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Synthesis of 1-(pyrrolidin-2-ylmethyl)-1*H*-azoles and their piperidine-derived homologues

Research Article

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Abstract: A convenient preparation of 1-(pyrrolidin-2-yl)-1*H*-pyrazoles, -imidazoles, and -1*H*-1,2,4-triazoles, 1-(piperidin-2-yl)-1*H*-pyrazoles and -1*H*-1,2,4-triazoles, and 1-(piperidin-3-yl)-1*H*-1,2,4-triazoles by alkylation of azoles (*viz.* pyrazoles, imidazoles, and triazoles) with *N*-Cbz-prolinol mesylate or its analogues and subsequent deprotection is reported. The two-step method allows for synthesis of the title compounds in 16–65% yields. The utility of the procedure has been demonstrated by multigram preparation of a 15-member building block mini-library for the lead-oriented synthesis of compound libraries. These building blocks perfectly fit the definition of low-molecular-weight hydrophilic three-dimensional templates, which leave much room for the lead-oriented synthesis of the compound libraries.

Keywords: *Azoles • Saturated nitrogen heterocycles • Molecular rigidity • Lead-oriented synthesis • Alkylation*

1. Introduction

Contemporary drug discovery relies heavily on the careful choice of chemotypes that can serve as the starting points for the design and synthesis of compound libraries. The so-called lead-likeness methodology for drug design, which relies on a number of concepts such as privileged structures, three-dimensional molecular shape, conformational restriction, and control of physicochemical properties of the potential lead compounds, have received much attention in the chemical literature recently [1–4]. The need for the "lead-oriented synthesis" [5] has guided the efforts of organic chemists towards novel low-molecular-weight hydrophilic three-dimensional scaffolds.

Among the numerous possible ways to design such structures we have turned our attention to the approach shown schematically in Fig. 1: a highly polar aromatic heterocycle is mounted onto a three-dimensional saturated template bearing an easily modifiable functional group (such as amino) [6–9]. The use of this approach is encountered among natural compounds (*e.g.* alkaloids nicotine **1** and anabasine **2**, Fig. 2). Other examples comprise of synthesis of compounds of established biological activity, *e.g*. inhibitors of deacetylases (**3**) [10], tyrosine kinases (**4**) [11], or thrombin-activated fibrinolyse (**5**) [12]. In this work, we have focused on the scaffolds **6** – **11** obtained by linking the azole and pyrrolidine (or piperidine) heterocyclic rings by a single methylene unit (Table 1). Some examples of biologically relevant compounds derived from these templates are given in Fig. 2. Recently, derivatives of **7** have attracted additional attention as enantioselective catalysts [13,14] and chiral ionic liquids [15–19].

2. Experimental procedures

2.1. General

The solvents were purified according to the standard procedures. Compounds **13**, **17**, and **18** were prepared according to the methods reported in the literature [20]. All other starting materials were purchased from Acros, Merck, Fluka, and UkrOrgSyntez. All the chiral starting

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materials were used as racemates. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) or Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

2.2. General procedure for the synthesis of 6–11

To a suspension of NaH (0.12 mol) in DMF (200 mL), compound **14**, **15**, or **16** (0.1 mol) in DMF (100 mL) was added. After the hydrogen evolution was complete, compound **13**, **17**, or **18** was added, and the resulting mixture was heated at 60°C (**14**) or 100°C (**15** or **16**) for 8 h, then cooled and evaporated in vacuo. The residue was quenched with H_2O (1000 mL) and EtOAc (300 mL). The organic phase was separated, and aqueous phase was extracted with EtOAc (2×300 mL). The combined organic extracts were washed with brine (2×400 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography (Hexanes – EtOAc (1 : 1) as an eluent) and then dissolved in MeOH (400 mL). 10% Pd-C (2–3 g) was added, and the mixture was hydrogenated at 1 bar until the reaction was complete (NMR control, usually 1 day). The catalyst was filtered off, the filtrate was evaporated, and the crude product was purified by column chromatography (CH_2Cl_2 – MeOH – Et_3N (9 : 1 : 0.1)) to give **6** – **11** (Table 1). To obtain the final compounds as dihydrochlorides, **6** – **11** (0.05 mol) were taken up in 10% HCl in dioxane (50 mL) and evaporated to dryness.

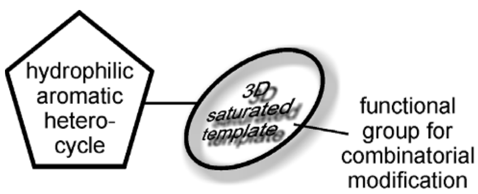


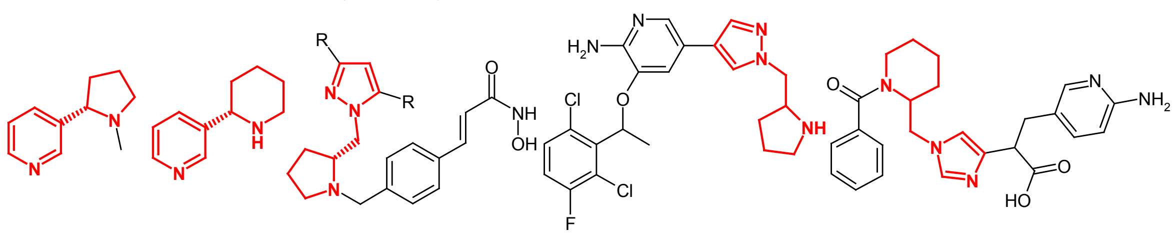
Figure 1. Scaffolds for lead-oriented synthesis By combining saturated and aromatic nitrogen heterocycles.

1-(Pyrrolidin-2-ylmethyl)-1*H*-pyrazole (6a): yield 58 g (44%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), δ 7.47 (s, 1H), 7.42 (s, 1H), 6.20 (s, 1H), 4.15 (dd, J = 13.6 Hz and 4.8 Hz, 1H), 3.99 (dd, J = 13.6 Hz and 7.9 Hz, 1H), 3.49–3.56 (m, 1H), 2.91–2.96 (m, 1H), 2.83–2.89 (m, 1H), 2.14 (s, 1H), 1.79–1.90 (m, 1H), 1.64–1.79 (m, 2H), 1.36–1.44 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 139.5, 129.7, 105.3, 58.6, 57.1, 46.4, 29.0, 25.2. Anal. calcld. for $C_8H_{13}N_3$ C 63.55, H 8.67, N 27.79. Found C 63.94, H 8.30, N 27.96. MS (APCI): 152 (MH^+).

4-Methyl-1-(pyrrolidin-2-ylmethyl)-1*H*-pyrazole (6b): yield 106 g (65%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), δ 7.22 (s, 1H), 7.14 (s, 1H), 4.03 (dd, J = 13.6 Hz and 4.4 Hz, 1H), 3.87 (dd, J = 13.6 Hz and 7.7 Hz, 1H), 3.42–3.48 (m, 1H), 2.87–2.92 (m, 1H), 2.78–2.84 (m, 1H), 2.28 (s, 1H), 1.99 (s, 3H), 1.75–1.84 (m, 1H), 1.62–1.73 (m, 2H), 1.30–1.39 (m, 1H). ^{13}C NMR ($CDCl_3$), δ 139.7, 128.5, 115.7, 58.5, 56.8, 46.3, 28.9, 25.1, 8.8. Anal. calcld. for $C_9H_{15}N_3$ C 65.42, H 9.15, N 25.43. Found C 65.63, H 8.94, N 25.11. MS (APCI): 166 (MH^+).

3,5-Dimethyl-1-(pyrrolidin-2-ylmethyl)-1*H*-pyrazole (6c) dihydrochloride: yield 29 g (19%). White powder. Mp 178–179 °C. ^{1}H NMR (DMSO-d^6), δ 10.59 (br s, 1H), 9.93 (br s, 1H), 9.83 (br s, 1H), 6.12 (s, 1H), 4.58 (dd, J = 14.7 Hz and 7.5 Hz, 1H), 4.44 (dd, J = 14.7 Hz and 5.7 Hz, 1H), 3.86–3.95 (m, 1H), 3.21–3.28 (m, 1H), 3.07–3.14 (m, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.91–2.04 (m, 2H), 1.80–1.89 (m, 1H), 1.64–1.72 (m, 1H). ^{13}C NMR (DMSO-d^6), δ 146.4, 143.2, 106.7, 58.9, 47.9, 44.9, 28.0, 22.8, 12.6, 11.3. Anal. calcld. for $C_{10}H_{19}Cl_2N_3$ C 47.63, H 7.59, Cl 28.12, N 16.66. Found C 47.50, H 7.74, Cl 27.89, N 16.38. MS (APCI): 180 (MH^+).

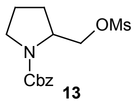
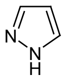
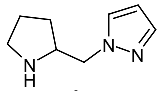
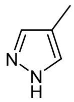
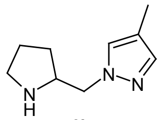
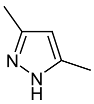
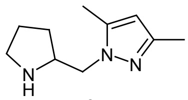
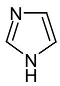
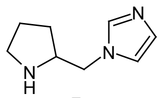
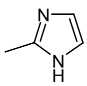
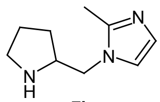
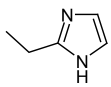
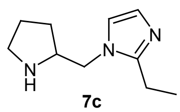
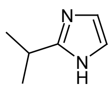
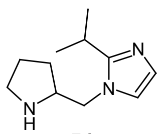
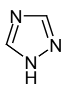
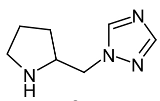
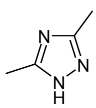
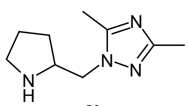
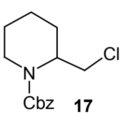
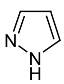
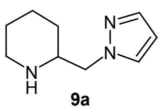
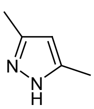
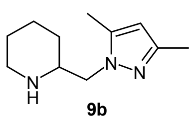
1-(Pyrrolidin-2-ylmethyl)-1*H*-imidazole (7a): yield 82 g (54%). White amorphous solid. ^{1}H NMR (D_2O), δ 7.83 (s, 1H), 7.29 (s, 1H), 7.14 (s, 1H), 4.49 (dd, J = 14.7 Hz and 4.5 Hz, 1H), 4.41 (dd, J = 14.7 Hz and 8.9 Hz, 1H), 4.00–4.07 (m, 1H), 3.41–3.46 (m, 1H), 3.32–3.38 (m, 1H), 2.24–2.30 (m, 1H), 2.03–2.18



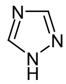
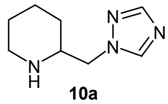
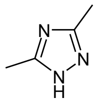
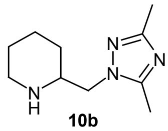
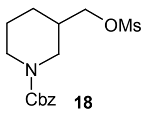
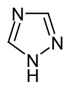
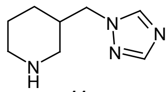
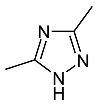
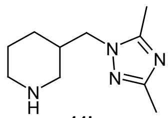
1 2 3, R= H, Me, CF_3 4 5

Figure 2. Biologically active derivatives of the scaffolds defined in Fig. 1 (the scaffolds are shown in red).

Table 1. Synthesis of 1-(pyrrolidinylmethyl)-1*H*-azoles and their piperidine-derived homologues **6** – **11**. Conditions: (i) NaH (1 eq), DMF, 60°C or 100°C, 8 h; (ii) H_2, 10% Pd-C, MeOH, 1 atm, rt, monitored by NMR.

Entry No.	Substrate	Azole	Product	Yield, %
1	 **13**	 **14a**	 **6a**	44
2		 **14b**	 **6b**	65
3		 **14c**	 **6c**	19
4		 **15a**	 **7a**	54
5		 **15b**	 **7b**	43
6		 **15c**	 **7c**	16
7		 **15d**	 **7d**	17
8		 **16a**	 **8a**	56
9		 **16b**	 **8b**	23
10	 **17**	 **14a**	 **9a**	22
11		 **14c**	 **9b**	26

Continued **Table 1.** Synthesis of 1-(pyrrolidinylmethyl)-1*H*-azoles and their piperidine-derived homologues **6** – **11**. Conditions: (i) NaH (1 eq), DMF, 60°C or 100°C, 8 h; (ii) H_2, 10% Pd-C, MeOH, 1 atm, rt, monitored by NMR.

Entry No.	Substrate	Azole	Product	Yield, %
12		 **16a**	 **10a**	22
13		 **16b**	 **10b**	60
14	 **18**	 **16a**	 **11a**	52
15		 **16b**	 **11b**	45

(m, 2H), 1.79–1.87 (m, 1H). ^{13}C NMR (D_2O), *δ* 138.0, 128.5, 120.1, 60.4, 47.3, 45.9, 27.6, 22.8. Anal. calcld. for $C_8H_{13}N_3$ C 63.55, H 8.67, N 27.79. Found C 63.42, H 8.76, N 27.65. MS (APCI): 152 (MH^+).

2-Methyl-1-(pyrrolidin-2-ylmethyl)-1*H*-imidazole (7b): yield 71 g (43%). Yellowish liquid. ^{1}H NMR (DMSO-d^6), *δ* 7.05 (s, 1H), 6.70 (s, 1H), 3.71–3.80 (m, 2H), 3.28 (quint, *J* = 6.7 Hz, 1H), 3.09 (br s, 1H), 2.79 (t, *J* = 6.7 Hz, 2H), 2.29 (s, 3H), 1.65–1.77 (m, 2H), 1.55–1.64 (m, 1H), 1.28–1.36 (m, 1H). ^{13}C NMR (DMSO-d^6), *δ* 144.3, 126.4, 120.4, 58.9, 50.8, 46.4, 29.5, 25.6, 13.4. Anal. calcld. for $C_9H_{15}N_3$ C 65.42, H 9.15, N 25.43. Found C 65.17, H 9.49, N 25.36.
MS (EI): 165 (M^+), 96, 70.

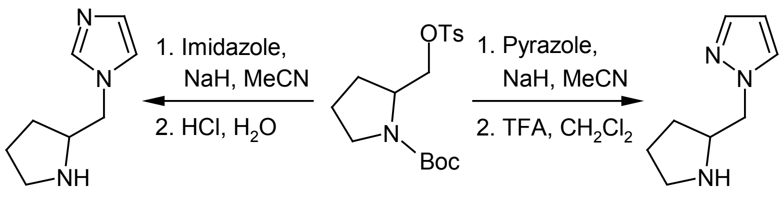
2-Ethyl-1-(pyrrolidin-2-ylmethyl)-1*H*-imidazole (7c): yield 23.5 g (16%).White amorphous solid. ^{1}H NMR (D_2O), *δ* 7.18 (s, 1H), 7.02 (s, 1H), 4.29–4.38 (m, 2H), 3.91 (quint, *J* = 7.4 Hz, 1H), 3.39–3.44 (m, 1H), 3.27–3.33 (m, 1H), 2.77 (q, *J* = 7.3 Hz, 2H), 2.19–2.25 (m, 1H), 2.00–2.17 (m, 2H), 1.74–1.82 (m, 1H), 1.28 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (D_2O), *δ* 150.6, 125.6, 120.4, 59.8, 46.3, 45.8, 27.7, 22.6, 19.2, 11.2. Anal. calcld. for $C_{10}H_{17}N_3$ C 67.00, H 9.56, N 23.44. Found C 67.32, H 9.47, N 23.15. MS (APCI): 180 (MH^+).

2-Isopropyl-1-(pyrrolidin-2-ylmethyl)-1*H*-imidazole (7d): yield 14.5 g (17%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 6.93 (s, 1H), 6.86 (s, 1H), 3.86 (dd, *J* = 13.8 Hz and 5.4 Hz, 1H), 3.77 (dd, *J* = 13.8 Hz and 7.8 Hz, 1H), 3.34 (quint, *J* = 6.4 Hz, 1H), 2.94–3.06 (m, 2H), 2.87–2.95 (m, 1H), 1.94 (br s, 1H), 1.77–1.92 (m, 2H), 1.69–1.77 (m, 1H), 1.36–1.44 (m, 1H), 1.31 (d, *J* = 7.0 Hz, 3H). 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$), *δ* 153.1, 127.2, 119.0, 59.1, 50.9, 46.4, 29.3, 26.0, 25.1, 22.1, 22.0. Anal. calcld. for $C_{11}H_{19}N_3$ C 68.35, H 9.91, N 21.74. Found C 68.07, H 10.02, N 21.70. MS (APCI): 194 (MH^+).

1-(Pyrrolidin-2-ylmethyl)-1*H*-1,2,4-triazole (8a): yield 56.6 g (56%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 8.15 (s, 1H), 7.90 (s, 1H), 4.17 (dd, *J* = 13.8 Hz and 3.6 Hz, 1H), 4.05 (dd, *J* = 13.8 Hz and 8.0 Hz, 1H), 3.37 (quint, *J* = 6.6 Hz, 1H), 2.92 (td, *J* = 6.6 Hz and 1.0 Hz, 2H), 2.34 (br s, 1H), 1.88–1.94 (m, 1H), 1.67–1.80 (m, 2H), 1.40–1.47 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 151.7, 143.5, 57.4, 54.7, 46.4, 28.9, 25.3. Anal. calcld. for $C_7H_{12}N_4$ C 55.24, H 7.95, N 36.81. Found C 54.99, H 8.17, N 36.52. MS (APCI): 153 (MH^+).

3,5-Dimethyl-1-(pyrrolidin-2-ylmethyl)-1*H*-1,2,4-triazole (8b): yield 35 g (23%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 3.89 (dd, *J* = 13.7 Hz and 4.9 Hz, 1H), 3.79 (dd, *J* = 13.7 Hz and 7.8 Hz, 1H), 3.49 (quint, *J* = 6.8 Hz, 1H), 2.81–2.90 (m, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 2.18 (br s, 1H), 1.78–1.85 (m, 1H), 1.61–1.77 (m, 2H), 1.32–1.40 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 159.4, 152.6, 58.0, 53.1, 46.4, 29.1, 25.3, 13.9, 12.1. Anal. calcld. for $C_9H_{16}N_4$ C 59.97, H 8.95, N 31.08. Found C 59.96, H 8.61, N 31.33. MS (EI): 180 (M^+), 111, 70.

2-(1*H*-pyrazol-1-ylmethyl)piperidine (9a): yield 24.4 g (22%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 7.51



Scheme 1. 1-(Pyrrolidinylmethyl)-1*H*-azoles reported in the literature.

(s, 1H), 7.40 (s, 1H), 6.22 (s, 1H), 4.10 (dd, *J* = 13.6 Hz and 4.1 Hz, 1H), 3.94 (dd, *J* = 13.6 Hz and 8.7 Hz, 1H), 2.97–3.04 (m, 2H), 2.55 (td, *J* = 11.5 Hz and 2.5 Hz, 1H), 2.04 (br s, 1H), 1.79 (d, *J* = 11.5 Hz, 1H), 1.60 (t, *J* = 14.0 Hz, 2H), 1.27–1.46 (m, 2H), 1.14 (qd, *J* = 11.8 Hz and 3.4 Hz, 1H). ^{13}C NMR ($CDCl_3$), *δ* 139.8, 130.1, 105.2, 58.1, 56.5, 46.6, 30.1, 26.0, 24.3. Anal. calcld. for $C_9H_{15}N_3$ C 65.42, H 9.15, N 25.43. Found C 65.73, H 9.06, N 25.62.
MS (APCI): 166 (MH$^+$).

2-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)methyl]piperidine (9b): yield 12 g (26%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 5.73 (s, 1H), 3.78–3.88 (m, 2H), 2.97–3.06 (m, 2H), 2.56 (td, *J* = 11.8 Hz and 2.5 Hz, 1H), 2.48 (br s, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 1.72–1.80 (m, 1H), 1.53–1.60 (m, 2H), 1.25–1.47 (m, 2H), 1.10–1.20 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 147.7, 139.5, 104.7, 56.7, 54.1, 46.6, 30.2, 26.0, 24.4, 13.5, 11.2. Anal. calcld. for $C_{11}H_{19}N_3$ C 68.35, H 9.91, N 21.74. Found C 68.26, H 10.15, N 21.51. MS (APCI): 194 (MH$^+$).

2-(1*H*-1,2,4-triazol-1-ylmethyl)piperidine (10a): yield 24.7 g (22%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 8.04 (s, 1H), 7.89 (s, 1H), 4.08 (dd, *J* = 13.6 Hz and 4.2 Hz, 1H), 3.99 (dd, *J* = 13.6 Hz and 8.3 Hz, 1H), 2.93–3.00 (m, 2H), 2.52 (td, *J* = 11.7 Hz and 2.6 Hz, 1H), 1.75–1.79 (m, 2H), 1.52–1.61 (m, 2H), 1.24–1.40 (m, 2H), 1.06–1.16 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 152.3, 143.7, 55.8, 55.5, 46.5, 30.0, 25.9, 24.2. Anal. calcld. for $C_8H_{14}N_4$ C 57.81, H 8.49, N 33.70. Found C 58.06, H 8.49, N 34.01. MS (APCI): 167 (MH$^+$).

2-[(3,5-Dimethyl-1*H*-1,2,4-triazol-1-yl)methyl]piperidine (10b): yield 19 g (60%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 3.81–3.90 (m, 2H), 2.98–3.04 (m, 2H), 2.57 (td, *J* = 11.6 Hz and 1.7 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 2.03 (br s, 1H), 1.79 (d, *J* = 13.5 Hz, 1H), 1.56–1.62 (m, 2H), 1.28–1.46 (m, 2H), 1.11–1.21 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 159.5, 152.6, 56.1, 53.7, 46.5, 30.0, 25.8, 24.1, 13.7, 11.9. Anal. calcld. for $C_{10}H_{18}N_4$ C 61.82, H 9.34, N 28.84. Found C 61.89, H 9.07, N 29.10. MS (APCI): 195 (MH$^+$).

3-(1*H*-1,2,4-triazol-1-ylmethyl)piperidine (11a) dihydrochloride: yield 150 g (52%). White powder. Mp 198–200 °C. ^{1}H NMR (D_2O), *δ* 9.65 (s, 1H), 8.69 (s, 1H), 4.48–4.52 (m, 2H), 3.46 (t, *J* = 11.7 Hz, 2H), 2.91–3.00 (m, 2H), 2.52–2.59 (m, 1H), 2.01 (d, *J* = 14.8 Hz, 1H), 1.89 (d, *J* = 12.5 Hz, 1H), 1.72–1.81 (m, 1H), 1.41 (qd, *J* = 12.5 Hz and 3.5 Hz, 1H). ^{13}C NMR (D_2O), *δ* 144.6, 142.1, 53.6, 45.9, 44.1, 33.5, 25.2, 21.3. Anal. calcld. for $C_8H_{16}Cl_2N_4$ C 40.18, H 6.74, N 23.43. Found C 39.87, H 6.51, N 23.62. MS (APCI): 167 (MH$^+$).

3-[(3,5-Dimethyl-1*H*-1,2,4-triazol-1-yl)methyl]piperidine (11b): yield 87.6 g (45%). Yellowish liquid. ^{1}H NMR ($CDCl_3$), *δ* 3.70–3.82 (m, 2H), 2.86 (t, *J* = 13.6 Hz, 2H), 2.50 (td, *J* = 11.8 Hz and 2.1 Hz), 2.30 (s, 3H), 2.22 (s, 3H), 1.97 (br s, 1H), 1.56–1.71 (m, 3H), 1.31–1.40 (m, 1H), 1.04–1.13 (m, 1H). ^{13}C NMR ($CDCl_3$), *δ* 159.2, 152.1, 51.4, 50.2, 46.8, 37.6, 28.8, 25.5, 13.7, 11.9. Anal. calcld. for $C_{10}H_{18}N_4$ C 61.82, H 9.34, N 28.84. Found C 61.64, H 9.48, N 29.08. MS (APCI): 195 (MH$^+$).

3. Results and discussion

Only a few reports on the synthesis of compounds **6** – **11** can be found in the literature: namely, the preparation of compounds **6a** [13] and **7a** [14,18] has been documented (Scheme 1). Both compounds were obtained by alkylation of the corresponding azole anions with *N*-Boc-prolinol tosylate (**12**). For the preparation of compounds **6** – **8**, we have used an analogous method commencing from *N*-Cbz-prolinol mesylate (**13**) (Table 1), which is more reactive than *N*-Boc-prolinol tosylate, is shelf-stable and can be easily obtained on a hundred gram scale [20]. Azoles **14** – **16** were used to generate anions for the reaction with **13** (Table 1, Entries 1–9).

It was found that anions of pyrazoles **14a–c** were more reactive towards alkylation with **13** than anions of imidazoles **15a–d** or 1,2,4-triazoles **16a,b**. Whereas **13** and anions of **14a–c** reacted smoothly in DMF already at 60°C, in the case of **15a–d** or **16a,b**, the reaction was successful only at 100°C. It should be noted that in the case of **16**, the alkylation proceeded regioselectively at N-1 atom of the heterocycle. The corresponding Cbz derivatives were not characterized but subjected to catalytic hydrogenation (10% Pd-C, MeOH, 1 atm, rt) to give pure **6** – **8** in 16–65% overall yields.

Table 2. Physicochemical parameters of *N*-methyl derivatives of the amines **6** – **11**.

Parameter	Value range
Molecular weight (MW)	165…207
Calculated logarithm of octanol-water partition coefficient (cLogP)	0.20…1.93
Number of H-bond donors	0
Number of H-bond acceptors	2…3
Fraction of sp^3 carbon atoms (Fsp^3)	0.67…0.82
Number of rotatable bonds (RotB)	2…3
Total polar surface area (TPSA), Å^2	21.0…34.0

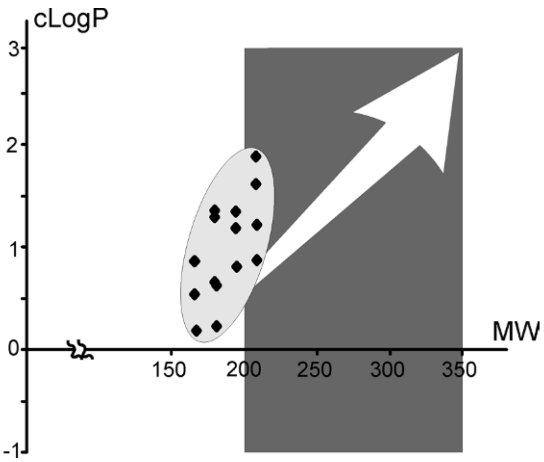


Figure 3. Physicochemical parameters of *N*-methyl derivatives of the amines **6** – **11** (black dots within the ellipse), shown together with the lead-likeness criteria as given by Churcher *et al.* [5] (dark grey rectangle). The white arrow shows that there is much room for the design of compound libraries.

As was described previously by our group [20], the mesylate of benzyl 2-(hydroxymethyl)piperidine-1-carboxylate is not stable enough to be isolated. Therefore the corresponding chloride **17** was used in the reaction with the azole anions (Table 1, Entries 10–13). This change did not affect the outcome of the reaction sequence described above: the corresponding products **9a,b** and **10a,b** were obtained in 22–60% yields. The method was equally efficient for the preparation of 1-(pyrrolidin-2-yl)-1*H*-1,2,4-triazoles **11a,b** (45–52% yields) starting from mesylate **18** [20] and anions of **16a,b** (Table 1, Entries 14 and 15).

Compounds **6** – **11** were obtained as rather hygroscopic liquids or oils, therefore any aqueous work-up should be avoided during their isolation and/or purification. In some cases, the compounds were isolated as dihydrochlorides; 10% HCl in dioxane was used for that purpose. Although the synthetic scheme included chromatographic purifications, it was easily scaled up for the preparation of 100 g of the final products in a single run.

Analysis of the physicochemical properties of the simplest (*N*-methyl) derivatives of the amines **6** – **11** (Table 2) showed that these building blocks perfectly fit the definition of low-molecular-weight hydrophilic three-dimensional templates [21]. They provide an opportunity for the lead-oriented synthesis of the compound libraries even if the strictest current criteria of lead-likeness are considered [5] (Fig. 3).

4. Conclusions

A convenient approach to multigram synthesis of 1-(pyrrolidin-2-yl)-1*H*-pyrazoles, -imidazoles, and -1*H*-1,2,4-triazoles, 1-(piperidin-2-yl)-1*H*-pyrazoles and -1*H*-1,2,4-triazoles, and 1-(piperidin-3-yl)-1*H*-1,2,4-triazoles was developed. The method allowed for the preparation of the target compounds in 16–65% yields. The building blocks obtained comply with the strictests definitions of templates for lead-oriented synthesis of the compound libraries.

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References

[1] M.P. Gleeson, J. Med. Chem. 51, 817 (2008)
[2] T.I. Oprea, A.M. Davis, S.J. Teague, P.D. Leeson, J. Chem. Inf. Comp. Sci. 41, 1308 (2001)
[3] P.D. Leeson, B. Springthorpe, Nat. Rev. Drug Discovery 6, 881 (2007)
[4] A. Polinsky, In: C. G. Wermuth (Ed.), Practice of Medicinal Chemistry, 3rd edition (Academic Press/Elsevier, Amsterdam, 2008) 244
[5] A. Nadin, C. Hattotuwagama, I. Churcher, Angew. Chem. Int. Ed. 51, 1114 (2012)
[6] N.V. Shevchuk, K. Liubchak, K.G. Nazarenko, A.A. Yurchenko, D.M. Volochnyuk, O.O. Grygorenko, A.A. Tolmachev, Synthesis 44, 2041 (2012)
[7] A.V. Borisov, V.V. Voloshchuk, M.A. Nechayev, O.O. Grygorenko, Synthesis 45, 2413 (2013)
[8] A.G. Yaremenko, D.M. Volochnyuk, V.V. Shelyakin, O.O. Grygorenko, Tetrahedron 69, 6799 (2013)
[9] R. Kombarov, A. Altieri, D. Genis, M. Kirpichenok,

V. Kochubey, N. Rakitina, Z. Titarenko, Mol. Diversity 14, 193 (2010)
[10] C.A. Brooks, C.H.-T. Chen, Y.S. Cho, L. Jiang, G. Liu, M. Shultz, PCT International Patent WO 2012/025164, 2012.03.01
[11] J.J. Cui, L.A. Funk, L. Jia, P.-P. Kung, J.J. Meng, M.D. Nambu, M.A. Pairish, H. Shen, M.B. Tran-Dube, PCT International Patent WO 2006/021881, 2006.03.02
[12] C. Kallus, H. Heitsch, A. Lindenschmidt, S. Grueneberg, H. Szillat, PCT International Patent WO 2005/105781, 2005.11.10
[13] S. Chandrasekhar, T.P. Kumar, K. Haribabu, C.R. Reddy, C.R. Kumar, Tetrahedron: Asymmetry 22, 697 (2011)
[14] D. Dang, P. Wu, C. He, Z. Xie, C. Duan, J. Am. Chem. Soc. 132, 14321 (2010)
[15] L. Zhang, J.-P. Cheng, S. Luo, X. Mi, S. Liu, Y. Qiao, H. Xu, Org. Biomol. Chem. 6, 567 (2008)
[16] Y. Abe, T. Hirakawa, S. Nakajima, N. Okano, S. Hayase, M. Kawatsura, T. Itoh, Y. Hirose, Adv. Synth. Cat. 350, 1954 (2008)
[17] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, Tetrahedron 63, 1923 (2007)
[18] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, Angew. Chem. Int. Ed. 45, 3093 (2006)
[19] D. Xu, S. Luo, H. Yue, L. Wang, Y. Liu, Z. Xu, Synlett 2569 (2006)
[20] S. Zhersh, V.V. Buryanov, O.V. Karpenko, O.O. Grygorenko, A.A. Tolmachev, Synthesis 3669 (2011)
[21] Instant JChem 6.0.2 (ChemAxon, Budapest, Hungary, 2013) (www.chemaxon.com)