].

The structure of amides **1**–**4** was confirmed by elemental analyses and ^1H and ^{13}C NMR, IR, and mass spectra. The IR spectra of **1**–**4** contained absorption bands due to stretching vibrations of the N–H (3450–3280 cm^{-1}) and carbonyl groups (1630–1620 cm^{-1}) and N–H bending vibrations (1580–1570 cm^{-1}). In the ^1H NMR spectra of these compounds we observed signals from protons in the benzene, pyrimidine, and pyridine rings (δ 6.0–10.0 ppm), methyl groups (δ 2.05–3.00 ppm), primary amino group (δ 3.40–4.80 ppm), and NH groups [δ 6.10–8.80 and 8.03–10.10 ppm (NHCO), depending on the solvent]. The NH proton in the CH_2NH fragment resonated as

Scheme 1.



Ar = 2-$H_2NC_6H_4$ (**a**), R = 4-$H_2NC_6H_4$ (**b**), R = 3-$H_2NC_6H_4$ (**c**), R = 2-Me-5-$H_2NC_6H_3$ (**d**).

a triplet at δ 5.8–6.9 ppm, and the CH_2 signal was a doublet at δ 3.6–4.4 ppm (^3J = 5.5–6.8 Hz). The latter signal was not split when no NH signal was observed (as a result of fast H–D exchange with the solvent).

The carbonyl carbon signal appeared in the ^{13}C NMR spectra at δ_C 165.00–185.00 ppm, and it was not observed in the DEPT spectrum. Carbon signals belonging to methyl (δ_C 16.0–21.0 ppm) and methylene groups (δ_C 46–63 ppm) were distinguished by the DEPT spectrum.

EXPERIMENTAL

The IR spectra were recorded in the range 400–4000 cm^{-1} on a Bruker Tensor 27 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-500 spectrometer at 500 and 125 MHz, respectively, using tetramethylsilane as internal standard. Gas chromatographic and mass spectrometric analyses were obtained on Accela-LCQ Fleet (APCI or ESI), Hewlett Packard HP 6850/5973, and Thermo Scientific Trace GC Ultra/DSQ II (direct inlet probe) instruments. The progress of reactions was monitored, and the purity of products was checked, by TLC on Merk DC-Plasticfolien Kieselgel 60 F_{254} plates using butan-1-ol–ethanol–aqueous ammonia (8:1:1) and chloroform–methanol (95:5) as eluents. The elemental compositions were determined using a Vario MICRO CHNS analyzer. The melting points were measured on a Kofler hot stage.

Phenylenediamines **6a**–**6d** were synthesized by reduction of the corresponding nitroanilines with hydrazine hydrate over a skeletal catalyst [7] and were used as hydrochlorides. The synthesis of diamine **8** was described in [8].

4-({4-Methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)benzoic acid dihydrochloride (5). A suspension of 2.0 g (0.053 mol) of sodium tetrahydridoborate in 16 mL of chloroform was cooled to 0–5°C, 14 mL (0.23 mol, 9 equiv) of acetic acid was slowly added over a period of 1 h, and the mixture was stirred for 1.5 h on cooling. A mixture of 7.2 g (0.026 mol, 1 equiv) of 4-methyl-N^3-[4-(pyridin-3-yl)pyrimidin-2-yl]benzene-1,3-diamine (**8**) and 4.3 g (0.26 mol, 1 equiv) of methyl 4-formylbenzoate (**7**) in 30 mL of chloroform was then added, maintaining the temperature at 0–5°C. The mixture was stirred for 1.5 h on cooling and for 12 h at room temperature, treated with 20 mL of water, and neutralized with a saturated aqueous solution of sodium carbonate. The organic layer was separated, the aqueous phase was extracted with chloroform and ethyl acetate, and the extracts were combined with the organic phase, washed with one portion of water, dried over Na_2SO_4, and evaporated. The residue was 4-substituted methyl benzoate which was subjected (without purification) to hydrolysis with dilute aqueous HCl (60 mL of water and 120 mL of concentrated aqueous HCl per mole of ester). The mixture was heated to the boiling point, diluted with a double volume of hot water, and heated for 4–6 h under reflux. When the reaction was complete, 2 g of charcoal was added to the hot solution, the mixture was heated for 30 min under reflux and filtered, and the filtrate was evaporated. Benzene,

15 mL, was added to the residue, and the mixture was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The precipitate of acid **5** dihydrochloride was filtered off and washed with benzene (3×10 mL). Yield 81%, yellow crystals, mp 185–186°C. IR spectrum (KBr), ν, cm^{-1}: 3432 (N–H), 3169–2598 (C–H), 1699 (C=O), 1632, 1610, 1441. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.24 s (3H, CH_3), 4.57 s (2H, CH_2), 7.14 d (1H, J = 7.2 Hz), 7.28 d (1H, J = 8.3 Hz), 7.67 d (2H, J = 7.9 Hz), 7.69 s (1H), 7.83 s (1H), 7.85 d (2H, J = 7.9 Hz), 8.18 d.d (1H, J = 8.2, 5.6 Hz), 8.66 d (1H, J = 5.2 Hz), 9.02 d (1H, J = 4.9 Hz), 9.21 d (1H, J = 8.2 Hz), 9.32 s (1H), 9.55 d (1H, J = 1.7 Hz), 10.09 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.43, 51.85, 108.46, 117.64, 117.73, 127.01, 128.96, 130.07, 130.53, 130.92, 134.81, 134.92, 137.39, 137.88, 141.10, 142.61, 142.66, 143.56, 158.71, 159.67, 160.10, 166.69. Mass spectrum: m/z 483 (I_{rel} 100%) $[M]^+$. Found, %: C 59.63; H 4.75; N 14.49. $C_{24}H_{25}Cl_2N_5O_2$ ($C_{24}H_{23}N_5O_2 \cdot 2HCl$). Calculated, %: C 59.51; H 4.79; N 14.46.

Amides 1–4 (*general procedure*). Triethylamine, 5.7 ml (40.1 mmol, 10 equiv), was added to a solution of 2.0 g (4.1 mmol, 1 equiv) of acid **5** dihydrochloride in 10 mL of dimethylformamide, and the mixture was stirred for 1 h at room temperature. Diamine **6a**–**6d**, 4.1 mmol (1 equiv) and 2.0 mL (14.4 mmol, 3.5 equiv) of triethylamine were then added, and the mixture was stirred for 0.5 h at room temperature. The mixture was cooled to 0°C, 0.6 g (4.5 mmol, 1.1 equiv) of 1-hydroxybenzotriazole and 0.9 g (4.5 mmol, 1.1 equiv) of *N*,*N*′-dicyclohexylcarbodiimide were added, and the mixture was stirred for 1.5 h on cooling and for 20 h at 50°C. The precipitate of *N*,*N*′-dicyclohexylurea was filtered off, the filtrate was evaporated to dryness, the residue was treated with 20% aqueous sodium hydroxide to pH 10–11 and extracted with chloroform. The extract was evaporated, and the residue was recrystallized from methylene chloride–diethyl ether.

***N*-(2-Aminophenyl)-4-({4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)-benzamide (1).** Yield 53%, light yellow crystals, mp 145–147°C. IR spectrum (KBr), ν, cm^{-1}: 3443–3279 (N–H), 3060–2922 (C–H), 1626 (C=O), 1577, 1535, 1449. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, Me), 4.34 d (2H, CH_2, J = 6.0 Hz), 4.87 s (2H, NH_2), 6.21 t (1H, NH, J = 6.2 Hz), 6.33 d.d (1H, J = 8.2, 2.3 Hz), 6.59 t (1H, J = 7.1 Hz), 6.77 d (1H, J = 8.0 Hz), 6.88 m (2H), 6.96 t (1H, J = 7.0 Hz), 7.14 d (1H, J = 7.7 Hz), 7.36 d (1H, J = 1.6 Hz), 7.46 d (2H, J = 8.1 Hz), 7.53 d.d (1H, J = 7.9, 4.9 Hz), 7.90 d (2H, J = 8.0 Hz), 8.40 d (1H, J = 8.0 Hz), 8.45 d (1H, J = 5.1 Hz), 8.69 s (2H, NH, =CHN=), 9.25 d [1H, HNC(N)N, J = 1.8 Hz], 9.61 s (1H, NHCO, J = 0.86 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.00, 46.31, 107.02, 108.92, 109.36, 115.94, 116.10, 119.30, 123.18, 123.65, 126.27, 126.48, 126.66, 127.60, 130.22, 132.10, 132.74, 134.09, 137.87, 142.92, 144.22, 146.68, 147.92, 151.17, 159.19, 160.99, 161.28, 165.04. Mass spectrum: m/z 501 (I_{rel} 18%) $[M]^+$. Found, %: C 71.95; H 5.46; N 19.48. $C_{30}H_{27}N_7O$. Calculated, %: C 71.84; H 5.43; N 19.55.

***N*-(4-Aminophenyl)-4-({4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)-benzamide (2).** Yield 54%, light brown crystals, mp 136–137°C. IR spectrum (KBr), ν, cm^{-1}: 3406–3054 (N–H), 3050–2928 (C–H), 1622 (C=O), 1576, 1450, 1419. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.97 s (3H, Me), 3.66 s (2H, CH_2), 5.22 br.s (2H, NH_2), 7.17 d.d (1H, J = 8.1, 1.5 Hz), 7.40 d (1H, J = 8.6 Hz), 7.43 d (1H, J = 8.6 Hz), 7.72 d (1H, J = 8.2 Hz), 8.11 d.d (1H, J = 5.1, 1.7 Hz), 8.14 t (1H, J = 3.0 Hz), 8.28–8.24 m (4H), 8.51 d.t (1H, J = 8.6, 2.2 Hz), 8.56 s (1H), 8.64 d (1H, J = 8.4 Hz), 8.66 d (1H, J = 8.3 Hz), 9.21 d (1H, J = 8.0 Hz), 9.24 d.d (1H, J = 5.1, 1.6 Hz), 9.45 d.t (1H, J = 4.8, 1.7 Hz), 9.93 s (1H, NH, J = 0.31 Hz), 10.07 s (1H), 10.18 s (1H, NHCO, J = 0.4 Hz). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 18.21, 48.99, 109.61, 110.63, 115.88, 119.79, 121.28, 122.41, 122.51, 123.48, 125.29, 128.82, 129.16, 131.13, 132.27, 135.74, 136.00, 136.45, 140.11, 146.26, 146.61, 149.02, 149.56, 150.15, 153.11, 161.01, 163.06, 163.84, 166.83. Found, %: C 71.90; H 5.41; N 19.62. $C_{30}H_{27}N_7O$. Calculated, %: C 71.84; H 5.43; N 19.55.

***N*-(3-Aminophenyl)-4-({4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)-benzamide (3).** Yield 75%, light brown crystals, mp 132–134°C. IR spectrum (KBr), ν, cm^{-1}: 3417–3343 (N–H), 3033–2928 (C–H), 1623 (C=O), 1576, 1533, 1450, 1417. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.23 s (3H, Me), 4.38 s (2H, CH_2), 6.31 d.d (1H, J = 8.1, 2.6 Hz), 6.43 d.d (1H, J = 7.9, 1.7 Hz), 6.80 d (1H, J = 7.9 Hz), 6.99–6.97 m (2H), 7.08 d (2H, J = 7.9 Hz), 7.40–7.35 m (4H), 7.52 d (1H, J = 2.1 Hz), 7.74 d (2H, J = 8.1 Hz), 8.13 s (1H, NH), 8.27 d.t (1H, J = 7.9, 1.7 Hz), 8.41 d (1H, J = 5.2 Hz), 8.67 d.d (1H, J = 4.7, 1.4 Hz), 9.21 d (1H, J = 1.9 Hz), 9.51 s (1H, NH, J = 0.16 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C,

ppm: 17.13, 48.05, 106.36, 108.02, 108.09, 108.34, 108.49, 110.08, 111.19, 117.48, 123.56, 127.21, 127.35, 127.48, 129.65, 130.99, 132.79, 133.82, 134.45, 137.94, 139.08, 143.88, 146.72, 147.26, 148.47, 151.28, 158.94, 160.66, 162.48, 165.65. Found, %: C 71.98; H 5.47; N 19.60. $C_{30}H_{27}N_7O$. Calculated, %: C 71.84; H 5.43; N 19.55.

***N*-(3-Amino-4-methylphenyl)-4-({[4-methyl-3-[4-(pyridin-3-yl)pyrimidin-2-ylamino]phenyl}aminomethyl)benzamide (4).** Yield 65%, light yellow crystals, mp 134–136°C. IR spectrum (KBr), ν cm^{-1}: 3407–3332 (N–H), 3055–2927 (C–H), 1623 (C=O), 1577, 1450, 1313. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.12 (3H, Me), 2.23 (3H, Me), 3.47 br.s (2H, NH_2), 4.40 s (2H, CH_2), 6.32 d.d (1H, *J* = 8.2, 2.4 Hz), 6.74 d.d (1H, *J* = 7.9, 1.8 Hz), 7.00–6.96 m (4H), 7.09 d (1H, *J* = 5.1 Hz), 7.39 d.d (1H, *J* = 8.2, 2.3 Hz), 7.42 d (2H, *J* = 7.9 Hz), 7.54 d (1H, *J* = 1.8 Hz), 7.76 d (2H, *J* = 7.9 Hz), 7.97 s (1H, NH), 8.29 d (1H, *J* = 7.9 Hz), 8.43 d (1H, *J* = 5.1 Hz), 8.68 d (1H, *J* = 3.8 Hz), 9.22 s (1H, NHCO, *J* = 0.96 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.61, 16.89, 47.88, 106.12, 106.61, 107.85, 108.04, 109.90, 117.25, 117.30, 118.31, 123.31, 126.91, 127.14, 130.76, 132.55, 134.20, 137.71, 143.52, 144.80, 146.43, 148.25, 151.06, 158.69, 160.41, 162.27, 165.18, 179.76, 180.08, 181.39, 182.95. Found, %: C 72.55; H 5.66; N 19.10. $C_{31}H_{29}N_7O$. Calculated, %: C 72.21; H 5.67; N 19.02.

REFERENCES

1. Mahboobi, S., Dove, S., Sellmer, A., Winkler, M., Eichhorn, E., Pongratz, H., Ciossek, Th., Baer, Th., Maier, Th., and Beckers, Th., *J. Med. Chem*., 2009, vol. 52, p. 2265.
2. Zhou, N., Moradei, O., Raeppel, S., Leit, S., Frechette, S., Gaudette, F., Paquin, I., Bernstein, N., Bouchain, G., Vaisburg, A., Jin, Zh., Gillespie, J., Wang, J., Fournel, M., Yan, P.T., Trachy-Bourget, M.-C., Kalita, A., Lu, A., Rahil, J., MacLeod, A.R., Li, Z., Besterman, J.M., and Delorme, D., *J. Med. Chem*., 2008, vol. 51, p. 4072.
3. Druker, B.J. and Lydon, N.B., *J. Clin. Invest*., 2000, vol. 105, p. 3.
4. Koroleva, E.V., Kadutskii, A.P., Farina, A.V., Ignatovich, J.V., Ermolinskaya, A.L., Gusak, K.N., and Kalinichenko, E.N., *Tetrahedron Lett*., 2012, vol. 53, p. 5056.
5. Koroleva, E.V., Ignatovich, Zh.V., Ermolinskaya, A.L., and Yarovskaya, I.Yu., *Izv. Nats. Akad. Nauk Belarusi, Ser. Khim. Nauk*, 2015, no. 1, p. 63.
6. Koroleva, E.V., Ignatovich, Zh.V., Gusak, K.N., Ermolinskaya, A.L., and Sinyutich, Yu.V., *Russ. J. Org. Chem*., 2015, vol. 51, p. 101.
7. Szczepek, W., Luniewsky, W., Kaczmarek, L., Zagrodzki, B., Samson-Lazinska, D., Szelejewski, W., and Skarzynski, M., WO Patent no. 071130, 2006; *Chem. Abstr*., 2007, vol. 145, no. 103728 d.
8. Koroleva, E.V., Ignatovich, Zh.V., Ermolinskaya, A.L., Sinyutich, Yu.V., Baranovskii, A.V., and Makhnach, S.A., *Izv. Nats. Akad. Nauk Belarusi, Ser. Khim. Nauk*, 2013, no. 3, p. 79.