Supporting Information for

Synthesis of [1,2,4]triazole[4,3- α]piperazines via highly reactive
chloromethyloxadiazoles.

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GENERAL METHODS

Proton and carbon-13 NMR spectra were recorded in DMSO-d₆ on either a Bruker DPX400 or DRX500 spectrometer at a frequency of 400.13 MHz and 100.62 MHz or 500.13 MHz and 125.77 MHz respectively. The chemical shifts (δ) are reported in ppm relative to residual DMSO-d₅ for proton (δ =2.50) and DMSO-d₆ for carbon (δ =39.5). (The solubility characteristics of some of the synthesized compounds made it necessary to run in an alternative deuterated solvent. This is indicated with the specific compound and the internal reference is footnoted.) The nitrogen-15 assignments were obtained from observed correlations extracted from a ¹H-¹⁵N HMBC (Hetero Multiple Bond Correlated) 2-D experiment run in CD₃OD on a Bruker DRX 500 at a frequency of 500.13 and 50.68 MHz respectively. The chemical shifts are reported in ppm relative to external NH₃ for nitrogen (δ =0). Proton multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, q=quartet, m-multiplet, br=broad. All coupling constants (J) are reported in Hertz (Hz).

Infrared spectra were recorded on a Nicolet 560 FT-IR spectrometer (3M disposable IR card, type 62, polytetrafluoroethylene). Peaks are reported in cm⁻¹. HPLC analysis were carried out on a Hewlett Packard 1100 system. Melting points were determined on a Buchi B-545 apparatus and are uncorrected. Combustion analysis was performed by Quantitative Technologies Inc., Whitehouse, NJ.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, 0.25 mm thick with F-254 indicator. Visualization was accomplished by UV light, 5%

phosphomolybdic acid solution in ethanol. Flash column chromatography was performed by the method of Still¹ with 32-63 μm silica gel (Woelm).

Solvents for extraction and chromatography were reagent grade and used as received. Titration for water level was performed with a Fisher Coulomatic K-F titrator. All manipulations were carried out under an inert atmosphere of nitrogen. Reagents were purchased from Aldrich Chemical Co. unless otherwise noted and were used without prior purification.

Reaction procedures and characterization of new compounds.

***N'*-(chloroacetyl)-2,2,2-trifluoroacetohydrazide, 2a.** Hydrazine (2.01 Kg, 35 wt% in water, 22 mol)

was mixed with 31 L of acetonitrile. 3.16 Kg of ethyl trifluoroacetate (22.2 mol) were added over 75 min. Internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. Reaction completion was checked by GC (< 1% of hydrazine left). The

solution was cooled to 7 °C. 1.80 Kg of 50 wt% NaOH (22.4 mol) and 2.53 Kg of chloroacetyl chloride (22.4 mol) were added simultaneously over 130 min at <16 °C. When the reaction was complete (< 2 A% of intermediate monohydrazide) the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation 72 L of acetonitrile were added slowly to maintain constant volume (approx. 40-60 L). After the distillation, the KF value of supernatant was 993 ppm. The slurry was filtered to remove NaCl and the cake was rinsed with about 10 L of acetonitrile. The filtrate was concentrated at reduced pressure to approximately 9 L of volume and this solution used in the next step. By HPLC, the yield of bishydrazide **2a** was 95% (4.27 Kg, 20.9 mol, 94.4 A% pure, 50 wt% in solution). An analytical sample can be obtained by crystallization from the liquors. m.p. 139 °C; IR(KBr): 3184, 3049, 1675, 1611, 1498, 1226, 1156 cm^{-1} ; ¹H-NMR (400.13 MHz, DMSO-*d*₆): δ (ppm): 4.20 (s, 2H), 10.75 (s, 1H), and 11.63 (s, 1H). ¹³C-NMR (100.62 MHz, DMSO-*d*₆): δ (ppm): 41.0, 116.1 (q, J = 362.0 Hz), 155.8 (q, J = 50.0 Hz), 165.4. **HPLC conditions:** Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H₂O (0.1% H₃PO₄); flow rate: 1 mL/min; retention time: 2.9 min.

¹ Still, W.C.; Ammon, H.L.; Deshong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

2-(chloromethyl)-5-(trifluoromethyl)-1,3,4-oxadiazole, 3a. Phosphorus oxychloride (3.20 Kg, 20.9

mmol.) was added to the solution of bishydrazide **2a** (4.27 Kg, 20.9 mol, 94.4 A% pure, 50 wt% in solution) in acetonitrile. The mixture was heated to 80 °C and aged at that temperature for 24 h until HPLC showed <2A% of **2a**. In a separate vessel, 20 L of MTBE and 20 L of H₂O were mixed and cooled to 0

°C. The reaction mixture was cooled to room temperature and added to the quench solution keeping the internal temperature below 10 °C. After the addition was complete, the mixture was agitated vigorously for 30 min., the temperature was warmed to 22 °C and the aqueous layer was cut. The organic layer was then washed with 20 L of 5 wt% KHCO₃ and with 20 L of 20 wt% brine. Solvents were removed by distillation at 75-80 mm Hg, 45°C to obtain **3a** as an orange oil in 79% yield (3.08 Kg, 16.5 mol, 88 wt% in solution). This oil was used directly in the preparation of **4a**. An analytically pure sample can be obtained by distillation, b.p. 55-60 °C at 10 mm Hg; IR(film): 1587, 1568, 1408, 1288, 1135, 1020 cm⁻¹; HRMS(ES⁺) calc. for (M+H)⁺: 186.9886, found: 186.9893 (3.7 ppm); ¹H-NMR (500.13 MHz, CD₃OD^a): δ(ppm): 4.99 (s, 2H). ¹³C-NMR (125.77 MHz, CD₃OD^b): δ(ppm): 33.7, 117.9 (q, J = 270.7 Hz), 157.2 (q, J = 43.7 Hz), 166.9. HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H₂O (0.1% H₃PO₄); flow rate: 1 mL/min; retention time: 8.8 min.

2,2,2-trifluoro-N'-[(2Z)-piperazin-2-ylidene]acetohydrazide, 4a. To a solution of ethylenediamine

(1.55 L, 23.2 mol) in 7.8 L of methanol cooled at -20 °C was added the crude oxadiazole **3a** (1.50 Kg, 8.2 mol, 88 wt% in solution) keeping the internal temperature below -20 °C. After the addition was complete the resulting slurry was aged at -20 °C for 1 h and the reaction assayed for completion. 11.6 L of ethanol were then charged and the slurry slowly

warmed to -5 °C. After 60 min at -5 °C, the slurry was filtered and washed with 3 L of ethanol at -5 °C and dried under a nitrogen flow. Amidine **4a** was obtained as a white solid in 74% yield (1.31 Kg, 6.2 mol, 99.5 wt%). m.p. 141 °C, dec.; Anal., Calc. for C₆H₉F₃N₄O: C: 34.29%, H: 4.32%, N: 26.66%, F: 27.12%; Found: C: 34.14%, H: 4.39%, N: 25.93%, F: 27.47%; IR(KBr): 3031, 1615, 1558, 1197, 1129 cm⁻¹; MS (ES) 211 (M+H), 100%; HRMS(ES⁺) calc. for (M+H)⁺: 211.0807, found: 211.0808 (0.5 ppm); ¹H-NMR (500.13 MHz, DMSO), δ(ppm): 2.88 (t, J=5.6, 2H), 3.18 (t, J=5.6, 2H), 3.31 (br s, 1H), 3.63 (s, 2H), 8.26 (br s, 1H), 10.79 (very br s, 1H). ¹³C-NMR (125.77 MHz, DMSO), δ(ppm): 40.4, 41.6, 42.9, 118.9 (q, J = 286.1 Hz), 153.8, 155.8 (q, J = 31.4 Hz). HPLC conditions:

Symmetry 4.6 x 250 mm C18 column; UV detection at 254 nm; mobile phase: 5:95 ACN: H₂O (0.1% H₃PO₄); flow rate: 1 mL/min; retention time: 2.1 min.

3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine hydrochloride salt 1a. A 50

L round bottom flask was charged with 1.25 Kg (5.95 mol) of amidine **4a**. 5 L of methanol were charged and the resulting slurry warmed to 55 °C. HCl (492 mL, 37 wt%, 6.0 mol) was charged over 1 hr at this temperature. All solids dissolved during the course of the addition. The reaction was aged for 30 min and assayed for completion (< 1% **4a**). The solution was cooled to 20 °C and

aged at this temperature until a seed bed formed (10 min to 1 hour). 13.8 L of MTBE were charged at 20 °C over 2 hours. After charging all the MTBE, the resulting slurry was cooled to 2 °C, aged for 30 min and filtered. The white solids obtained were washed with 2.5 L of ethanol:MTBE (1:3 v/v) and dried under vacuum at 45 °C. Yield of triazole **1a** hydrochloride salt is 92% (1.25 Kg, 5.47 mol, 99.5 wt%). m.p. 264 °C (decomp); Anal., Calc. for C₆H₈ClF₃N₄: C: 31.52%, H: 3.53%, N: 24.51%, Cl: 15.51%; F: 24.93%; Found: C: 31.38%, H: 3.37%, N: 24.35%, Cl: 15.51%; F: 25.21%; IR(KBr): 3016, 2947, 1572, 1518, 1499, 1271, 1210, 1181 cm⁻¹; MS (ES): 192 (M⁺); HRMS(ES⁺) calc. for (M+H)⁺: 193.0701, found: 193.0702 (0.5 ppm); ¹H-NMR (400.13 MHz, DMSO), δ(ppm): 3.61 (t, 2H), 4.40 (t, 2H), 4.66 (s, 2H), 10.62 (br, 2H). ¹³C-NMR (100.62 MHz, DMSO), δ(ppm): 39.4, 39.6, 41.0, 118.6 (q, J = 260 Hz), 142.9 (q, J = 40 Hz), 148.8; HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H₂O (0.1% H₃PO₄); flow rate: 1 mL/min; retention time: 2.5 min.

2-chloro-N'-(trifluoroacetyl)propanohydrazide, 2b. The procedure for the preparation of **2a** was

followed using 18.2 mL (201 mmol) of a 35 wt% aqueous solution of hydrazine, 24 mL (201.5 mmol) of ethyl trifluoroacetate, 20 mL (204.7 mmol) of 2-chloropropionyl chloride and 16.4 g (205 mmol) of 50 wt% sodium hydroxide. After azeotropic removal of water and filtration of salts, a solution of **2b** in 90 mL of acetonitrile was obtained. Removal of solvent at

reduced pressure afforded 41.5 g of **2b** as a white solid, 95% yield. An analytically pure sample was obtained by recrystallization from acetonitrile. m.p. 160 °C; IR(KBr): 3191, 3057, 1684, 1623, 1494, 1202 cm⁻¹; HRMS(ES⁺) calc. for (M+Na)⁺: 240.9968, found: 240.9975 (2.9 ppm); ¹H-NMR (400.13

MHz, CD₃OD^a), δ (ppm): 1.68 (d, J = 7.5 Hz, 3H), 4.52 (q, J = 7.5 Hz, 1H), 4.85 (b, 2H); ¹³C-NMR (100.62 MHz, CD₃OD^b), δ (ppm): 20.5, 51.7, 115.0 (q, J = 280 Hz), 156.3 (q, J = 40 Hz), 169.1

***N'*-[chloro(phenyl)acetyl]-trifluoroacetohydrazide, 2c.** The procedure for the preparation of **2a** was

followed using 4.7 mL (51.8 mmol) of a 35 wt% aqueous solution of hydrazine, 6.2 mL (52.0 mmol) of ethyl trifluoroacetate, 10 g (52.9 mmol) of 2-chloro-2-phenylacetyl chloride and 4.25 g (53 mmol) of 50 wt% sodium hydroxide. After azeotropic removal of water and filtration of salts, a solution

of **2c** in 40 mL of acetonitrile was obtained. Removal of solvent at reduced pressure afforded 13.85 g of **2c** as a white solid, 95% yield. An analytical sample was obtained by recrystallization from acetonitrile. m.p. 128 °C; Anal., Calc. for $C_{10}H_8ClF_3N_2O_2$: C: 42.80%, H: 2.87%, N: 9.98%, Cl: 12.63%; F: 20.31%; Found: C: 42.72%, H: 2.64%, N: 9.97%, Cl: 12.83%; F: 20.37%; IR(KBr): 3265, 3038, 1756, 1694, 1651, 1210, 1173 cm⁻¹; HRMS(ES+) calc. for (M+H)⁺: 281.0305, found: 281.0314 (3.2 ppm); ¹H-NMR (400.13 MHz, CD₃OD^a), δ (ppm): 4.86 (br, 2H), 5.60 (s, 1H), 7.30-7.50 (m, 3H), 7.50-7.65 (m, 2H); ¹³C-NMR (100.62 MHz, CD₃OD^b), δ (ppm): 58.2, 115.8 (q, J = 280 Hz), 127.7, 128.3(2C), 128.8(2C), 136.3, 156.4 (q, J = 30.0 Hz), 167.5

***N'*-(2-chloroacetyl)benzohydrazide, 2d.** To a slurry of 40 g of benzoylhydrazide (294 mmol) in 320

mL acetonitrile were added simultaneously 23.6 mL of chloroacetylchloride (297 mmol) and 11.9 g of 50 wt% sodium hydroxide (297 mmol) while maintaining the internal temperature below 10°C. After 30 min., all starting materials were consumed as determined by HPLC assay. The resulting slurry

was filtered and the solids were washed with twice with 80 mL of water. Solids were dried in the vacuum oven at 30-35°C to afford 42.6g of **2d** as a white solid, 70% yield. m.p. 165 °C; IR(KBr): 3251, 3041, 1686, 1642, 1520, 1486, 1314, 1241 cm⁻¹; HRMS(ES+) calc. for (M+Na)⁺: 235.0250, found: 235.0256 (2.6 ppm); ¹H-NMR (400.13 MHz, DMSO), δ (ppm): 4.2 (s, 2H), 7.40-7.55 (m, 2H), 7.56-7.63 (m, 1H), 7.80-7.90 (m, 2H), 10.38 (s, 1H), 10.50 (s, 1H); ¹³C-NMR (100.62 MHz, DMSO), δ (ppm): 41.3, 127.8, 127.9, 128.8, 132.3, 132.6, 165.7

2-(1-chloroethyl)-5-(trifluoromethyl)-1,3,4-oxadiazole, 3b. The procedure for the preparation of **3a**

was followed using 43.6g (200 mmol) of **2b** and 20 mL (218.5 mmol) of POCl₃ in 90 mL of acetonitrile. After aqueous workup, the brown oil obtained was purified by chromatography on silica gel to obtain 30.1g of **3b** as a colorless oil, 71% yield. IR(film): 1585, 1409, 1211, 1172, 1137, 1077, 1009 cm⁻¹; HRMS(ES⁺) calc. for (M+H)⁺: 201.0043, found: 201.0049 (3.0 ppm); ¹H-NMR (400.13 MHz, CDCl₃^c): δ(ppm): 2.00 (d, J = 7 Hz, 3H), 5.23 (q, J = 7.0 Hz, 1H). ¹³C-NMR (100.62 MHz, CDCl₃^d): δ(ppm): 21.9, 44.7, 116.0 (q, J = 270.0 Hz), 155.8 (q, J = 50.0 Hz), 167.6

2-[chloro(phenyl)methyl]-5-(trifluoromethyl)-1,3,4-oxadiazole, 3c. The procedure for the

preparation of **3a** was followed using 16 g (57 mmol) of **2c** and 5.7 mL (62.3 mmol) of POCl₃ in 40 mL of acetonitrile. After aqueous workup, the brown oil obtained was purified by chromatography on silica gel to obtain 9.73 g of **3c** as a pale yellow oil that crystallized on standing, 65% yield. m.p. 41 °C; IR(KBr): cm⁻¹; Anal., Calc. for C₁₀H₆ClF₃N₂O: C: 45.73%, H: 2.30%, N: 10.67%, Cl: 13.50%, F: 21.70%; Found: C: 45.61%, H: 2.11%, N: 10.65%, Cl: 13.48%, F: 22.03%; IR(KBr): 2962, 1589, 1543, 1458, 1418, 1212, 1176 cm⁻¹; ¹H-NMR (400.13 MHz, CDCl₃^c): δ(ppm): 6.23 (s, 1H), 7.40-7.50 (m, 3H), 7.50-7.60 (m, 2H); ¹³C-NMR (100.62 MHz, CDCl₃^d): δ(ppm): 51.2, 116.0 (q, J = 270.0 Hz), 127.8, 129.3(2C), 130.1(2C), 133.9, 156.0 (q, J = 40.0 Hz), 166.4

3-(chloromethyl)-5-phenyl-1,3,4-oxadiazole, 3d. The procedure for the preparation of **3d** was

followed using 40.3 g of **2d** (190 mmol) and 19.5 mL of POCl₃ (208 mmol) in 200 mL acetonitrile at reflux for 4 hrs. After aqueous workup, volatiles were removed under reduced pressure to afford 29.2 g of **3d** as an off-white solid, 80% yield. m.p. 118 °C; Anal., Calc. for C₉H₇ClN₂O: C: 55.54%, H: 3.63%, N: 14.39%, Cl: 18.22%; Found: C: 55.12%, H: 3.46%, N: 14.19%, Cl: 18.36%; IR(KBr): 3028, 2970, 1605, 1574, 1551, 1484, 1449 cm⁻¹; HRMS(ES⁺) calc. for (M+H)⁺: 195.0325, found: 195.0324 (2.9 ppm); ¹H-NMR (400.13 MHz, CDCl₃^c): δ(ppm): 4.78 (s, 2H), 7.5-7.6 (m, 3H), 8.05-8.10 (m, 2H); ¹³C-NMR (100.62 MHz, CDCl₃^d): δ(ppm): 32.9, 123.2, 127.0, 129.0(2C), 132.1(2C), 162.1, 165.9

2,2,2-trifluoro-*N'*-'[(2*Z*)-3-methylpiperazin-2-ylidene]acetohydrazide, 4b. The procedure for the

preparation of **4a** was followed using 1.0g (4.99 mmol) of **3b** and 1 mL (14.96 mmol) of ethylenediamine in 5 mL of methanol. After crystallization, 760 mg of **4b** were obtained as a white solid, 68% yield. m.p. 141 °C, dec.; Anal., Calc. for C₇H₁₁F₃N₄O: C: 37.50%, H: 4.95%, N: 24.99%, F: 25.42%; Found: C: 37.43%, H: 4.87%, N: 24.92%, F: 25.49%; IR(KBr): 3046, 1607,

1558, 1351, 1199, 1135 cm⁻¹; MS (ES) 225 (M+H), 100%; ¹H-NMR (400.13 MHz, DMSO), δ(ppm): 1.31 (d, J = 7.5 Hz, 3H), 2.75-2.85 (m, 1H), 2.90-3.0 (m, 1H), 3.10-3.20 (m, 2H), 3.90 (qt, J = 7.5 Hz, 1H). ¹³C-NMR (100.62 MHz, DMSO), δ(ppm): 20.1, 37.7, 41.0, 46.9, 119.1 (q, J = 280.0 Hz), 156.3 (q, J = 30.0 Hz), 157.9.

2,2,2-trifluoro-*N'*-'[(2*Z*)-3-phenylpiperazin-2-ylidene]acetohydrazide, 4c. The procedure for the

preparation of **4a** was followed using 300 mg (1.14 mmol) of **3c** and 0.38 mL (5.70 mmol) of ethylenediamine in 2 mL of methanol. After crystallization, 176 mg of **4c** were obtained as a white solid, 54% yield. m.p. 141 °C, dec.; Anal., Calc. for C₁₂H₁₃F₃N₄O: C: 50.35%, H: 4.58%, N: 19.57%, F: 19.91%; Found: C: 50.10%, H: 4.44%, N: 19.33%, F: 20.23%;

IR(KBr): 3030, 1615, 1548, 1198, 1131 cm⁻¹; MS (ES) 287 (M+H), 20%; HRMS(ES+) calc. for (M+H)⁺: 287.1120, found: 287.1121 (0.3 ppm); ¹H-NMR (400.13 MHz, DMSO), δ(ppm): 2.70-2.90 (m, 2H), 3.15-3.40 (m, 2H), 5.09 (s, 1H), 7.25-7.45 (m, 5H). ¹³C-NMR (100.62 MHz, DMSO), δ(ppm): 37.7, 40.8, 55.2, , 119.1 (q, J = 280.0 Hz), 128.2, 128.3, 128.8, 139.3, 155.0, 156.3 (q, J = 30.0 Hz).

2,2,2-trifluoro-*N'*-'[(2*Z*)-4-methylpiperazin-2-ylidene]acetohydrazide, 4f. The procedure for the

preparation of **4a** was followed with 2.07g (11.1 mmol) of **3a** and 1.65g (22.26 mmol) of *N*-methylethylenediamine, to afford 1.85g (8.25 mmol) of **4f** as a white solid, 74% yield. m.p. 139 °C, dec.; Anal., Calc. for C₇H₁₁F₃N₄O: C: 37.50%, H: 4.95%, N: 24.99%, F: 25.42%; Found: C:

37.63%, H: 4.83%, N: 24.88%, F: 25.38%; IR(KBr): 3077, 2964, 1603, 1557, 1351, 1196, 1136 cm⁻¹; MS (ES) 225 (M+H), 100%; HRMS(ES+) calc. for (M+H)⁺: 225.0963, found: 225.0968 (2.2 ppm); ¹H-NMR (400.13 MHz, DMSO), δ(ppm): 2.22 (s, 3H), 2.60 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz,

2H), 3.34 (s, 2H). ^{13}C -NMR (100.62 MHz, DMSO), $\delta(\text{ppm})$: 40.7, 44.7, 50.7, 51.7, 119.2 (q, $J = 280.0$ Hz), 152.8, 156.2 (q, $J = 30.0$ Hz).

***N'*-[*(2Z)*-4-benzylpiperazin-2-ylidene]2,2,2-trifluoroacetohydrazide, 4g.** The procedure for the

preparation of **4a** was followed with 2.0g (11.1 mmol) of **3a** and 3.34g (22.26 mmol) of *N*-benzylethylenediamine, to afford 2.1g (7.0 mmol) of **4f** as a white solid, 67% yield. m.p. 138 °C, dec.; Anal., Calc. for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_4\text{O}$: C: 52.00%, H: 5.04%, N: 18.66%, F: 18.98%; Found: C: 52.13%, H: 4.87%, N: 18.49%, F: 19.18%; IR(KBr): 3379, 3064, 2970,

1622, 1566, 1359, 1207, 1170, 1132 cm^{-1} ; MS (ES) 301 ($\text{M}+\text{H}$), 100%; HRMS(ES+) calc. for ($\text{M}+\text{H}$) $^{+}$: 301.1276, found: 301.1285 (3.0 ppm); ^1H -NMR (400.13 MHz, DMSO), $\delta(\text{ppm})$: 2.70 (t, $J = 7.0$ Hz, 2H), 3.30 (t, $J = 7.0$ Hz, 2H), 3.41 (s, 2 H), 3.58 (s, 2 H), 7.2-7.4 (m, 5H). ^{13}C -NMR (100.62 MHz, DMSO), $\delta(\text{ppm})$: 40.6, 48.7, 49.7, 60.6, 119.0 (q, $J = 280.0$ Hz), 127.7(2C), 128.7(2C), 129.2, 137.4, 152.8, 156.4 (q, $J = 30.0$ Hz).

8-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine hydrochloride, 1b.

The procedure for the preparation of **1a** was followed using 5.1 g (22.75 mmol) of **4b** and 1.88 mL (23 mmol) of 37% HCl. Removal of volatiles at reduced pressure afforded 5.5 g of **1b** hydrochloride salt as a colorless oily residue, 99% yield. IR(KBr): 3426, 1558, 1520, 1255, 1183, 1038 cm^{-1} ; MS (ES) 207 ($\text{M}+\text{H}$), 100%; HRMS(ES+) calc. for ($\text{M}+\text{H}$) $^{+}$: 207.0858, found: 207.0865 (3.4 ppm); ^1H -NMR (400.13 MHz, CD_3OD^a), $\delta(\text{ppm})$: 1.90 (d, $J = 7$

Hz, 3H), 3.70-3.80 (m, 1H), 3.95-4.05 (m, 1H), 4.50-4.60 (m, 1H), 4.60-4.70 (m, 1H), 4.80 (b, 2H), 4.98 (q, $J = 7$ Hz, 1H); ^{13}C -NMR (100.62 MHz, CD_3OD^b), $\delta(\text{ppm})$: 14.8, 39.4, 40.7, 48.9, 118.1 (q, $J = 270.0$ Hz), 143.8 (q, $J = 40.0$ Hz), 151.5

8-phenyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine, 1c. The procedure

for the preparation of **1a** was followed using 116 mg (0.41 mmol) of **4c** and 40 μL (0.5 mmol) of 37% HCl in 0.5 mL of methanol. Removal of volatiles at reduced pressure afforded 119 mg of **1c** hydrochloride salt as a colorless oily residue, 97% yield. IR(KBr): 3446, 3309, 1558, 1539, 1267, 1195, 1170, 1138 cm^{-1} ; MS (ES) 269 ($\text{M}+\text{H}$), 100%; HRMS(ES+) calc. for ($\text{M}+\text{H}$) $^{+}$: 269.1014, found: 269.1016 (0.7 ppm); ^1H -NMR (400.13 MHz, CD_3OD^a), $\delta(\text{ppm})$: 3.85-4.00 (m, 2H), 4.65-4.80

(m, 2H), 4.80-5.00 (b, 2H), 6.20 (s, 1H), 7.45-7.65 (m, 5H). ^{13}C -NMR (100.13 MHz, CD_3OD^b), $\delta(\text{ppm})$: 39.5, 40.8, 56.2, 118.1 (q, $J = 270.0$ Hz), 129.1, 129.6(2C), 130.6(2C), 131.0, 144.0 (q, $J = 40.0$ Hz), 150.3

7-methyl-3-phenyl-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine, 1d. Oxadiazole **3e** (2.0g,

10.28 mmol) was combined with *N*-methylethylenediamine (1.52g, 20.6 mmol) in 10 mL of methanol and the mixture warmed at 50 °C for 22 hours. The brown solution was cooled to room temperature and the solvent removed at reduced pressure. The residue was dissolved in water and extracted with ethyl acetate 5 times. The organic extracts were combined, dried with magnesium sulfate and the volatiles were removed at reduced pressure to afford 1.13g of triazole **1d** as a tan solid, 51% yield. m.p. 86 °C; Anal., Calc. for $\text{C}_{12}\text{H}_{14}\text{N}_4$: C: 67.27%, H: 6.59%, N: 26.15%; Found: C: 67.60%, H: 6.46%, N: 26.55%; IR(KBr): 3299, 3224, 1662, 1616, 1577 cm^{-1} ; MS (ES) 215 (M+H), 100%; HRMS(ES+) calc. for (M+H) $^+$: 215.1297, found: 215.1295 (-0.9 ppm); ^1H -NMR (500.13 MHz, CDCl_3^a), $\delta(\text{ppm})$: 7.64 (m, 2H), 7.47-7.43 (om, 3H), 4.06 (t, $J = 5.6$, 2H), 3.80 (s, 2H), 2.79 (t, $J = 5.6$, 2H) 2.49 (s, 3H). ^{13}C -NMR (125.77 MHz, CDCl_3^b), $\delta(\text{ppm})$: 152.9, 150.4, 130.0, 129.0 (2C), 128.1 (2C), 127.0, 51.8, 51.6, 45.4, 44.0

7-benzyl-3-phenyl-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine, 1e. Oxadiazole **3e** (2.0g,

10.28 mmol) was combined with *N*-benzylethylenediamine (3.1g, 20.6 mmol) in 10 mL of methanol and the mixture warmed at 50 °C for 20 hours. The brown solution was cooled to room temperature and the solvent removed at reduced pressure. The residue was purified by chromatography on silica gel to afford 1.6g of triazole **1e** as a white solid, 54% yield. m.p. 102 °C; Anal., Calc.

for $\text{C}_{18}\text{H}_{18}\text{N}_4$: C: 74.46%, H: 6.25%, N: 19.30%; Found: C: 74.39%, H: 6.26%, N: 19.23%; IR(KBr): 3299, 3227, 1653, 1616, 1522, 1491 cm^{-1} ; MS (ES) 291 (M+H), 100%; HRMS(ES+) calc. for (M+H) $^+$: 291.1610, found: 291.1618 (2.7 ppm); ^1H -NMR (400.13 MHz, CDCl_3^c), $\delta(\text{ppm})$: 2.84 (t, $J = 6.5$ Hz, 2H), 3.77 (s, 2H), 3.91 (s, 2H), 4.07 (t, $J = 6.5$ Hz, 2H), 7.2-7.8 (m, 10 H). ^{13}C -NMR (100.62 MHz, CDCl_3^d), $\delta(\text{ppm})$: 44.0, 49.0, 49.9, 61.7, 126.9, 127.7(2C), 127.9(2C), 128.5(2C), 128.8, 128.9(2C), 129.7, 136.7, 150.4, 152.7

7-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine hydrochloride,

1f. The procedure for the preparation of **1a** was followed using 200 mg (0.89 mmol) of **4f** and 73 μ l (0.9 mmol) of 37% HCl. After crystallization, 209 mg of **1f** hydrochloride salt were obtained as a white solid, 97% yield. m.p. 175 °C; Anal., Calc. for $C_7H_{10}ClF_3N_4$: C: 34.65%, H: 4.15%, N: 23.09%, Cl: 14.61%, F: 23.49%; Found: C: 34.54%, H: 3.95%, N: 22.88%, Cl: 14.37%; F: 23.44%; IR(KBr): 3023, 2968, 1512, 1175, 1150, 1033 cm^{-1} ; MS (ES) 207 (M+H), 100%; HRMS(ES+) calc. for (M+H)⁺: 207.0858, found: 207.0860 (1.0 ppm); ¹H-NMR (400.13 MHz, CD₃OD^a), δ (ppm): 3.20 (s, 3H), 3.96 (t, J = 6.5 Hz, 2H), 4.63 (t, J = 6.5 Hz, 2H), 4.90 (s, 2H). ¹³C-NMR (100.62 MHz, CD₃OD^b), δ (ppm): 40.3, 41.9, 48.4, 49.1, 118.1 (q, J = 270.0 Hz), 143.7 (q, J = 40.0 Hz), 147.4

7-benzyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4,]triazolo[4,3-*a*]pyrazine hydrochloride,

1g. The procedure for the preparation of **1a** was followed using 660 mg (2.2 mmol) of **4g** and 180 μ l (2.2 mmol) of 37% HCl. After crystallization, 695 mg of **1g** hydrochloride salt were obtained as a white solid, 99% yield. m.p. 215 °C; Anal., Calc. for $C_{13}H_{14}ClF_3N_4$: C: 48.99%, H: 4.43%, N: 17.58%, Cl: 11.12%, F: 17.88%; Found: C: 48.74%, H: 4.36%, N: 17.41%, Cl: 11.23%; F: 18.43%; IR(KBr): 2999, 1541, 1253, 1211, 1172 cm^{-1} ; MS (ES) 283 (M+H), 100%; HRMS(ES+) calc. for (M+Na)⁺: 283.1171, found: 283.1177 (2.1 ppm); ¹H-NMR (400.13 MHz, CD₃OD^a), δ (ppm): 3.92 (t, J = 6.5 Hz, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.68 (s, 2H), 4.74 (s, 2H), 7.5-7.6 (m, 3 H), 7.6-7.7 (m, 2H). ¹³C-NMR (100.62 MHz, CD₃OD^b), δ (ppm): 40.6, 46.5, 47.2, 59.7, 118.0 (q, J = 270.0 Hz), 128.2, 129.2(2C), 130.2(2C), 130.9, 143.6 (q, J = 40.0 Hz), 147.6

3-methoxy-5-methylene-3-(trifluoromethyl)-4,5-dihydro-3-*H*-pyrazole, **6²**

¹H-NMR (500.13 MHz, CH₃OH:CD₃OD^a): δ (ppm): 5.63 (d, J=4.0, 1H), 5.77 (d, J=4.0, 1H) ¹³C-NMR (125.77 MHz, CD₃OD^b): δ (ppm): 94.9, 120.6 (q, J_{CF}=284.3), 128.0 (q, J_{CF}=33.8), 172.2, CD₃O- not observed; ¹⁵N-NMR (50.68 MHz, CD₃OD): δ (ppm): 486 (N=N).

N-[[5-methoxy-5-(trifluoromethyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]methyl]ethane-1,2-diamine,

7a²

¹H-NMR (500.13 MHz, CH₃OH:CD₃OD^a): δ(ppm): 2.71 (t, J=6.4, 2H), 2.78 (d, J=6.4, 2H), 3.32 (s, 3H), 3.60 (m, 2H) 8.23 (br s, 1H)^{3,4} ¹³C-NMR (125.77 MHz, CD₃OD^b): δ(ppm): ~41, 43.8, ~49, 51.2, 113.5(q, J_{CF}=35.1), 121.9 (q, J_{CF}=283.0), 154.0; ¹⁵N-NMR (50.68 MHz, CD₃OD): δ(ppm):

256 (C=N).

N-[[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]methyl]ethane-1,2-diamine, 5a²

¹H-NMR (500.13 MHz, CH₃OH:CD₃OD^a): δ(ppm): 2.79 (t, J=6.0, 2H), 2.92 (d, J=6.0, 2H), 4.19 (s, 2H)³, ¹³C-NMR (125.77 MHz, CD₃OD^b): δ(ppm): ~41, 43.9, 51.0, 118.1(q, J_{CF}=270.1), 156.6 (q, J_{CF}=43.7), 169.4; ¹⁵N-NMR (50.68 MHz, CD₃OD): δ(ppm): 301 (N=C).

^a Referenced to CHD₂OD at δ= 3.31.ppm

^b Referenced to CD₃OD at δ= 49.0.ppm

^c Referenced to CHCl₃ at δ= 7.26 ppm

^d Referenced to CDCl₃ at δ= 77.0 ppm

² In unpublished work we have identified and fully characterized by proton, carbon-13 and nitrogen-15 NMR, three intermediates **6**, **7a** and **5a** via in situ NMR studies of the Amidine (**4a**) formation, conducted at -40°C.

³ The three NH protons from the ethylene diamine moiety are exchanged with the deuterium from the solvent.

⁴ Residual oxadiazole NH is observed and suggests slow exchange.