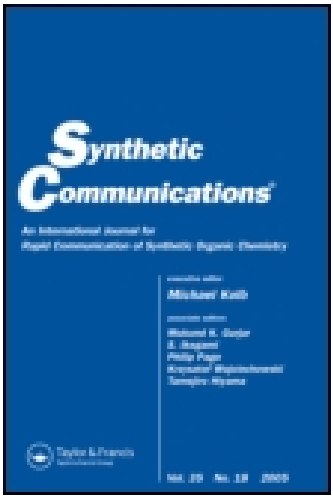

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Synthesis and Practical Use of 1H-1,2,3-Benzotriazole-5-carboxal for Reductive Amination

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Synthesis and Practical Use of *1H*-1,2,3-Benzotriazole-5-carboxaldehyde for Reductive Amination

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Abstract: A reliable synthetic procedure to obtain multigram quantities of *1H*-1,2,3-benzotriazole-5-carboxaldehyde has been developed. This material can be used in reductive amination reactions with primary and secondary amines to provide good to excellent yields of the desired products without protection of the starting material.

Keywords: 1*H*-1,2,3-benzotriazole, building blocks, compound libraries, reductive amination

1H-1,2,3-Benzotriazole moiety has a documented prominence in a number of antitumor aromatase inhibitors[1] and is present, for instance, in the marketed antiemetic dopamine D_2 antagonist Alizapride.[2] Additionally, there are reports on benzotriazole derivatives having an auxin-like effect on plant growth.[3] This prompted us to consider benzotriazole as an attractive structural feature to be utilized in the development of combinatorial compound libraries of medicinal and agricultural relevance. In particular, we required multigram quantities of *1H*-1,2,3-benzotriazole-5-carboxaldehyde (**1a**) (or any N-protected form thereof, such as **1b**) to be used as a *1H*-1,2,3-benzotriazole-containing building block in reductive amination by primary and secondary amines.

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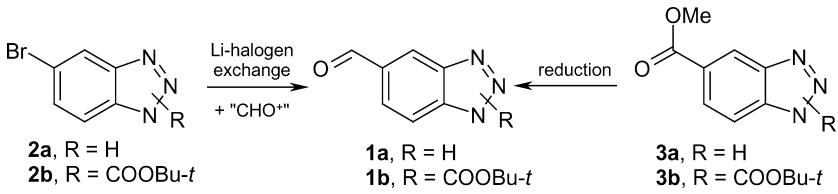
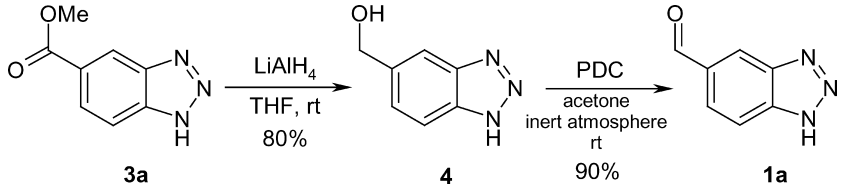
In selecting the starting point for synthesis of this hitherto unreported aldehyde, we considered two options: 1) generation of 5-*1H*-1,2,3-benzotriazolyl anion via lithium–halogen exchange on the Boc-protected version of the known 5-bromo-*1H*-1,2,3-benzotriazole[4] (**2b**) with subsequent trapping with an electrophilic formylating agent; or 2) reductive manipulation on the ester group of the unprotected (**3a**) or protected methyl 1*H*-1,2,3-benzotriazole-5-carboxylate[5] (**3b**) (Scheme 1).

Initial attempts to perform lithium–halogen exchange on the unprotected bromide **2a** (2.5 equiv of *t*-BuLi, ether, $-78^{\circ}C$, then DMF, $-78^{\circ}C \rightarrow$ rt) resulted in destruction of the *1H*-1,2,3-triazole nucleus. Boc-protection of **2a** (Boc_2O, DMF, rt[6]) and repeated attempts to introduce a formyl group using the same set of reagents at different temperatures ($-78^{\circ}C$ to $-40^{\circ}C$) and with various workup techniques provided the desired aldehyde **1b**, albeit in $<20\%$ yield. (The yield was estimated based on examination of ^1H NMR spectrum of the crude reaction mixture. When acidic workup conditions were used, the unprotected aldehyde **1a** was detected, in similar low yield.)

Seeking to increase the yield of the desired aldehyde **1**, we turned to the reduction of the ester **3**. Boc-protection was viewed as inappropriate because it would be incompatible with the harsh reduction conditions. (The *Boc* group in **2b** was found to be extremely labile even upon attempted chromatographic isolation of that material on silica gel.) Before exploring alternative protecting groups, we attempted reduction of the ester **3a** with DIBAL-H (THF, $-78^{\circ}C$) and found it difficult to avoid overreduction of the aldehyde. Several attempts to suppress the formation of the unwanted alcohol (formed in 10–25% yield) were unsuccessful. However, no disruption of the "uncapped" *1H*-1,2,3-triazole moiety was observed. We therefore relied on the literature precedence[7] and reduced the ester **3a** completely to the alcohol **4** at room temperature. Reoxidation of **4** to the corresponding aldehyde (**1a**) was found to be most efficient with pyridinium dichromate (PDC) using either THF or acetone, and not the traditional dichloromethane. (Other oxidation conditions tried included MnO_2/acetone and Swern oxidation [DMSO-oxalyl chloride or DMSO-trifluoroacetic anhydride].) Because both these solvents are prone to forming potentially explosive peroxides, the reactions were carried out in an inert argon atmosphere (the reaction medium was tested for the presence of peroxides using potassium iodide–starch strip. The solution gave negative peroxide test results throughout the process.)



Scheme 1.

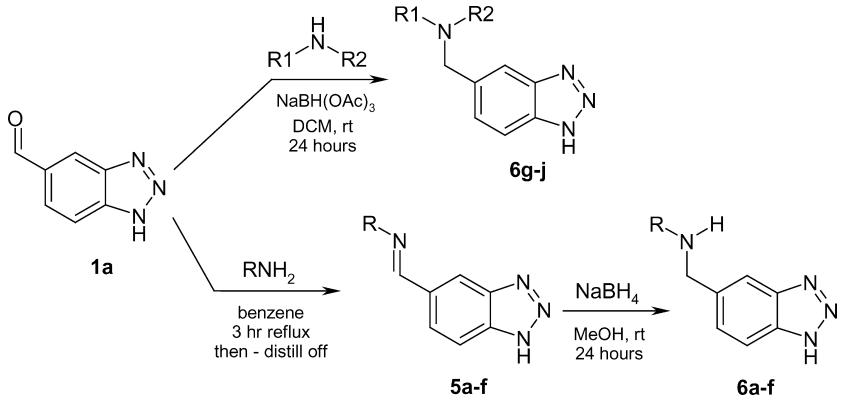


Scheme 2.

The overall yield of the target aldehyde **1a** was satisfactory: 72% (Scheme 2). The yield was found to be reproducible on a multigram scale (see the Experimental Section).

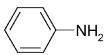
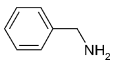
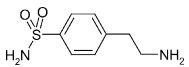
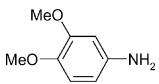
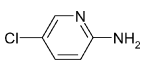
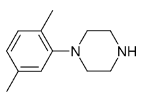
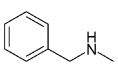
Having prepared the target aldehyde **1a**, we proceeded to explore its utility as a reagent in the reductive amination by primary and secondary amines. Because we encountered no reports in the literature about the reductive amination in presence of the unprotected *1H*-1,2,3-triazole moiety, we first tried to protect the aldehyde **1a** as its Boc-derivative (**1b**). The resulting 4 : 1 mixture of N_1- and N_3-substituted products was again found unstable, even after prolonged storage. (Upon prolonged storage at room temperature, the solutions of **1b** tend to accumulate N-*tert*-butylated 6-formyl-*1H*-benzotriazole via extrusion of CO_2, as evidenced by LC MS analysis.) Thus, our goal was to establish that the aldehyde **1a** itself could be used without protection.

As illustrated in Scheme 3, reductive amination of **1a** with a set of various primary and secondary amines (aliphatic as well as aromatic) yielded the desired 5-aminomethyl *1H*-1,2,3-benzotriazole derivatives **6a**–**j** in good to excellent yields (Table 1). Primary amines were first reacted with **1a** in benzene to form Schiff bases **5**. The latter were isolated and, without further purification, reduced with sodium borohydride in methanol.



Scheme 3.

Table 1. Results of the reductive amination reactions with aldehyde **1a** (Scheme 3)

Compound	R_1NHR_2 or RNH_2	Imine **5** details	Amine **6** details	Yield of **6** (%)
6a		Pale-yellow solid, crystallized from benzene	Crystalline solid, isolated as free base, crystallized from EtOH-toluene	79
6b		Colorless crystals, used without purification	White crystals, isolated as dihydrochloride	91
6c		Yellow semicrystalline oil, used without purification	White crystals, isolated as dihydrochloride	72
6d		White crystals, used without purification	White crystals, isolated as free base, crystallized from EtOH-toluene	89
6e		Yellow crystals, used without purification	Purified by chromatography (SiO_2, 0 → 20% EtOH-EtOAc); dark viscous oil	70
6f		Pale yellow oil, used without purification	Off-white crystals, isolated as trihydrochloride, crystallized from EtOH	82
6g		—	Colorless glassy solid, isolated by chromatography (SiO_2, 0 → 20% EtOH-EtOAc)	65
6h		—	White crystals, isolated as dihydrochloride (highly hygroscopic)	94
6i		—	Colorless oil, isolated by chromatography (SiO_2, EtOAc)	68
6j		—	White crystals, isolated as dihydrochloride, crystallized from MeOH	75

Secondary amines reacted directly in the presence of sodium triacetoxy borohydride to give the respective tertiary amine products. All of the products thus obtained were found to be stable compounds of at least 95% purity as confirmed by LC MS and ^{1}H NMR spectroscopy (see Experimental Section).

In summary, we have developed a reliable synthetic procedure that provides access to multigram quantities of hitherto unknown *1H*-1,2,3-benzotriazole-5-carboxaldehyde **1a** and demonstrated its utility as a carbonyl partner in reductive amination reactions with a structurally diverse set of amines requiring no protection of the *1H*-1,2,3-triazole fragment.

EXPERIMENTAL

All reactions were run in oven-dried glassware in an atmosphere of nitrogen. Melting points were measured with a Buchi B-520 melting-point apparatus and are not corrected. Analytical thin-layer chromatography was carried out on EM Separations Technology F_{254} silica-gel plates. Compounds were visualized with short-wavelength UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometers in DMSO-d_6 using TMS as an internal standard. Mass-spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer. All solvents and reagents were obtained from commercial sources and used without purification.

5-Hydroxymethyl-*1H*-1,2,3-benzotriazole (4)

Dry methyl *1H*-1,2,3-benzotriazole-5-carboxylate (**3a**) (88.5 g, 0.50 mol) in four portions at room temperature was added to a stirred suspension of lithium aluminum hydride (21.8 g, 0.57 mol) in anhydrous THF (1.2 L). Slight exothermic reaction was observed. The mixture was stirred at room temperature for 4 h and then treated with ethyl acetate (50 mL). After additional stirring for 30 min, the reaction mixture was poured into ice water (1.5 L). The resulting slurry was acidified to pH 3–4 with 10% sulfuric acid, the aqueous layer was saturated with NaCl, and the organic layer was separated. The aqueous layer was extracted with THF (2×500 mL); the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield a grey solid that was dried in high vacuum (approx. 1 mm of Hg). This material contained a small amount of the unreacted ester **3a** (as indicated by ^{1}H NMR analysis). The latter was removed by boiling the crude product in diethyl ether (100 mL), cooling the mixture to room temperature, and filtering the solids off. The product was air dried to provide **4** (68.0 g, 80%) as grey solid: mp = 148–150°C. The spectral data of this material were consistent with those reported previously:[7] ^{1}H NMR (300 MHz, d_6-DMSO) δ 15.64 (br s, 1H, N_1-H), 7.84 (unresolved d, 1H), 7.80 (s, 1H), 7.36 (d, $J = 8.1$ Hz, 1H),

5.41 (br s, 1H, O<u>H</u>), 4.68 (s, 2H, C<u>H</u>$_2$); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 141.9, 136.8, 136.7, 126.0, 114.2, 62.9; LCMS m/z 150 ($M + H^+$).

1H-1,2,3-Benzotriazole-5-carboxaldehyde (1a)

5-Hydroxymethyl-*1H*-1,2,3-benzotriazole (**4**) (35.0 g, 0.23 mol) was dissolved in anhydrous acetone (500 mL) and treated with pyridinium dichromate (99 g, 1.1 equiv, added in small portions over 30 min). The reaction vessel was thoroughly degassed and filled with argon. The dark reaction mixture was stirred at room temperature for 4 h. At that point TLC analysis (5% MeOH-CH_2Cl_2) indicated full conversion of the starting material. The solution was decanted off the solid catalyst and the latter was washed with several portions of acetone (3 × 200 mL) until full disappearance of the product in the washings (checked by TLC). The solvent was removed *in vacuo* and the resultant oily mixture was loaded on a silica-gel column and eluted with 50 → 100% ethyl acetate in hexanes. The fractions containing the product were pooled and concentrated to give **1a** (30.4 g, 90%) as a fine colorless crystalline solid: mp = 178–179°C. ^{1}H NMR (300 MHz, d$_6$-DMSO) δ 16.08 (br s, 1H), 10.12 (s, 1H), 8.59 (s, 1H), 7.98 (d, $J = 8.5$ Hz, 1H), 7.91 (dd, $J = 8.5$, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, d$_6$-DMSO) δ 192.4, 140.8 (br), 139.3 (br), 133.3, 124.4, 122.0, 114.3; LCMS m/z 148 ($M + H^+$); Anal. calcd. for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.15; H, 3.45; N, 28.57.

General Procedure 1: Preparation of Secondary Amines 6a–f

A primary amine (1 equiv.) was added to a suspension of the aldehyde **1a** (200 mg, 1.36 mmol) in benzene (5 mL) and the resulting mixture was heated at reflux for 3–5 h. (The suspension cleared up shortly after reaching the reflux temperature, if the solution remained cloudy, a small amount [0.2–0.3 mL] of anhydrous ethanol was added.) Then the solution was evaporated to dryness. The resulting solid or oil-like imines **5a–f** were used in the next step without purification (except **5a**—see Table 1).If necessary, the oily products may be triturated with petroleum ether to initiate crystallization.

The imines **5a–f** were dissolved in anhydrous methanol (5 mL), treated with $NaBH_4$ (0.5 equiv), and stirred at room temperature until full consumption of the starting imine was evidenced by TLC analysis (typically 24 h). The solvent was removed in vacuo. The oily residue was purified by one of the three techniques (see Table 1): 1) dissolved in a small amount of methanol (2 mL). Large excess of ethereal HCl was added, the precipitated hydrochloride was filtered off, and it was dried in vacuo, 2) The product was crystallized from an appropriate solvent system, 3) The crude product was purified by column chromatography.

N-(1*H*-1,2,3-benzotriazol-5-ylmethyl)-N-phenylamine (6a): mp = 165–168°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.61 (s, 1H), 7.58 (s, 1H), 6.97–7.05 (m, 3H), 6.62 (dd, J = 0.9, 8.7 Hz, 2H), 6.48 (tt, J = 0.9, 7.4 Hz, 1H), 6.14 (br s, 1H), 4.31 (s, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 148.9, 144.4 (br), 143.9 (br), 131.5, 128.6, 120.2, 115.4, 115.3, 113.7, 112.2, 47.2; MS MH^+ = 225; HRMS (EI) m/z calcd. for $C_{13}H_{13}N_4$ (MH^+): 225.2674. Found: 225.2670.

N-(*1H*-1,2,3-benzotriazol-5-ylmethyl)-N-benzylamine dihydrochloride (6b): mp = 175°C (decomp.). ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.01 (br s, 1H), 8.18 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 1.3, 8.5 Hz, 1H), 7.56–7.60 (m, 2H), 7.37–7.45 (m, 3H), 4.32 (t, J = 5.7 Hz, 2H), 4.15 (t, 5.7 Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 140.0 (br), 138.6 (br), 131.9, 130.0, 129.1, 128.7, 128.5, 127.4, 117.0, 114.9, 49.6 (two signals); MS MH^+ = 239; HRMS (EI) m/z calcd. for $C_{14}H_{15}N_4$ (MH^+): 239.2945. Found: 239.2944.

N-(*1H*-1,2,3-benzotriazol-5-ylmethyl)-N-(3-methoxypropyl)amine dihydrochloride (6c): mp = 137–138°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.67 (br s, bound HCl and two N-H, 4H), 8.19 (s, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.67 (dd, J = 1.5, 8.5 Hz, 1H), 4.29 (t, J = 5.6 Hz, 2H), 3.37 (t, J = 6.0 Hz, 2H), 3.20 (s, 3H), 2.90 (m, 2H), 1.94 (m, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 138.6 (two signals), 129.3, 127.3, 116.9, 115.0, 68.8, 57.8, 49.7, 44.0, 25.5; MS MH^+ = 221; HRMS (EI) m/z calcd. for $C_{11}H_{17}N_4O$ (MH^+): 221.2764. Found: 221.2767.

4-{2-[(*1H*-1,2,3-benzotriazol-5-ylmethyl)amino]ethyl}benzenesulfonamide (6d): mp = 173–175°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.34 (s, 1H), 7.90 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.60 (AXA′X′, J = 8.3 Hz, 4H), 7.52 (dd, J = 1.3, 8.5 Hz, 1H), 3.81 (t, J = 7.0 Hz, 2H), 3.01 (t, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 145.4, 144.4, 144.1, 141.8, 129.2, 128.8, 125.5, 119.0, 118.2, 115.6, 61.4, 52.8, 49.8; MS MH^+ = 332; HRMS (EI) m/z calcd. for $C_{15}H_{18}N_5O_2S$ (MH^+): 332.3990. Found: 332.3993.

N-(*1H*-1,2,3-benzotriazol-5-ylmethyl)-N-(3,4-dimethoxyphenyl)amine (6e): ^{1}H NMR (300 MHz, d_6-DMSO) δ 15.6 (br s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.81 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 6.36 (d, J = 2.5 Hz, 1H), 6.04 (dd, J = 2.5, 8.7 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 4.39 (d, J = 5.6 Hz, 2H), 3.65 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 150.8, 145.0, 144.5, 141.2, 139.6 (br), 126.1 (br), 125.7, 116.0, 115.4, 112.9, 103.9, 99.8; MS MH^+ = 285; HRMS (EI) m/z calcd. for $C_{15}H_{17}N_4O_2$ (MH^+): 285.3204. Found: 285.3207.

N-(*1H*-1,2,3-benzotriazol-5-ylmethyl)-5-chloropyridin-2-amine trihydrochloride (6f): mp = 110–112°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.00–11.00 (br, bound HCl, 3H), 8.05 (d, J = 2.3 Hz, 1H), 7.95 (s, 1H), 7.90

(d, $J = 8.5$ Hz, 1H), 7.85 (dd, $J = 2.3$, 9.4 Hz, 1H), 7.47 (d, $J = 8.5$ Hz, 1H), 7.11 (d, J = 9.4 Hz, 1H), 4.82 (s, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 153.0, 141.5, 138.7 (br), 138.4 (br), 136.6, 135.0, 125.5, 117.8, 115.4, 113.7, 113.0, 56.0; MS $MH^+ = 260$; HRMS (EI) m/z calcd. for $C_{12}H_{11}ClN_5$ (MH^+): 260.7000. Found: 260.6998.

General Procedure 2: Preparation of Tertiary Amines 6g–j

An amine (1.1 equiv) and $NaBH(OAc)_3$ (2.2 equiv) were added to a solution of the aldehyde **1a** (200 mg, 1.36 mmol) in anhydrous dichloromethane (10 mL). The resulting mixture was stirred at room temperature until full consumption of the starting imine was evidenced by TLC analysis (typically 24 h). The solvent was removed in vacuo and water (5 mL) and ethyl acetate (15 mL) were added to the residue. The biphasic mixture was stirred vigorously for 15 min; then, the aqueous phase was made basic with 1M aqueous KOH, and the organic layer was separated. The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic solutions were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was either dissolved in small amount of ether (3–5 mL) and the product **6** was isolated as hydrochloride upon addition of excess ethereal HCl, or it was purified by column chromatography.

5-{[4-(2,5-dimethylphenyl)piperazin-1-yl]methyl}-*1H*-1,2,3-benzotriazole (6 g): mp = 58–60°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.87 (d, $J = 8.5$ Hz, 1H), 7.80 (s, 1H), 7.43 (dd, $J = 1.3$, 8.5 Hz, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 6.81 (s, 1H), 6.73 (d, $J = 7.5$ Hz, 1H), 3.70 (s, 2H), 2.82 (t, $J = 4.3$ Hz, 4H), 2.55 (br s, 4H), 2.22 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 137.0 (br), 136.2 (br), 133.3, 132.5, 131.4, 129.3, 127.6, 126.4, 124.2, 120.3, 119.6, 119.5, 62.8, 54.0, 52.2, 21.7, 18.0; MS $MH^+ = 322$; HRMS (EI) m/z calcd. for $C_{19}H_{24}N_5$ (MH^+): 322.4287. Found: 322.4290.

5-(piperidin-1-ylmethyl)-*1H*-1,2,3-benzotriazole dihydrochloride (6h): mp = 111–113°C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 8.26 (s, 1H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.75 (dd, $J = 1.3$, 8.7 Hz, 1H), 4.43 (d, $J = 5.3$ Hz, 2H), 3.25 (m, 2H), 2.87 (m, 2H), 1.61–1.87 (m, 6H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 138.7 (br), 138.6 (br), 128.4, 127.0, 118.6, 114.8, 58.5, 51.4, 22.0, 21.6; MS $MH^+ = 217$; HRMS (EI) m/z calcd. for $C_{13}H_{17}N_4$ (MH^+): 217.2881. Found: 217.2885.

N-(*1H*-1,2,3-benzotriazol-5-ylmethyl)-N-benzyl-N-methylamine (6i): ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.87 (d, $J = 8.5$ Hz, 1H), 7.80 (s, 1H), 7.44 (dd, $J = 1.1$, 8.5 Hz, 1H), 7.29–7.37 (m, 4H), 7.20–7.26 (m, 1H), 3.63 (s, 2H), 3.51 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 171.9, 170.2, 139.0, 137.0, 128.5, 128.1, 126.8, 126.0, 115.0 (br), 113.5 (br), 61.0,

59.7, 41.6; MS $MH^+ = 253$; HRMS (EI) m/z calcd. for $C_{15}H_{17}N_4$ (MH^+): 253.3216. Found: 253.3212.

5-(pyrrolidin-1-ylmethyl)-*1H*-1,2,3-benzotriazole dihydrochloride (6j): mp >180°C (decomp.). ^{1}H NMR (300 MHz, d_6-DMSO) δ 11.65 (br s, 1H), 8.25 (s, 1H), 8.01 (br s, bound HCl, 2H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.75 (dd, $J = 1.1$, 8.5 Hz, 1H), 4.52 (d, $J = 6.0$ Hz, 2H), 3.29 (m, 2H), 3.08 (m, 2H), 1.97 (m, 2H), 1.88 (m, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 138.9 (br), 138.5 (br), 128.8, 127.7, 117.7, 115.0, 56.3, 52.4, 22.6; MS $MH^+ = 203$; HRMS (EI) m/z calcd. for $C_{11}H_{15}N_4$ (MH^+): 203.2610. Found: 203.2612.

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