Synthesis and Antitumor Activity of 1,5-Disubstituted 1,2,4-Triazoles as *cis*-Restricted Combretastatin Analogues

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SUPPORTING INFORMATION

Characterization for compounds **6a-f, 6hi, 7a-f, 7hi,**. **3a-f, 3h-k, 4a-f**, **4ij**, **4mn** and **4r**.

Chemistry. Materials and Methods. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in ppm upfield from tetramethylsilane as internal standard, and the spectra were recorded in appropriate deuterated solvents, as indicated. Positive-ion electrospray ionization (ESI) mass spectra were recorded on a double-focusing Finnigan MAT 95 instrumental with BE geometry. Melting points (mp) were determined on a Buchi-Tottoli apparatus and are uncorrected. All products reported showed ^{1}H NMR spectra in agreement with the assigned structures. The purity of tested compounds was determined by combustion elemental analyses conducted by the Microanalytical Laboratory of the Chemistry Department of the University of Ferrara with a Yanagimoto MT-5 CHN recorder elemental analyzer. All tested compounds yielded data consistent with a purity of at least 95% as compared with the theoretical values. All reactions were carried out under an inert atmosphere of dry nitrogen, unless otherwise indicated. Standard syringe techniques were applied for transferring dry solvents. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates), and compounds were visualized with aqueous $KMnO_4$. Flash chromatography was performed using 230-400 mesh silica gel and the indicated solvent system. Organic solutions were dried over anhydrous Na_2SO_4. Arylhydrazine hydrochloride **5a-i** and arylboronic acids are commercially available and used as received.

1-Phenyl-1H-1,2,4-triazole (6a). Following general procedure A, compound **6a** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow oil, yield: 57%. ^{1}H NMR ($CDCl_3$) δ: 7.42 (m, 3H), 7.62(d, J=8.8 Hz, 2H), 8.10 (s, 1H), 8.55 (s, 1H).

1-(4-Fluorophenyl)-1H-1,2,4-triazole (6b). Following general procedure A, compound **6b** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Yellow solid, yield: 58%, mp 84-86 °C. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J=8.0 Hz, 2H), 7.67 (m, 2H), 8.10 (s, 1H), 8.50 (s, 1H).

1-(3-Fluorophenyl)-1H-1,2,4-triazole (6c). Following general procedure A, compound **6c** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). White solid, yield: 63%, mp 72-74 °C. ^{1}H NMR ($CDCl_3$) δ: 7.13 (m, 1H), 7.49 (m, 3H), 8.12 (s, 1H), 8.58 (s, 1H).

1-(4-Chlorophenyl)-1H-1,2,4-triazole (6d). Following general procedure A, compound **6d** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 73%, mp 125-127 °C. ^{1}H NMR ($CDCl_3$) δ: 7.48 (d, J=9.0 Hz, 2H), 7.63 (d, J=9.0 Hz, 2H), 8.11 (s, 1H), 8.54 (s, 1H).

1-(2, 4-Dichlorophenyl)-1H-1,2,4-triazole (6e). Following general procedure A, compound **6e** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Yellow solid, yield: 64%, mp 167-169 °C. ^{1}H NMR ($CDCl_3$) δ: 7.41 (dd, J=8.6 and 2.0 Hz, 1H), 7.55 (d, J=8.6 Hz, 2H), 7.58 (d, J=2.0 Hz, 1H), 8.14 (s, 1H), 8.54 (s, 1H).

1-(3, 4-Dichlorophenyl)-1H-1,2,4-triazole (6f). Following general procedure A, compound **6f** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). White solid, yield: 77%, mp 134-136 °C. ^{1}H NMR ($CDCl_3$) δ: 7.57 (dd, J=8.6 and 2.0 Hz, 1H), 7.59 (d, J=8.6 Hz, 2H), 7.87 (d, J=2.0 Hz, 1H), 8.12 (s, 1H), 8.56 (s, 1H).

1-(4-Nitrophenyl)-1H-1,2,4-triazole (6h). Following general procedure A, compound **6h** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 73%, mp 167-169 °C. ^{1}H NMR ($CDCl_3$) δ: 7.92 (d, J=9.0 Hz, 2H), 8.18 (s, 1H), 8.42 (d, J=9.0 Hz, 2H), 8.72 (s, 1H).

1-(3-Nitrophenyl)-1H-1,2,4-triazole (6i). Following general procedure C, compound **6i** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Yellow solid, yield: 52%, mp 145-147 °C. ^{1}H NMR ($CDCl_3$) δ: 7.74 (t, J=8.0 Hz, 1H), 8.08 (d, J=7.0 Hz, 1H), 8.18 (s, 1H), 8.26 (d, J=7.0 Hz, 1H), 8.60 (s, 1H), 8.70 (s, 1H).

Synthesis of 1-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (8). To a round bottom flask was charged with CuI 8382 mg, 2 mmol), $CsCO_3$ (6.52 g., 20 mmol), 1,2,4-triazole (1 g., 14.5 mmol), 3,4,5-trimethoxyphenylboronic acid (2.47 g., 10 mmol) and DMF (20 mL) under nitrogen. The system was then evacuated twice, back filled with nitrogen and heated at 120 °C for 24h.The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and water (10 mL). The aqueous phase as filtered on a pad of celite, and the filtrate washed with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography on silica gel (EtOAc) to provide **8** as a white solid, yield 78%, mp 119-121 °C. ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H), 3.93 (s, 6H), 6.88 (s, 2H), 8.09 (s, 1H), 8.49 (s, 1H). Anal. ($C_{17}H_{17}N_3O_3$): C, H, N.

5-Bromo-1-phenyl-1H-1,2,4-triazole (7a). Following general procedure B, compound **7a** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 80%, mp 73-75 °C. ^{1}H NMR ($CDCl_3$) δ: 7.55 (m, 5H), 8.05 (s, 1H).

5-Bromo-1-(4-fluorophenyl)-1H-1,2,4-triazole (7b). Following general procedure B, compound **7b** was purified by chromatography eluting with petroleum ether-EtOAc (8:2). White solid, yield: 71%, mp 151-153 °C. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J=8.0 Hz, 2H), 7.53 (m, 2H), 8.03 (s, 1H).

5-Bromo-1-(3-fluorophenyl)-1H-1,2,4-triazole (7c). Following general procedure B, compound **7c** was purified by chromatography eluting with petroleum ether-EtOAc (8.5:1.5). White solid, yield: 78%, mp 82-84 °C. ^{1}H NMR ($CDCl_3$) δ: 7.24 (m, 1H), 7.43 (m, 3H), 8.04 (s, 1H).

5-Bromo-1-(4-chlorophenyl)-1H-1,2,4-triazole (7d). Following general procedure B, compound **7d** was purified by chromatography eluting with petroleum ether-EtOAc (9.5:0.5). Yellow solid, yield: 53%, mp 111-113 °C. ^{1}H NMR ($CDCl_3$) δ: 7.46 (d, J=8.8 Hz, 2H), 7.62 (d, J=8.8 Hz, 2H), 8.04 (s, 1H).

5-Bromo-1-(2, 4-dichlorophenyl)-1H-1,2,4-triazole (7e). Following general procedure B, compound **7e** was purified by chromatography eluting with petroleum ether-EtOAc (8:2). White solid, yield: 83%, mp 88-89 °C. ^{1}H NMR ($CDCl_3$) δ: 7.41 (dd, J=8.6 and 2.0 Hz, 1H), 7.43 (d, J=8.6 Hz, 2H), 7.62 (d, J=2.0 Hz, 1H), 8.08 (s, 1H).

5-Bromo-1-(3, 4-dichlorophenyl)-1H-1,2,4-triazole (7f). Following general procedure B, compound **7f** was purified by chromatography eluting with petroleum ether-EtOAc (8:2). White solid, yield: 86%, mp 116-118 °C. ^{1}H NMR ($CDCl_3$) δ: 7.45 (dd, J=8.8 and 2.2 Hz, 1H), 7.62 (d, J=8.8 Hz, 2H), 7.74 (d, J=2.2 Hz, 1H), 8.05 (s, 1H).

5-Bromo-1-(4-nitrophenyl)-1H-1,2,4-triazole (7h). Following general procedure B, compound **7h** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Yellow solid, yield: 59%, mp 136-140 °C. ^{1}H NMR ($CDCl_3$) δ: 7.87 (d, J=8.8 Hz, 2H), 8.09 (s, 1H), 8.42 (d, J=8.8 Hz, 2H).

5-Bromo-1-(3-nitrophenyl)-1H-1,2,4-triazole (7i). Following general procedure B, compound **7i** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Yellow solid, yield: 56%, mp 110-112 °C. ^{1}H NMR ($CDCl_3$) δ: 7.76 (t, J=8.0 Hz, 1H), 8.02 (d, J=7.0 Hz, 1H), 8.09 (s, 1H), 8.42 (d, J=7.0 Hz, 1H), 8.54 (s, 1H).

General procedure (C, Suzuki coupling) for the synthesis of compounds 3a-i and 4a-r. A mixture of 5-bromo-1-aryl-1H-[1,2,4]triazoles **7a-i** or 1-(3,4,5-trimethoxyphenyl)-5-bromo-1H-1,2,4-triazole **9** (0.5 mmol), potassium carbonate (104 mg, 0.75 mmol, 1.5 equiv.), the appropriate arylboronic acid (1 mmol, 2 equiv.) and tetrakis (triphenylphosphine)palladium (13.5 mg, 0.012 mmol) in dry toluene (10 mL) was stirred at 100 °C under nitrogen for 18 h, cooled to ambient temperature, filtered through Celite and evaporated in vacuo. The residue was dissolved with EtOAc (30 mL), and the resultant solution was washed sequentially with 5% $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried, filtered and evaporated, and the residue was purified by flash chromatography on silica gel.

1-Phenyl-5-(3,4,5-trimethoxyphenyl)-1-phenyl-1H-1,2,4-triazole (3a). Following general procedure C, compound **3a** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 67%, mp 129-131 °C. ^{1}H NMR ($CDCl_3$) δ: 3.66 (s, 6H), 3.87 (s, 3H), 6.72 (s, 2H), 7.47 (m, 5H), 8.09 (s, 1H). MS (ESI): $[M+H]^+$=312.1. Anal. ($C_{17}H_{17}N_3O_3$): C, H, N.

1-(4-Fluorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3b). Following general procedure C, compound **3b** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 56%, mp 106-108 °C. ^{1}H NMR ($CDCl_3$) δ: 3.68 (s, 6H), 3.87 (s, 3H), 6.70 (s, 2H), 7.17 (d, J=7.4 Hz, 2H), 7.37 (m, 2H), 8.07 (s, 1H). MS (ESI): $[M]^+$=329.7. Anal. ($C_{17}H_{16}FN_3O3$): C, H, N.

1-(3-Fluorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3c). Following general procedure C, compound **3c** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Colourless oil, yield: 48%. ^{1}H NMR ($CDCl_3$) δ: 3.70 (s, 6H), 3.88 (s, 3H), 6.72 (s, 2H), 7.17 (m, 2H), 7.42 (m, 2H), 8.09 (s, 1H). MS (ESI): $[M]^+$=329.8. Anal. ($C_{17}H_{16}FN_3O3$): C, H, N.

1-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3d). Following general procedure C, compound **3d** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow oil, yield: 55%. ^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 6H), 3.88 (s, 3H), 6.69 (s, 2H), 7.33 (d, J=9.0 Hz, 2H), 7.45 (d, J=9.0 Hz, 2H), 8.08 (s, 1H). MS (ESI): $[M+H]^+$=346.1. Anal. ($C_{17}H_{16}ClN_3O_3$): C, H, N.

1-(2, 4-Dichlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3e). Following general procedure C, compound **3e** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow oil, yield: 56%. ^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 6H), 3.86 (s, 3H), 6.71 (s, 2H), 7.33 (d, J=9.0 Hz, 1H), 7.42 (d, J=8.6 and 1.8 Hz, 1H), 7.61 (d, J=2.0 Hz, 1H), 8.13 (s, 1H). MS (ESI): $[M+H]^+$=380.1. Anal. ($C_{17}H_{15}Cl_2N_3O_3$): C, H, N.

1-(3, 4-Dichlorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3f). Following general procedure C, compound **3f** was purified by chromatography eluting with petroleum ether-EtOAc (4:6). Brown solid, yield: 48%, mp 160-161 °C. ^{1}H NMR ($CDCl_3$) δ: 3.72 (s, 6H), 3.88 (s, 3H), 6.70 (s, 2H), 7.20 (dd, J=8.6 and 2.2 Hz, 2H), 7.51 (d, J=8.6 Hz, 1H), 7.62 (d, J=2.2 Hz, 1H), 8.07 (s, 1H). MS (ESI): $[M+H]^+$=380.2. Anal. ($C_{17}H_{15}Cl_2N_3O_3$): C, H, N.

1-(4-Nitrophenyl)5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3h). Following general procedure C, compound **3h** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 52%, mp 152-154 °C. ^{1}H NMR ($CDCl_3$) δ: 3.71 (s, 6H), 3.89 (s, 3H), 6.68 (s, 2H), 7.62 (d, J=9.0 Hz, 2H), 8.13 (s, 1H), 8.31 (d, J=9.0 Hz, 2H). MS (ESI): $[M+H]^+$=357.1. Anal. ($C_{17}H_{16}N_4O_5$): C, H, N.

1-(3-Nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (3i). Following general procedure C, compound **TR434** was purified by chromatography eluting with petroleum ether-

EtOAc (1:1). Yellow solid, yield: 65%, mp 138-140 °C. ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 6H), 3.92 (s, 3H), 6.71 (s, 2H), 7.78 (t, J=8.0 Hz, 1H), 8.03 (d, J=7.0 Hz, 1H), 8.09 (s, 1H), 8.40 (d, J=7.0 Hz, 1H), 8.54 (s, 1H). MS (ESI): $[M+H]^+$=357.3. Anal. ($C_{17}H_{16}N_4O_5$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-phenyl-1H-1,2,4-triazole (4a). Following general procedure C, compound **4a** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). White solid, yield: 58%, mp 125-127 °C. ^{1}H NMR ($CDCl_3$) δ: 3.72 (s, 6H), 3.88 (s, 3H), 6.56 (s, 2H), 7.40 (m, 3H), 7.52 (m, 2H), 8.08 (s, 1H). MS (ESI): $[M]^+$=311.4. Anal. ($C_{17}H_{17}N_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(4-fluorophenyl)-1H-1,2,4-triazole (4b). Following general procedure C, compound **4b** was purified by chromatography eluting with petroleum ether-EtOAc (4:6). White solid, yield: 83%, mp 125-127 °C. ^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 6H), 3.88 (s, 3H), 6.55 (s, 2H), 7.06 (m, 2H), 7.54 (m, 2H), 8.08 (s, 1H). MS (ESI): $[M]^+$=329.3. Anal. ($C_{17}H_{16}FN_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(3-fluorophenyl)-1H-1,2,4-triazole (4c). Following general procedure C, compound **4c** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). White solid, yield: 78%, mp 130-132 °C. ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 6H), 3.87 (s, 3H), 6.55 (s, 2H), 7.12 (m, 1H), 7.29 (m, 3H), 8.07 (s, 1H). MS (ESI): $[M]^+$=329.4. Anal. ($C_{17}H_{16}FN_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(4-chlorophenyl)-1H-1,2,4-triazole (4d). Following general procedure C, compound **4d** was purified by chromatography eluting with petroleum ether-EtOAc (4:6). White solid, yield: 84%, mp 107-109 °C. ^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 6H), 3.89 (s, 3H), 6.55 (s, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.50 (d, J=8.8 Hz, 2H), 8.07 (s, 1H). MS (ESI): $[M+1]^+$=346.1. Anal. ($C_{17}H_{16}ClN_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(3-chlorophenyl)-1H-1,2,4-triazole (4e). Following general procedure C, compound **4e** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 70%, mp 105-107 °C. ^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 6H), 3.88 (s, 3H), 6.56 (s, 2H), 7.32 (m, 3H), 7.66 (s, 1H), 8.08 (s, 1H). MS (ESI): $[M+1]^+$=346.4. Anal. ($C_{17}H_{16}ClN_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(3,4-dichlorophenyl)-1H-1,2,4-triazole (4f). Following general procedure C, compound **4f** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). White solid, yield: 66%, mp 139-141 °C. ^{1}H NMR ($CDCl_3$) δ: 3.77 (s, 6H), 3.89 (s, 3H), 6.56 (s, 2H), 7.29 (dd, J=8.6 and 2.0 Hz, 1H), 7.41 (d, J=8.6 Hz, 1H), 7.79 (d, J=2.0 Hz, 1H), 8.07 (s, 1H). MS (ESI): $[M+1]^+$=380.1. Anal. ($C_{17}H_{15}Cl_2N_3O_3$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(4-methoxyphenyl)-1H-1,2,4-triazole (4h). Following general procedure C, compound **4h** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). White solid, yield: 56%, mp 72-74 °C. ^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 6H), 3.86 (s, 3H), 3.88 (s, 3H), 6.58 (s, 2H), 6.90 (d, J=9.0 Hz, 2H), 7.48 (d, J=9.0 Hz, 2H), 8.04 (s, 1H). MS (ESI): $[M]^+$=341.7. Anal. ($C_{18}H_{19}N_3O_4$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole (4i). Following general procedure C, compound **4i** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow oil, yield: 82%. ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 6H), 3.76 (s, 3H), 3.88 (s, 3H), 6.58 (s, 2H), 6.92 (dd, J=9.0 and 1.8 Hz, 1H), 7.02 (m, 2H), 7.18 (d, J=1.8 Hz, 1H), 8.08 (s, 1H). MS (ESI): $[M]^+$=341.9. Anal. ($C_{18}H_{19}N_3O_4$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(2-methoxyphenyl)-1H-1,2,4-triazole (4j). Following general procedure C, compound **4j** was purified by chromatography eluting with petroleum ether-EtOAc (6:4). Colorless oil, yield: 54%. ^{1}H NMR ($CDCl_3$) δ: 3.43 (s, 3H), 3.63 (s, 6H), 3.80 (s, 3H), 6.51 (s, 2H), 6.82 (d, J=7.6 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.52 (d, J=7.6 Hz, 1H), 8.09 (s, 1H). MS (ESI): $[M]^+$=341.4. Anal. ($C_{18}H_{19}N_3O_4$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(3-ethoxyphenyl)-1H-1,2,4-triazole (4m). Following general procedure C, compound **4m** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). White solid, yield: 65%, mp 92-94 °C. ^{1}H NMR ($CDCl_3$) δ: 1.38 (t, J=7.2 Hz, 3H), 3.74 (s, 6H), 3.86 (s, 3H), 3.98 (q, J=7.2 Hz, 2H), 6.58 (s, 2H), 6.84 (m, 1H), 6.92 (d, J=8.8 Hz, 1H), 7.13 (s, 1H), 7.33 (d, J=8.8 Hz, 1H), 8.07 (s, 1H). MS (ESI): $[M+H]^+$=356.5. Anal. ($C_{19}H_{21}N_3O_4$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(2-ethoxyphenyl)-1H-1,2,4-triazole (4n). Following general procedure C, compound **4n** was purified by chromatography eluting with petroleum ether-EtOAc (4:6). Yellow solid, yield: 58%, mp 80-82 °C. ^{1}H NMR ($CDCl_3$) δ: 0.87 (t, J=7.2 Hz, 3H), 3.64 (s, 6H), 3.72 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 6.55 (s, 2H), 6.81 (d, J=8.4 Hz, 1H), 7.06 (t, J=8.4 Hz, 1H), 7.42 (t, J=8.4 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 8.10 (s, 1H). MS (ESI): $[M+H]^+$=356.2. Anal. ($C_{19}H_{21}N_3O_4$): C, H, N.

1-(3,4,5-Trimethoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)-1H-1,2,4-triazole (4q). Following general procedure C, compound **4q** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 83%, mp 115-117 °C. ^{1}H NMR ($CDCl_3$) δ: 3.73 (s, 6H), 3.88 (s, 3H), 6.54 (s, 2H), 7.22 (d, J=9.0 Hz, 2H), 7.60 (d, J=9.0 Hz, 2H), 8.08 (s, 1H). MS (ESI): $[M+1]^+$=396.5. Anal. ($C_{18}H_{16}F_3N_3O_4$): C, H, N.

1-(3,4,5-trimethoxyphenyl)-5-(3-nitrophenyl)-1H-1,2,4-triazole (4r). Following general procedure C, compound **4r** was purified by chromatography eluting with petroleum ether-EtOAc (1:1). Yellow solid, yield: 74%, mp 126-128 °C. ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 6H), 3.90 (s, 3H), 6.72 (s, 2H), 7.74 (t, J=8.0 Hz, 1H), 8.03 (d, J=7.2 Hz, 1H), 8.06 (s, 1H), 8.43 (d, J=7.2 Hz, 1H), 8.55 (s, 1H). MS (ESI): $[M+H]^+$=357.4. Anal. ($C_{17}H_{16}N_4O_5$): C, H, N.

4-(5-(3,4,5-Trimethoxyphenyl)-1H-1,2,4-triazol-1-yl)benzenamine (3j). Following general procedure D, compound **3j** was purified by chromatography eluting with petroleum ether-EtOAc (1:9). Light brown solid, yield: 98%, mp 144-146 °C. ^{1}H NMR ($CDCl_3$) δ: 3.44 (bs, 2H), 3.68 (s, 6H), 3.84 (s, 3H), 6.69 (d, J=6.8 Hz, 2H), 6.78 (s, 2H), 7.13 (d, J=6.8 Hz, 2H), 8.02 (s, 1H). MS (ESI): $[M+H]^+$=327.3. Anal. ($C_{17}H_{18}N_4O_3$): C, H, N.

3-(5-(3,4,5-Trimethoxyphenyl)-1H-1,2,4-triazol-1-yl)benzenamine (3k). Following general procedure D, compound **3k** was purified by chromatography eluting with petroleum ether-EtOAc (3:7). White solid, yield: 87%, mp 180-182 °C. ^{1}H NMR ($CDCl_3$) δ: 3.52 (bs, 2H), 3.68 (s, 6H), 3.85 (s, 3H), 6.70 (m, 3H), 6.75 (s, 2H), 7.38 (t, J=8.0 Hz, 1H), 8.04 (s, 1H). MS (ESI): $[M+H]^+$=327.2. Anal. ($C_{17}H_{18}N_4O_3$): C, H, N.