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Polyfunctional Imidazoles: VII.* 1-Aryl-4-chloro-5-[hydroxy(halo)methyl]-1*H*-imidazoles and Their Derivatives

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Abstract—The reduction of 1-aryl-4-chloro-1*H*-imidazole-5-carbaldehydes with sodium tetrahydridoborate gave 1-aryl-4-chloro-1*H*-imidazol-5-ylmethanols which were converted into 5-chloromethyl and 5-fluoromethyl derivatives. 1-Aryl-4-chloro-5-chloromethyl-1*H*-imidazoles reacted with sodium azide, secondary amines, thiols, and triphenylphosphine to produce the corresponding products of chlorine replacement in the 5-chloromethyl group.

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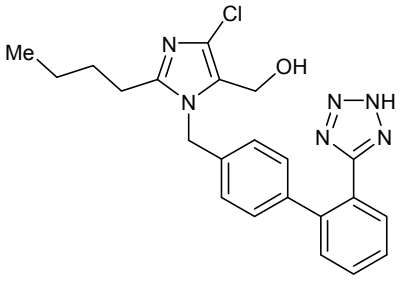
Extensive development of the chemistry of polyfunctional imidazoles during the past two decades has been determined to some extent by the discovery of nonpeptide angiotensine II receptor blockers among 2-butyl-4-chloroimidazoles with a functionalized methyl group in the 5-position [2–6]. These studies led to the creation of Losartan, a highly efficient drug for the treatment of arterial hypertension [7, 8].

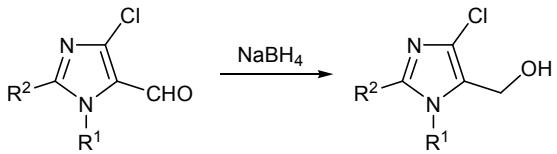


Losartan

However, simpler representatives of 4-chloro-5-(X-methyl)imidazoles, in particular those having no substituent in the 2-position or chlorine-substituted, as well as those containing simple aromatic substituents on N^1, still remain unknown, though such compounds may be versatile building blocks convenient for synthetic purposes, e.g., for the design of biologically active compounds. Of specific interest are new 5-[hydroxy(chloro)methyl]imidazoles which are the subjects of the present study.

1-Benzyl- and 1-(diphenylmethyl)-4-chloro-5-(hydroxymethyl)imidazoles are generally synthesized by benzylation [3, 5, 9] or diphenylmethylation [4, 6] of the corresponding 1-unsubstituted imidazoles. Arylation of N^1H imidazoles was carried out only with the use of 1-fluoro-4-nitrobenzene [10, 11], and this reaction has not been further developed. We now propose to synthesize 1-aryl-5-(hydroxymethyl)imidazoles by reduction of previously prepared 1-aryl-4-chloro-1*H*-imidazole-5-carbaldehydes **Ia**–**Ih** [12, 13] with sodium tetrahydridoborate in boiling ethanol. In this way, 5-hydroxymethyl derivatives **IIa**–**IIh** were obtained in high yield (Scheme 1).

Scheme 1.



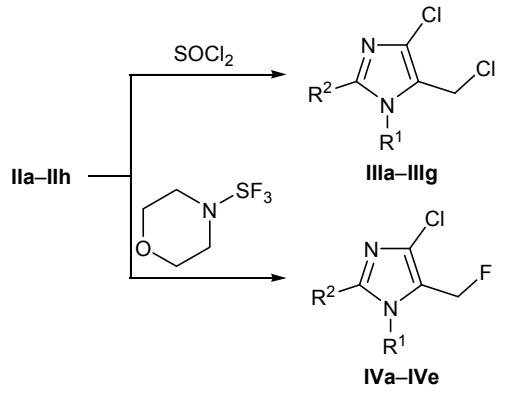
Ia–Ih **IIa–IIh**

R^2 = H, R^1 = Ph (**a**), 3-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**), 4-ClC_6H_4 (**d**), 4-MeC_6H_4 (**e**); R^2 = Cl, R^1 = Ph (**f**), 4-FC_6H_4 (**g**), 4-MeC_6H_4 (**h**).

* For communication VI, see [1].

The hydroxy group in **II** was successfully replaced by halogen. By heating alcohols **IIa** and **IIc**–**IIh** with excess thionyl chloride in boiling toluene we obtained 72–78% of 5-chloromethyl derivatives **IIIa**–**IIIg**. Treatment of imidazoles **IIa**, **IIb**, **IId**, **IIg**, and **IIh** with 4-(trifluoro-λ^4-sulfanyl)morpholine [14] afforded 5-fluoromethyl derivatives **IVa**–**IVe** (Scheme 2) whose structural analogs are selective CB_1 cannabinoid receptor antagonists [15].

Scheme 2.



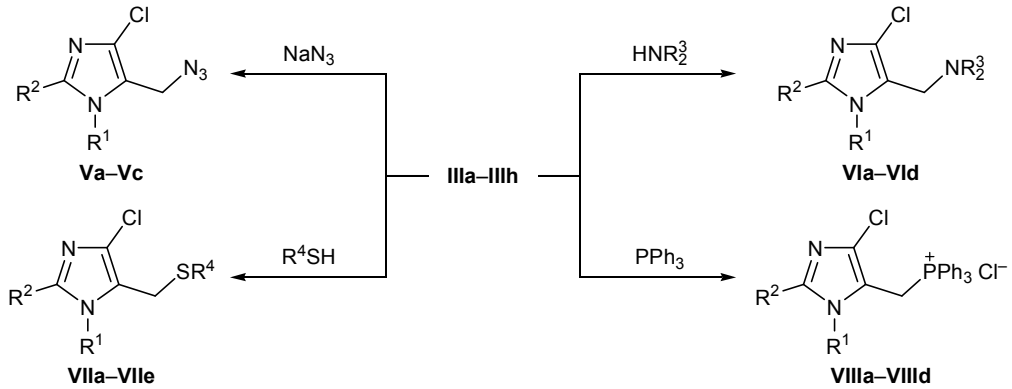
III, R^2 = H, R^1 = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-Me-C_6H_4 (**d**); R^2 = Cl, R^1 = Ph (**e**), 4-FC_6H_4 (**f**), 4-MeC_6H_4 (**g**); **IV**, R^2 = H, R^1 = Ph (**a**), 3-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**); R^2 = Cl, R^1 = 4-FC_6H_4 (**d**), 4-MeC_6H_4 (**e**).

Imidazoles **III** are polyfunctional electrophilic systems possessing two (**IIIa**–**IIId**) or three (**IIIe**–**IIIg**) reaction centers. Study of their behavior toward various nitrogen-, sulfur-, and phosphorus-centered nucleophiles showed that these transformations selectively involved only the chloromethyl group. Compounds **IIIc**, **IIIe**, and **IIIf** reacted with excess sodium azide in DMF at room temperature to afford 5-(azidomethyl)imidazoles **Va**–**Vc**. The reaction of 5-(chloromethyl)imidazoles **IIIa**, **IIIc**, **IIIe**, and **IIIh** with excess morpholine, piperidine, and dimethylamine at room temperature or on heating in acetonitrile gave 5-aminomethyl derivatives **VIa**–**VId**. Sulfides **VIIa**–**VIIe** were obtained by reaction of imidazoles **IIIb**–**IIIe** and **IIIg** with 3 equiv of 4-chlorobenzenethiol, 4-hydroxy-6-methylpyrimidine-2(1*H*)-thione, and 1,3-benzothiazole-2(3*H*)-thione at 90°C in DMF. The alkylation of triphenylphosphine with 5-(chloromethyl)imidazoles **IIIa**, **IIIc**, **IIIe**, and **IIIf** in boiling benzene resulted in the formation of phosphonium salts **VIIIa**–**VIIId** (Scheme 3).

The structure of imidazoles **V**–**VIII** was confirmed by the chemical shifts of the 5-CH_2 protons in their ^{1}H NMR spectra. The corresponding protons in initial chloromethyl derivatives **III** resonated at δ 4.34–4.49 ppm. Replacement of the chlorine atom in the chloromethyl group by azido- and sulfanyl groups with similar electron-acceptor power insignificantly changed the position of the 5-CH_2 signals. Electron-donating amino groups in **VIa**–**VId** induced upfield shift of the methylene proton signal (δ 3.16–3.28 ppm), whereas downfield shift to δ 4.98–5.25 ppm was observed for compounds **VIIIa**–**VIIId** where the methylene group was attached to acceptor phosphonium moiety.

Comparison of the results obtained in the reactions of 2,4-dichloro-5-(chloromethyl)imidazoles **IIIe**, **IIIf**, and **IIIh** with *N*- and *S*-nucleophiles with our previous data [13] on analogous reactions of 2,4-dichloroimidazole-5-carbaldehydes shows that the substituent

Scheme 3.



V, R^2 = H, R^1 = 4-ClC_6H_4 (**a**); R^2 = Cl, R^1 = Ph (**b**), 4-FC_6H_4 (**c**); **VI**, R^2 = H: R^1 = Ph, R^3_2N = morpholin-4-yl (**a**); R^1 = 4-ClC_6H_4, R^3_2N = piperidin-1-yl (**b**); R^1 = 4-MeC_6H_4, R^3 = Me (**c**); R^2 = Cl, R^1 = Ph, R^3 = Me (**d**); **VII**, R^2 = H, R^1 = 4-MeC_6H_4, R^4 = 4-ClC_6H_4 (**a**); R^1 = 4-ClC_6H_4, R^4 = 4-methyl-6-hydroxypyrimidin-2-yl (**b**); R^1 = 4-FC_6H_4, R^4 = 1,3-benzothiazol-2-yl (**c**); R^2 = Cl: R^1 = Ph, R^4 = 4-ClC_6H_4 (**d**); R^1 = 4-MeC_6H_4, R^4 = 1,3-benzothiazol-2-yl (**e**); VIII, R^2 = H, R^1 = Ph (a), 4-ClC_6H_4 (**b**); R^2 = Cl, R^1 = Ph (**c**), 4-FC_6H_4 (**d**).

in position *5* of the imidazole ring deactivates chlorine atoms in positions *2* and *4* so that they are not replaced by *N*- or *S*-nucleophiles.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H NMR spectra of **IIIa–IIIg** were recorded from solutions in $CDCl_3$, and of the other compounds, in DMSO-d_6, and the ^{13}C NMR spectra were recorded from solutions in DMSO-d_6 on a Bruker Avance DRX-500 instrument at 500.13 and 127.75 MHz, respectively, using tetramethylsilane as internal reference. The ^{19}F NMR spectra (DMSO-d_6) were measured on a Varian Gemini spectrometer at 188.14 MHz using CCl_3F as internal reference. The mass spectra were obtained on an Agilent 1100/DAD/HSD/VLG119562 instrument.

(4-Chloro-1*H*-imidazol-5-yl)methanols IIa–IIh (*general procedure*). Sodium tetrahydridoborate, 0.19 g (5 mmol), was added to a solution of 10 mmol of imidazole-5-carbaldehyde **Ia–Ih** in 20 ml of ethanol, the mixture was heated to the boiling point, and 100 ml of water was added. The precipitate was filtered off, washed with water, dried, and recrystallized from 80% aqueous ethanol.

(4-Chloro-1-phenyl-1*H*-imidazol-5-yl)methanol (IIa). Yield 85%, mp 158–160°C. IR spectrum: ν 3350 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 4.36 d (2H, CH_2, J = 5.0 Hz), 5.32 t (1H, OH, J = 5.0 Hz), 7.51–7.63 m (5H, H_{arom}), 7.93 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 50.67 (CH_2), 124.85 (C^2), 126.45 (C^5); 128.40, 128.56, 129.56, 135.87 (C_{arom}); 135.93 (C^4). Found, %: C 57.78; H 4.46; N 13.55. $[M + 1]^+$ 209. $C_{10}H_9ClN_2O$. Calculated, %: C 57.57; H 4.35; N 13.43. M 208.65.

[4-Chloro-1-(3-methylphenyl)-1*H*-imidazol-5-yl]-methanol (IIb). Yield 80%, mp 100–102°C. IR spectrum: ν 3340 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 4.36 d (2H, CH_2, J = 5.0 Hz), 5.30 t (1H, OH, J = 5.0 Hz), 7.31–7.46 m (4H, H_{arom}), 7.90 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 20.84 (CH_3), 50.66 (CH_2); 121.89, 125.30, 126.43, 129.10, 129.24, 135.87, 139.25 (C_{arom}, C^2); 128.52 (C^5), 135.82 (C^4). Found, %: C 59.08; H 4.90; N 12.70. $[M + 1]^+$ 223. $C_{11}H_{11}ClN_2O$. Calculated, %: C 59.33; H 4.98; N 12.58. M 222.68.

[4-Chloro-1-(4-fluorophenyl)-1*H*-imidazol-5-yl]-methanol (IIc). Yield 87%, mp 125–127°C. IR spectrum: ν 3340 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 4.32 d (2H, CH_2, J = 4.8 Hz), 5.30 t (1H, OH, J = 4.8 Hz), 7.40 m (2H, H_{arom}), 7.67 m (2H, H_{arom}), 7.91 s (1H, 2-H). Found, %: C 53.27; H 3.69; N 12.53. $[M + 1]^+$ 227. $C_{10}H_8ClFN_2O$. Calculated, %: C 53.00; H 3.56; N 12.36. M 226.64.

[4-Chloro-1-(4-chlorophenyl)-1*H*-imidazol-5-yl]-methanol (IId). Yield 82%, mp 132–134°C. IR spectrum: ν 3345 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 4.36 d (2H, CH_2, J = 5.0 Hz), 5.35 t (1H, OH, J = 5.0 Hz), 7.65 d (2H, H_{arom}, J = 8.0 Hz), 7.69 d (2H, H_{arom}, J = 8.0 Hz), 7.96 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 50.58 (CH_2), 126.39 (C^2), 126.64 (C^5); 128.55, 129.44, 130.03, 134.64 (C_{arom}); 136.06 (C^4). Found, %: C 49.65; H 3.43; N 11.70. $[M + 1]^+$ 244. $C_{10}H_8Cl_2N_2O$. Calculated, %: C 49.41; H 3.32; N 11.52. M 243.09.

[4-Chloro-1-(4-methylphenyl)-1*H*-imidazol-5-yl]methanol (IIe). Yield 88%, mp 154–156°C. IR spectrum: ν 3340 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 4.33 d (2H, CH_2, J = 5.0 Hz), 5.35 t (1H, OH, J = 5.0 Hz), 7.35 d (2H, H_{arom}, J = 7.8 Hz), 7.46 d (2H, H_{arom}, J = 7.8 Hz), 7.84 s (1H, 2-H). Found, %: C 59.08; H 4.90; N 12.70. $[M + 1]^+$ 223. $C_{11}H_{11}ClN_2O$. Calculated, %: C 59.33; H 4.98; N 12.58. M 222.68.

(2,4-Dichloro-1-phenyl-1*H*-imidazol-5-yl)methanol (IIf). Yield 90%, mp 122–124°C. IR spectrum: ν 3345 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 4.20 d (2H, CH_2, J = 5.2 Hz), 5.14 t (1H, OH, J = 5.2 Hz), 7.49–7.61 m (5H, H_{arom}). Found, %: C 49.69; H 3.22; N 11.35. $[M + 1]^+$ 244. $C_{10}H_8Cl_2N_2O$. Calculated, %: C 49.41; H 3.32; N 11.52. M 243.09.

[2,4-Dichloro-1-(4-fluorophenyl)-1*H*-imidazol-5-yl]methanol (IIg). Yield 80%, mp 135–137°C. IR spectrum: ν 3345 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 4.19 d (2H, CH_2, J = 5.2 Hz), 5.16 t (1H, OH, J = 5.2 Hz), 7.38–7.71 m (4H, H_{arom}). Found, %: C 46.26; H 2.58; N 10.55. $[M + 1]^+$ 262. $C_{10}H_7Cl_2FN_2O$. Calculated, %: C 46.00; H 2.70; N 10.73. M 261.08.

[2,4-Dichloro-1-(4-methylphenyl)-1*H*-imidazol-5-yl]methanol (IIh). Yield 89%, mp 128–130°C. IR spectrum: ν 3340 cm^{-1} (OH). ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 4.18 d (2H, CH_2, J = 5.0 Hz), 5.11 t (1H, OH, J = 5.0 Hz), 7.36 d (2H, H_{arom}, J = 7.8 Hz), 7.41 d (2H, H_{arom}, J = 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 20.40 (3H, CH_3), 51.10 (CH_2), 125.89 (C^5); 127.32, 129.50, 129.63, 139.53 (C_{arom}); 130.14 (C^2), 131.41 (C^4). Found, %: C 51.12; H 4.03; N 11.01. $[M + 1]^+$ 258. $C_{11}H_{10}Cl_2N_2O$. Calculated, %: C 51.39; H 3.92; N 10.90. M 257.12.

1-Aryl-4-chloro-5-chloromethyl-1*H*-imidazoles IIIa–IIIg (*general procedure*). A solution of 1.79 g (15 mmol) of thionyl chloride was added to a solution of 5 mmol of alcohol **IIa** or **IIc–IIh** in 20 ml of anhydrous toluene, and the mixture was heated for 2 h under reflux. The solvent was evaporated, and the residue was washed with hexane and dried under reduced pressure (water-jet pump).

4-Chloro-5-chloromethyl-1-phenyl-1*H*-imidazole (IIIa). Yield 72%, mp 60–62°C. ^{1}H NMR spectrum, δ, ppm: 4.49 s (2H, CH_2), 7.24–7.52 m (5H, H_{arom}), 7.59 s (1H, 2-H). Found, %: C 52.68; H 3.46; N 12.46. $C_{10}H_8Cl_2N_2$. Calculated, %: C 52.89; H 3.55; N 12.34.

4-Chloro-5-chloromethyl-1-(4-fluorophenyl)-1*H*-imidazole (IIIb). Yield 75 %, mp 65–67°C. ^{1}H NMR spectrum, δ, ppm: 4.48 s (2H, CH_2), 7.19–7.43 m (4H, H_{arom}), 7.57 s (1H, 2-H). Found, %: C 49.25; H 2.62; N 11.22. $C_{10}H_7Cl_2FN_2$. Calculated, %: C 49.01; H 2.88; N 11.43.

4-Chloro-5-chloromethyl-1-(4-chlorophenyl)-1*H*-imidazole (IIIc). Yield 76%, mp 98–100°C. ^{1}H NMR spectrum, δ, ppm: 4.48 s (2H, CH_2), 7.24–7.54 m (5H, H_{arom}, 2-H). Found, %: C 45.71; H 2.55; N 10.85. $C_{10}H_7Cl_3N_2$. Calculated, %: C 45.92; H 2.70; N 10.71.

4-Chloro-5-(chloromethyl)-1-(4-methylphenyl)-1*H*-imidazole (IIId). Yield 78%, mp 79–80°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 4.48 s (2H, CH_2), 7.29 d (2H, H_{arom}, J = 8.2 Hz), 7.51 d (2H, H_{arom}, J = 8.2 Hz), 7.59 s (1H, 2-H). Found, %: C 54.98; H 4.31; N 11.80. $C_{11}H_{10}Cl_2N_2$. Calculated, %: C 54.79; H 4.18; N 11.62.

2,4-Dichloro-5-chloromethyl-1-phenyl-1*H*-imidazole (IIIe). Yield 75%, mp 96–97°C. ^{1}H NMR spectrum, δ, ppm: 4.36 s (2H, CH_2), 7.24–7.55 m (5H, H_{arom}). Found, %: C 46.11; H 2.57; N 10.87. $C_{10}H_7Cl_3N_2$. Calculated, %: C 45.92; H 2.70; N 10.71.

2,4-Dichloro-5-chloromethyl-1-(4-fluorophenyl)-1*H*-imidazole (IIIf). Yield 77%, mp 94–95°C. ^{1}H NMR spectrum, δ, ppm: 4.34 s (2H, CH_2), 7.28 m (2H, H_{arom}), 7.52 m (2H, H_{arom}). Found, %: C 43.20; H 2.27; N 10.19. $C_{10}H_6Cl_3FN_2$. Calculated, %: C 42.97; H 2.16; N 10.02.

2,4-Dichloro-5-chloromethyl-1-(4-methylphenyl)-1*H*-imidazole (IIIg). Yield 78%, viscous oily substance. ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 4.37 s (2H, CH_2), 7.23 d (2H, H_{arom}, J = 8.4 Hz), 7.55 d (2H, H_{arom}, J = 8.4 Hz). Found, %: C 48.20; H 3.40; N 10.38. $C_{11}H_9Cl_3N_2$. Calculated, %: C 47.95; H 3.29; N 10.17.

1-Aryl-4-chloro-5-fluoromethyl-1*H*-imidazoles IVa–IVe (*general procedure*). A solution of 5 mmol of hydroxymethylimidazole **IIa**, **IIb**, **IId**, **IIg**, or **IIh** in 50 ml of methylene chloride was cooled to –50°C, 0.5 ml of 4-(trifluoro-λ^4-sulfanyl)morpholine was slowly added under stirring, and the mixture was allowed to warm up to room temperature, stirred for 12 h, treated with 30 ml of a saturated solution of sodium hydrogen carbonate, and stirred for 0.5 h more. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate, and filtered, the filtrate was evaporated, and the residue was purified by chromatography on silica gel using hexane–ethyl acetate (8:2) as eluent.

4-Chloro-5-fluoromethyl-1-phenyl-1*H*-imidazole (IVa). Yield 55%, mp 139–140°C. ^{1}H NMR spectrum, δ, ppm: 5.23 d (2H, CH_2, J_{HF} = 50.0 Hz), 7.49–7.64 m (6H, H_{arom}, 2-H). ^{19}F NMR spectrum: δ_F –196.48 ppm, t (FCH_2, J = 50.8 Hz). Found, %: C 57.19; H 3.70; N 13.44. $[M + 1]^+$ 211. $C_{10}H_8ClFN_2$. Calculated, %: C 57.02; H 3.83; N 13.30. M 210.64.

4-Chloro-5-fluoromethyl-1-(3-methylphenyl)-1*H*-imidazole (IVb). Yield 50%, mp 81–82°C. ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 5.23 d (2H, CH_2, J_{HF} = 50.0 Hz), 7.32–7.64 m (5H, H_{arom}, 2-H). ^{19}F NMR spectrum: δ_F –196.50 ppm, t (FCH_2, J = 50.6 Hz). Found, %: C 59.01; H 4.57; N 12.60. $[M + 1]^+$ 225. $C_{11}H_{10}ClFN_2$. Calculated, %: C 58.81; H 4.49; N 12.47. M 224.67.

4-Chloro-1-(4-chlorophenyl)-5-fluoromethyl-1*H*-imidazole (IVc). Yield 54%, mp 77–78°C. ^{1}H NMR spectrum, δ, ppm: 5.22 d (2H, CH_2, J_{HF} = 50.0 Hz), 7.38 d (2H, H_{arom}, J = 8.2 Hz), 7.51 d (2H, H_{arom}, J = 8.2 Hz), 7.60 s (1H, 2-H). ^{19}F NMR spectrum: δ_F –196.26 ppm, t (FCH_2, J = 50.2 Hz). Found, %: C 49.27; H 3.00; N 11.58. $[M + 1]^+$ 246. $C_{10}H_7Cl_2FN_2$. Calculated, %: C 49.01; H 2.88; N 11.43. M 245.09.

2,4-Dichloro-5-fluoromethyl-1-(4-fluorophenyl)-1*H*-imidazole (IVd). Yield 49%, viscous oily substance. ^{1}H NMR spectrum, δ, ppm: 5.07 d (2H, CH_2, J_{HF} = 50.0 Hz), 7.25–7.40 m (4H, H_{arom}). ^{19}F NMR spectrum: δ_F –197.35 ppm, t (FCH_2, J = 50.4 Hz). Found, %: C 45.40; H 2.45; N 10.50. $[M + 1]^+$ 264. $C_{10}H_6Cl_2F_2N_2$. Calculated, %: C 45.66; H 2.30; N 10.65. M 263.08.

2,4-Dichloro-5-fluoromethyl-1-(4-methylphenyl)-1*H*-imidazole (IVe). Yield 50%, viscous oily substance. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 5.12 d (2H, CH_2, J_{HF} = 50.0 Hz), 7.21 d (2H, H_{arom}, J = 7.8 Hz), 7.33 d (2H, H_{arom}, J = 7.8 Hz). ^{19}F NMR spec-

trum: δ_F –198.6 ppm, t (FCH_2, J = 49.8 Hz). Found, %: C 51.25; H 3.40; N 10.65. $[M + 1]^+$ 260. $C_{11}H_9Cl_2FN_2$. Calculated, %: C 50.99; H 3.50; N 10.81. M 259.11.

5-Azidomethyl-1-aryl-4-chloro-1*H*-imidazoles Va–Vc (*general procedure*). Sodium azide, 0.49 g (7.5 mmol), was added to a solution of 2.5 mmol of 5-(chloromethyl)imidazole **IIIc**, **IIIe**, or **IIIf** in 20 ml of anhydrous DMF. The mixture was stirred for 12 h at room temperature and poured into 100 ml of water, and the precipitate was filtered off, dried, and recrystallized from 80% aqueous ethanol.

5-Azidomethyl-4-chloro-1-(4-chlorophenyl)-1*H*-imidazole (Va). Yield 85%, mp 88–89°C. IR spectrum: ν 2160 cm^{-1} (N_3). ^1H NMR spectrum, δ, ppm: 4.47 s (2H, CH_2), 7.58 d (2H, H_{arom}, J = 8.0 Hz), 7.68 d (2H, H_{arom}, J = 8.0 Hz), 8.37 s (1H, 2-H). Found, %: C 44.59; H 2.50; N 26.34. $[M + 1]^+$ 269. $C_{10}H_7Cl_2N_5$. Calculated, %: C 44.80; H 2.63; N 26.12. M 268.11.

5-Azidomethyl-2,4-dichloro-1-phenyl-1*H*-imidazole (Vb). Yield 88%, mp 77–78°C. IR spectrum: ν 2160 cm^{-1} (N_3). ^1H NMR spectrum, δ, ppm: 4.30 s (2H, CH_2), 7.53–7.64 m (5H, H_{arom}). Found, %: C 45.01; H 2.51; N 26.00. $[M + 1]^+$ 269. $C_{10}H_7Cl_2N_5$. Calculated, %: C 44.80; H 2.63; N 26.12. M 268.11.

5-Azidomethyl-2,4-dichloro-1-(4-fluorophenyl)-1*H*-imidazole (Vc). Yield 84%, mp 64°C. IR spectrum: ν 2165 cm^{-1} (N_3). ^1H NMR spectrum, δ, ppm: 4.31 s (2H, CH_2), 7.41–7.67 m (4H, H_{arom}). Found, %: C 42.11; H 2.23; N 24.65. $[M + 1]^+$ 286. $C_{10}H_6Cl_2FN_5$. Calculated, %: C 41.98; H 2.11; N 24.48. M 285.10.

(4-Chloro-1-phenyl-1*H*-imidazol-5-ylmethyl)-cycloalkylamines VIa and VIb (*general procedure*). 5-(Chloromethyl)imidazole **IIIa** or **IIIc**, 2.5 mmol, was dissolved in 20 ml of anhydrous acetonitrile, 0.44 g (5 mmol) of morpholine or 0.43 g (5 mmol) of piperidine was added, and the mixture was heated for 2 h under reflux. The mixture was evaporated, the solid residue was dissolved in 10 ml of 30% aqueous HCl, the solution was filtered, 10 ml of 5% aqueous sodium hydroxide was added to the filtrate, and the precipitate was filtered off, washed with water, and recrystallized from 80% aqueous ethanol.

4-(4-Chloro-1-phenyl-1*H*-imidazol-5-ylmethyl)-morpholine (VIa). Yield 85%, mp 93–94°C. ^1H NMR spectrum, δ, ppm: 2.28 br.s (4H, CH_2), 3.19 s (2H, CH_2), 3.48 br.s (4H, CH_2), 7.49–7.70 m (5H, H_{arom}), 7.94 s (1H, 2-H). Found, %: C 60.30; H 5.93; N 15.31. $[M + 1]^+$ 278. $C_{14}H_{16}ClN_3O$. Calculated, %: C 60.54; H 5.81; N 15.13. M 277.76.

1-[4-Chloro-1-(4-chlorophenyl)-1*H*-imidazol-5-ylmethyl]piperidine (VIb). Yield 75%, mp 115–117°C. ^1H NMR spectrum, δ, ppm: 1.34–1.40 m (6H, CH_2), 2.26 s (4H, CH_2), 3.28 s (2H, CH_2), 7.61 d (2H, H_{arom}, J = 7.2 Hz) 7.75 d (2H, H_{arom}, J = 7.2 Hz), 7.94 s (1H, 2-H). Found, %: C 58.32; H 5.65; N 13.62. $[M + 1]^+$ 311. $C_{15}H_{17}Cl_2N_3O$. Calculated, %: C 58.08; H 5.52; N 13.54. M 310.23.

(1-Aryl-4-chloro-1*H*-imidazol-5-yl)-*N*,*N*-dimethylmethanamines VIc and VId (*general procedure*). 5-(Chloromethyl)imidazole **IIId** or **IIIe**, 2.5 mmol, was added to 10 ml of a 30% solution of dimethylamine in ethanol, and the mixture was stirred for 10 h at room temperature. The mixture was poured into 50 ml of water, 10 ml of 5% aqueous sodium hydroxide was added, and the precipitate was filtered off, dried, and recrystallized from 80% aqueous ethanol.

(4-Chloro-4-methylphenyl-1*H*-imidazol-5-yl)-*N*,*N*-dimethylmethanamine (VIc). Yield 72%, mp 66–67°C. ^1H NMR spectrum, δ, ppm: 2.08 s (6H, CH_3), 2.38 s (3H, CH_3), 3.26 s (2H, CH_2), 7.34 d (2H, H_{arom}, J = 7.6 Hz), 7.53 d (2H, H_{arom}, J = 7.6 Hz), 7.28 s (1H, 2-H). Found, %: C 62.74; H 6.60; N 16.97. $[M + 1]^+$ 250. $C_{13}H_{16}ClN_3$. Calculated, %: C 62.52; H 6.46; N 16.83. M 249.75.

(2,4-Dichloro-1-phenyl-1*H*-imidazol-5-yl)-*N*,*N*-dimethylmethanamine (VId). Yield 88%, mp 73–74°C. ^1H NMR spectrum, δ, ppm: 1.97 s (6H, CH_3), 3.16 s (2H, CH_2), 7.50–7.61 m (5H, H_{arom}). Found, %: C 53.54; H 4.93; N 15.68. $[M + 1]^+$ 271. $C_{12}H_{13}Cl_2N_3$. Calculated, %: C 53.35; H 4.85; N 15.55. M 270.16.

1-Aryl-4-chloro-5-(X-sulfanylmethyl)-1*H*-imidazoles VIIa–VIIe (*general procedure*). 5-(Chloromethyl)imidazole **IIIb**–**IIIe** or **IIIg**, 2.5 mmol, was dissolved in 10 ml of DMF, 0.35 g (2.5 mmol) of potassium carbonate and 0.36 g (2.5 mmol) of 4-chlorobenzenethiol [or 2.5 mmol of 4-hydroxy-6-methylpyrimidine-2(1*H*)-thione or 1,3-benzothiazole-2(3*H*)-thione] (in the reactions with **IIIb**–**IIId**) or 1.05 g (7.5 mmol) of potassium carbonate and 1.08 g (7.5 mmol) of 4-chlorobenzenethiol [or 7.5 mmol of 4-hydroxy-6-methylpyrimidine-2(1*H*)-thione or 1,3-benzothiazole-2(3*H*)-thione] (in the reactions with **IIIe** and **IIIg**) were added, and the mixture was stirred for 2 h at 90°C, cooled, and poured into water. The precipitate was filtered off, washed with 10 ml of 20% sodium hydrogen carbonate and 20 ml of water, dried, and recrystallized from 80% aqueous ethanol.

4-Chloro-5-[(4-chlorophenyl)sulfanylmethyl]-1-(4-methylphenyl)-1*H*-imidazole (VIIa). Yield 80%,

mp 76–77°C. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 4.14 s (2H, CH_2), 7.22 d (2H, H_{arom}, J = 7.6 Hz), 7.29 d (2H, H_{arom}, J = 7.6 Hz), 7.37 s (4H, H_{arom}), 7.79 s (1H, 2-H). Found, %: C 58.59; H 4.13; N 8.20. $[M + 1]^+$ 350. $C_{17}H_{14}Cl_2N_2S$. Calculated, %: C 58.46; H 4.04; N 8.02. M 349.28.

2-{[4-Chloro-1-(4-chlorophenyl)-1*H*-imidazol-5-ylmethyl]sulfanyl}-6-methylpyrimidin-4-ol (VIIb). Yield 82%, mp 215–217°C. ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, CH_3), 4.50 s (2H, CH_2), 5.97 s (1H, 5′-H), 7.56 d (2H, H_{arom}, J = 7.8 Hz), 7.61 d (2H, H_{arom}, J = 7.8 Hz), 7.97 s (1H, 2-H), 12.38 br.s (1H, OH). Found, %: C 49.27; H 3.40; N 15.10. $[M + 1]^+$ 367. $C_{15}H_{12}Cl_2N_4OS$. Calculated, %: C 49.06; H 3.29; N 15.26. M 367.26.

2-{[4-Chloro-1-(4-fluorophenyl)-1*H*-imidazol-5-ylmethyl]sulfanyl}-1,3-benzothiazole (VIIc). Yield 73%, mp 115–117°C. ^{1}H NMR spectrum, δ, ppm: 4.62 s (2H, CH_2), 7.33–7.62 m (6H, H_{arom}), 7.78 d (1H, H_{arom}, J = 8.4 Hz), 7.97 s (1H, 2-H), 8.00 d (1H, H_{arom}, J = 8.4 Hz). Found, %: C 54.52; H 3.07; N 11.32. $[M + 1]^+$ 376. $C_{17}H_{11}ClFN_3S_2$. Calculated, %: C 54.32; H 2.95; N 11.18. M 375.88.

2,4-Dichloro-5-[(4-chlorophenylsulfanyl)-methyl]-1-phenyl-1*H*-imidazole (VIId). Yield 70%, mp 70–71°C. ^{1}H NMR spectrum, δ, ppm: 3.99 s (2H, CH_2), 7.24 d (2H, H_{arom}, J = 8.4 Hz), 7.32 d (2H_{arom}, J = 8.4 Hz), 7.49–7.58 m (5H, H_{arom}). Found, %: C 52.20; H 3.13; N 7.42. $[M + 1]^+$ 370. $C_{16}H_{11}Cl_3N_2S$. Calculated, %: C 51.98; H 3.00; N 7.58. M 369.70.

2-{[2,4-Dichloro-1-(4-methylphenyl)-1*H*-imidazol-5-ylmethyl]sulfanyl}-1,3-benzothiazole (VIIe). Yield 73%, mp 108–109°C. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 4.54 s (2H, CH_2), 7.25 d (2H, H_{arom}, J = 8.1 Hz), 7.35–7.41 m (3H, H_{arom}), 7.47 t (1H, H_{arom}, J = 7.2 Hz), 7.78 d (2H, H_{arom}, J = 7.8 Hz), 7.96 d (2H, H_{arom}, J = 7.8 Hz). Found, %: C 54.52; H 3.07; N 11.32. $[M + 1]^+$ 407. $C_{18}H_{13}Cl_2N_3S_2$. Calculated, %: C 53.20; H 3.22; N 10.34. M 406.36.

(1-Aryl-4-chloro-1*H*-imidazol-5-ylmethyl)triphenylphosphonium chlorides VIIIa–VIIId (*general procedure***).** Triphenylphosphine, 0.66 g (2.5 mmol), was added to a solution of 2.5 mmol of 5-(chloromethyl)imidazole **IIIa**, **IIIc**, **IIIe**, or **IIIf** in 10 ml of anhydrous benzene, the mixture was heated for 2 h under reflux, and the precipitate was filtered off, washed with hexane, and dried.

(4-Chloro-1-phenyl-1*H*-imidazol-5-ylmethyl)triphenylphosphonium chloride (VIIIa**).** Yield 88%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 5.13 d (2H, CH_2, J_{HP} = 12.8 Hz), 7.13–7.94 m (21H, H_{arom}, 2-H). Found, %: C 68.52; H 4.85; N 5.88. $[M + 1]^+$ 490. $C_{28}H_{23}Cl_2N_2P$. Calculated, %: C 68.72; H 4.74; N 5.72. M 489.39.

[4-Chloro-1-(4-chlorophenyl)-1*H*-imidazol-5-ylmethyl]triphenylphosphonium chloride (VIIIb). Yield 80%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 5.12 d (2H, CH_2, J_{HP} = 12.8 Hz), 7.24–7.95 m (20H, H_{arom}, 2-H). Found, %: C 64.01; H 4.09; N 5.47. $[M + 1]^+$ 524. $C_{28}H_{22}Cl_3N_2P$. Calculated, %: C 64.20; H 4.23; N 5.35. M 523.83.

(2,4-Dichloro-1-phenyl-1*H*-imidazol-5-ylmethyl)-triphenylphosphonium chloride (VIIIc). Yield 82%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 4.98 d (2H, CH_2, J_{HP} = 12.8 Hz), 6.98 d (2H, H_{arom}, J = 8.0 Hz), 7.09 d (2H, H_{arom}, J = 8.0 Hz), 7.42–7.89 m (16H, H_{arom}). Found, %: C 64.42; H 4.34; N 5.50. $[M + 1]^+$ 524. $C_{28}H_{22}Cl_3N_2P$. Calculated, %: C 64.20; H 4.23; N 5.35. M 523.83.

[2,4-Dichloro-1-(4-fluorophenyl)-1*H*-imidazol-5-ylmethyl]triphenylphosphonium chloride (VIIId). Yield 85%, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 5.25 d (2H, CH_2, J_{HP} = 12.4 Hz), 7.15–7.25 m (4H, H_{arom}), 7.46–7.92 m (5H, H_{arom}). Found, %: C 62.30; H 4.04; N 5.04. $[M + 1]^+$ 542. $C_{28}H_{21}Cl_3FN_2P$. Calculated, %: C 62.07; H 3.91; N 5.17. M 541.82.

REFERENCES

1. Chornous, V.A., Grozav, A.N., and Vovk, M.V., *Russ. J. Org. Chem*., 2012, vol. 48, p. 705.
2. Duncia, J.V., Chiu, A.T., Carini, D.J., Gregory, G.B., Johnson, A.L., Price, W.A., Wells, G.J., Wong, P.C., Calabrese, J.C., and Timmermans, P.B.M.W.H., *J. Med. Chem*., 1990, vol. 33, p. 1312.
3. Carini, D.J., Duncia, J.V., Johnson, A.L., Chiu, A.T., Price, W.A., Wong, P.C., and Timmermans, P.B.M.W.H., *J. Med. Chem*., 1990, vol. 33, p. 1330.
4. Carini, D.J., Duncia, J.V., Aldrich, P.E., Chiu, A.T., Johnson, A.L., Pierce, M.E., Price, W.A., Santella, J.B., Wells, G.J., Wexler, R.R., Wong, P.C., Yoo, S.-E., and Timmermans, P.B.M.W.H., *J. Med. Chem*., 1991, vol. 34, p. 2525.
5. Sircar, I., Winters, R.T., Quin, J., Lu, G.H., Major, T.C., and Panek, R.L., *J. Med. Chem*., 1993, vol. 36, p. 1735.
6. Salimbeni, A., Canevotti, R., Paleari, F., Bonaccorsi, F., Renzetti, A.R., Belvisi, L., Bravi, G., and Scolastico, C., *J. Med. Chem*., 1994, vol. 37, p. 3928.
7. Duncia, J.V., Carini, D.J., Chiu, A.T., Johnson, A.L., Price, W.A., Wong, P.C., Wexler, R.R., and Timmermans, P.B.M.W.H., *Med. Res. Rev*., 1992, vol. 12, p. 149.

8. Griffiths, G.R., Hauck, M.B., Imwinkelried, R., Kohr, J., Roten, C.A., and Stucky, G.C., *J. Org. Chem*., 1999, vol. 64, p. 8084.
9. Larsen, R.D., King, A.O., Chen, C.Y., Corley, E.G., Foster, B.S., Roberts, F.E., Yang, C., Lieberman, D.R., Reamer, R.A., Tschaen, D.M., Verhoeven, T.R., and Reider, P.J., *J. Org. Chem*., 1994, vol. 59, p. 6391.
10. Carini, D.J., Duncia, J.V., and Wong, P.C.-B., WO Patent no. 9200067, 1992; *Chem. Abstr*., 1992, vol. 116, no. 166252x.
11. Carini, D.J., WO Patent 9200977, 1992; *Chem. Abstr*., 1992, vol. 116, no. 4158m.
12. Chornous, V.A., Bratenko, M.K., and Vovk, M.V., *Russ. J. Org. Chem*., 2009, vol. 45, p. 1210.
13. Chornous, V.A., Grozav, A.N., Rusanov, E.B., Nesterenko, A.M., and Vovk, M.V., *Russ. J. Org. Chem*., 2011, vol. 47, p. 702.
14. Pashinnik, V.E., Martyniuk, E.G., Tabachuk, H.R., Shermolovich, Yu.G., and Yagupolskii, L.M., *Synth. Commun*., 2003, vol. 33, p. 2505.
15. Lange, J.H.M., Stuivenberg, H.H., Cooben, H.K.A.C., Adolfs, T.J.P., MeCreary, A., Keizer, H.G., Wals, H.C., Veerman, W., Borst, A.J.M., Looff, W., Verveer, P.C., and Kruse, C.G., *J. Med. Chem*., 2005, vol. 48, p. 1823.