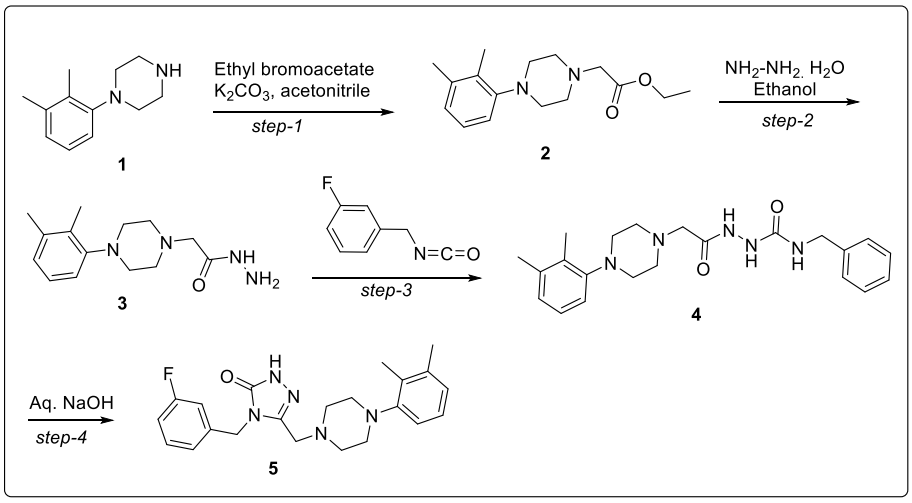
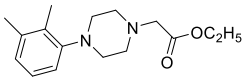
Supplement information 1. Chemical synthesis strategy of compound analogs.

Scheme 1: General Strategy for Synthesis of Compounds **5** and **5a-5i** :



Note: Compounds **5a-5i** (**Figure 1**) were synthesized by following general synthetic strategy shown in Scheme 1

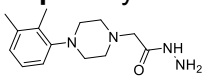
Step-1: Synthesis of ethyl 2-(4-(2,3-dimethylphenyl piperzin-1-yl)acetate (**2**):



A solution of 1-(2,4-difluorophenyl)piperazine (1 g, 5.05 mmol), ethyl 2-bromoacetate (0.843 g, 5.05 mmol) and potassium carbonate (0.906 g, 6.56 mmol) was refluxed for 4 hour at 85 °C. Then reaction mixture was cooled, concentrated, and residue was dissolved in DCM and washed with water. Organic layer was dried and concentrated, purified by Combiflash silica gel column chromatography eluting with a mixture of ethyl acetate and hexanes to afford the product as a pale yellow liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (t, *J* = 7.7 Hz, 1H), 6.98 – 6.81 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.30 (s, 2H), 2.94 (t, *J* = 4.8 Hz, 4H), 2.77 (bs, 4H), 2.26 (s, 3H), 2.22 (s, 3H), 1.30 (t, *J* = 8.0 Hz , 3H).

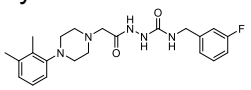
Step-2: Synthesis of 2-(4-(2,3-dimethylpheny)piperazin-1-yl)acetohydrazide:



Ethyl 2-(4-(2,3-dimethylphenyl piperzin-1-yl)acetate and 50-60% aq. hydrazine were dissolved in absolute ethanol. The solution was refluxed for 16 hours at 75 °C. Reaction mixture was cooled, concentrated *in vacuo*. The residue was diluted with 25 ml brine and extracted with dichloromethane three times (100 ml, 100ml, 50 ml). Organic layer was dried, concentrated to afford a white solid which was washed with diethyl ether and collected by vacuum filtration to afford the pure product as a white solid (88%, 0.85g).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 2H), 7.11 – 7.07 (m, 1H), 6.93 - 6.90 (m, 2H), 3.17 (s, 1H), 2.91 (t, *J* = 4.8 Hz, 4H), 2.71 (d, *J* = 4.8 Hz, 4H), 2.27 (s, 6H), 2.20 (s, 6H).

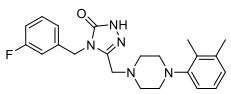
Step-3: Synthesis of 2-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)acetyl)-N-(3-fluorobenzyl) hydrazine carb- -oxamide



2-(4-(2,3-Dimethylpheny)piperazin-1-yl)acetohydrazide (0.3 g, 1.14 mmol) and 1-fluoro-3-(isocyanato-methyl)benzene (0.173 g, 1.14 mmol) were dissolved in dichloromethane and was allowed to stir at room temperature for 8-10 hours. Reaction mixture was concentrated on rotary evaporator followed by high vacuum pump to afford the product as a white solid (quantitative yield, 0.47 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (d, *J* = 1.7 Hz, 1H), 7.91 (d, *J* = 1.6 Hz, 1H), 7.32 (td, *J* = 8.1, 6.3 Hz, 1H), 7.17 – 6.66 (m, 6H), 5.74 (s, 2H), 4.23 (d, *J* = 6.1 Hz, 2H), 2.79 (t, *J* = 4.8 Hz, 4H), 2.63 (s, 4H), 2.18 (s, 3H), 2.12 (s, 3H).

Step-4: Synthesis of 3-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)-4-(3-fluorobenzyl)-1H-1,2,4-triazol-5(4H)-one (**5**):



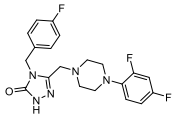
1M aq. NaOH (10 ml) was added to 2-(2-(4-(2,3-dimethylphenyl)piperazin-1-yl)acetyl)-N-(3-fluorobenzyl)hydrazinecarboxamide (0.3 g, 0.726 mmol) and the reaction mixture was stirred at 85 °C for 6-8 hours. Then reaction mixture was cooled and extracted with EtOAc (150 ml), and washed with water (40 ml x 2). Aqueous layer was extracted with EtOAc (100 ml). Combined organic layers were dried, concentrated *in vacuo* to afford a white solid (0.18 g, 62%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.93 (s, 1H), 7.34 – 7.29 (m, 1H), 7.11 – 6.88 (m, 6H), 5.08 (s, 2H), 3.34 (s, 2H), 2.83 (d, *J* = 4.9 Hz, 4H), 2.27 (s, 4H), 2.27 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 161.7, 156.5, 151.1, 144.9, 138.74 (d, *J* = 7.1 Hz), 138.0, 131.2, 130.38 (d, *J* = 8.0 Hz), 125.8, 125.1, 123.06 (d, *J* = 2.7 Hz), 116.6, 114.90 (d, *J* = 20.9 Hz), 114.55 (d, *J* = 21.9 Hz), 54.0, 53.4, 51.8, 44.1, 20.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -115.96 (dd, *J* = 9.1, 5.8 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{27}FN_5O$: 396.21942; found, 396.21903.

Using above 4 procedures compound **5a-5i** were synthesized.

5a) 3-((4-(2,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(4-fluorobenzyl)-1H-1,2,4-triazol-5(4H)-one

Compound **5a** was synthesized as a white solid (13%, 0.04 g), starting from 1-(2,4-difluorophenyl) piperazine using 4 steps as described above.

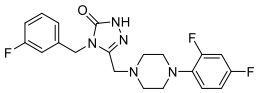


^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.35 (s, 1H), 7.30 – 7.25 (m, 3H), 7.06 – 7.00 (m, 1H), 6.91 – 6.78 (m, 3H), 5.02 (s, 2H) 3.30 (s, 2H), 2.99 (s, 4H), 2.58 (s, 4H); ^{13}C NMR (100 MHz, Chloroform-*d* + MeOH *d4*) δ 163.54, 161.08, 156.82 (d, *J* = 11.9 Hz), 156.1, 144.65, 136.17, 131.83 (d, *J* = 3.3 Hz), 129.12 (d, *J* = 8.2 Hz), 119.52 (d, *J* = 6.0 Hz), 115.65 (d, *J* = 21.6 Hz),

110.70 (dd, *J* = 21.4, 3.6 Hz), 104.67 (t, *J* = 25.3 Hz), 53.71, 52.83, 50.59, 43.83; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.95, -118.62 (d, *J* = 54.5 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{21}F_3N_5O$: 404.16927; found, 404.16879.

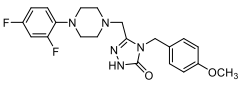
5b) 3-((4-(2,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(3-fluorobenzyl)-1H-1,2,4-triazol-5(4H)-one

Compound **5b** (77%, 0.22g) was synthesized, starting from 1-(2,4-difluorophenyl)piperazine by following 4 steps as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.11 (s, 1H), 7.34 – 7.30 (m, 2H), 7.08 – 6.96 (m, 1H), 6.90 – 6.77 (m, 4H), 5.04 (s, 2H), 3.31 (s, 2H), 2.96 (bs, 4H), 2.58 (t, *J* = 4.9 Hz, 4H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 168.09, 165.6, 163.23 (d, *J* = 11.7 Hz), 160.79 (dd, *J* = 12.0, 4.0 Hz), 160.17, 158.29 (d, *J* = 12.2 Hz), 148.77, 142.60 (d, *J* = 7.2 Hz), 140.14 (dd, *J* = 9.1, 3.5 Hz), 134.29 (dd, *J* = 8.1, 2.0 Hz), 126.68 (d, *J* = 3.0 Hz), 123.51, 118.36 (dd, *J* = 58.7, 21.7 Hz), 114.57 (d, *J* = 21.9 Hz), 108.42 (t, *J* = 25.3 Hz), 57.49, 56.69, 54.47 (d, *J* = 3.0 Hz), 47.95 (d, *J* = 2.0 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.18 (td, *J* = 9.0, 5.8 Hz), -118.56 – -118.65 (m), -118.71 (td, *J* = 11.3, 10.6, 5.1 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{21}F_3N_5O$: 404.16927; found, 404.16895.

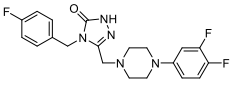
5c) 3-((4-(2,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(4-methoxybenzyl)-1H-1,2,4-triazol-5(4H)-one



Compound **5c** (79%, 0.4 g) was synthesized, starting from 1-(2,4-difluorophenyl)piperazine by following 4 steps as described above.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.22 (m, 2H), 6.92 – 6.78 (m, 5H), 4.99 (s, 2H), 3.78 (s, 3H), 3.28 (s, 2H), 3.01 (t, *J* = 4.5 Hz, 4H), 2.58 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 159.2, 156.6, 154.4 (d, *J* = 11.9 Hz), 144.8, 136.8 – 135.6 (m), 128.9, 128.2, 119.5 – 119.4 (m), 114.1, 110.8, 110.6 (d, *J* = 4.1 Hz), 104.7 (t, *J* = 25.1 Hz), 55.3, 53.8, 52.9, 50.7, 44.1; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -118.29 – -118.49 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{24}F_2N_5O_2$: 416.18926; found, 416.18872.

5d) 3-((4-(3,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(4-fluorobenzyl)-1H-1,2,4-triazol-5(4H)-one

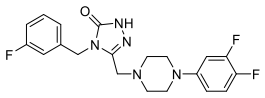


Compound **5d** (88%, 0.32 g) was synthesized, starting from 1-(3,4-difluorophenyl)piperazine by following 4 steps as described above.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 7.36 – 7.30 (m, 1H), 7.07 – 6.97 (m, 4H), 6.68 (ddd, *J* = 13.2, 6.8, 2.9 Hz, 1H), 6.56 (dtd, *J* = 9.0, 3.2, 1.5 Hz, 1H), 5.03 (s, 2H), 3.30 (s, 2H), 3.04 (s, 4H), 2.55 (t, *J* = 5.0 Hz, 4H); ^{13}C NMR (100 MHz, Chloroform-*d* + MeOH-*d4*) δ 164.09, 161.64, 156.12, 151.66, 148.2, 144.54, 138.49, 130.36 (d, *J* = 8.3 Hz), 122.76 (d, *J* = 2.9 Hz), 117.13 (d, *J* = 16.5 Hz), 114.85 (d, *J* = 21.0 Hz), 114.20 (d, *J* = 22.0 Hz), 111.70, 105.44 (d, *J* = 20.2 Hz), 53.60, 52.55, 49.27, 44.0; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -109.11 – -117.42 (m), -136.51 (dt, *J* = 22.2, 11.0 Hz), -149.14; HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{21}F_3N_5O$: 404.16927; found, 404.16870.

5e) 3-((4-(3,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(3-fluorobenzyl)-1H-1,2,4-triazol-5(4H)-one

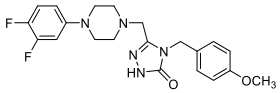
Compound **5e** (81%, 0.24 g) was synthesized, starting from 1-(3,4-difluorophenyl)piperazine by following 4 steps as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.03 (s, 1H), 7.34 – 7.26 (m, 1H), 7.07 – 6.94 (m, 4H), 6.67 (ddd, *J* = 13.2, 6.8, 2.8 Hz, 1H), 6.58 – 6.54 (m, 1H), 5.03 (s, 2H), 3.30 (s, 2H), 3.15 – 2.85 (m, 4H), 2.55 (t, *J* = 5.0 Hz, 4H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.0, 161.6, 156.1, 148.2, 144.5, 138.4 (d, *J* = 7.2 Hz), 130.3 (d, *J* = 8.2 Hz), 122.7 (d, *J* = 3.0 Hz), 117.0 (d, *J* = 17.2 Hz), 114.8 (d, *J* = 20.9 Hz), 114.1 (d, *J* = 22.1 Hz), 111.7, 109.9, 105.4 (d, *J* = 20.2 Hz), 53.53, 52.51, 49.22, 43.96; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.08 (td, *J* = 8.9, 5.9 Hz), -136.52 (ddd, *J* = 22.3, 13.1, 9.0 Hz), -145.99 – -155.49 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{20}H_{21}F_3N_5O$: 404.16927; found, 404.16889.

5f) 3-((4-(3,4-Difluorophenyl)piperazin-1-yl)methyl)-4-(4-methoxybenzyl)-1H-1,2,4-triazol-5(4H)-one

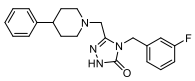
Compound **5f** (69%, 0.4 g) was synthesized, starting from 1-(3,4-difluorophenyl)piperazine by following 4 steps as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.69 (s, 1H), 7.47 – 7.41 (m, 2H), 7.24 (qd, *J* = 9.4, 3.0 Hz, 1H), 7.07 – 7.04 (m, 2H), 6.89 (ddd, *J* = 13.4, 6.8, 3.4 Hz, 1H), 6.83 – 6.73 (m, 1H), 5.18 (s, 2H), 3.99 (s, 3H), 3.48 (s, 2H), 3.28 (dt, *J* = 6.4, 3.5 Hz, 4H), 2.75 (dd, *J* = 6.2, 3.3 Hz, 4H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 159.1, 156.1, 144.7, 128.5, 127.9, 117.1, 116.9, 113.9, 111.6, 110.0, 105.3 (d, *J* = 20.2 Hz), 55.0, 53.4, 52.4, 49.2, 43.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -136.34 (ddd, *J* = 22.2, 13.2, 9.0 Hz), -149.06 (dddd, *J* = 21.3, 10.2, 6.7, 3.4 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{24}F_2N_5O_2$: 416.18926; found, 416.18898.

5g) 4-(3-Fluorobenzyl)-3-((4-phenylpiperidin-1-yl)methyl)-1H-1,2,4-triazol-5(4H)-one

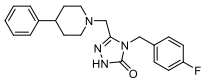
Compound **5g** (81%, 0.31 g) was synthesized, starting from 4-phenylpiperidine by following 4 steps procedure as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 7.36 – 7.27 (m, 3H), 7.25 – 7.15 (m, 3H), 7.11 – 6.98 (m, 3H), 5.06 (s, 2H), 3.28 (s, 2H), 2.85 (d, *J* = 11.2 Hz, 2H), 2.51 – 2.45 (m, 1H), 2.13 (t, *J* = 11.4 Hz, 2H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.67 – 1.57 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.1, 161.7, 156.4, 145.8, 145.2, 138.8 (d, *J* = 7.3 Hz), 130.3 (d, *J* = 8.4 Hz), 128.4, 126.7, 126.2, 123.0 (d, *J* = 3.0 Hz), 114.6 (dd, *J* = 27.4, 21.6 Hz), 54.3, 54.1, 44.2, 42.1, 33.1; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.29 (td, *J* = 8.9, 5.6 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{24}FN_5O$: 367.19287; found, 367.19227.

5h) 4-(4-Fluorobenzyl)-3-((4-phenylpiperidin-1-yl)methyl)-1H-1,2,4-triazol-5(4H)-one

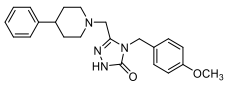
Compound **5h** (52%, 0.2 g) was synthesized, starting from 4-phenylpiperidine by following 4 steps procedure as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.37 (s, 1H), 7.34 – 7.29 (m, 4H), 7.26 – 7.19 (m, 3H), 7.07 – 7.01 (m, 2H), 5.05 (s, 2H), 3.27 (s, 2H), 2.86 (d, *J* = 11.2 Hz, 2H), 2.49 (tt, *J* = 12.2, 3.8 Hz, 1H), 2.29 – 2.01 (m, 2H), 1.88 – 1.77 (m, 2H), 1.65 (qd, *J* = 12.3, 3.7 Hz, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.5, 161.1, 156.3, 145.5 (d, *J* = 45.7 Hz), 132.1 (d, *J* = 3.3 Hz), 129.3 (d, *J* = 8.1 Hz), 128.4, 126.7, 126.3, 115.6, 54.3, 54.0, 43.9, 42.1, 33.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -114.22; HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{21}H_{24}FN_5O$: 367.19287; found, 367.19231.

5i) 4-(4-Methoxybenzyl)-3-((4-phenylpiperidin-1-yl)methyl)-1H-1,2,4-triazol-5(4H)-one

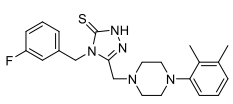
Compound **5i** (76%, 0.31 g) was synthesized, starting from 4-phenylpiperidine by following 4 steps procedure as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.02 (s, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 2H), 7.21 (dtd, *J* = 9.1, 3.6, 2.8, 1.6 Hz, 3H), 6.89 – 6.83 (m, 2H), 5.01 (s, 2H), 3.79 (s, 3H), 3.25 (s, 2H), 2.87 (d, *J* = 11.1 Hz, 2H), 2.49 (ddt, *J* = 12.0, 7.4, 3.8 Hz, 1H), 2.15 – 2.09 (m, 2H), 1.83 (d, *J* = 12.9 Hz, 2H), 1.70 (td, *J* = 12.4, 3.7 Hz, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 159.2, 156.6, 145.9, 145.4, 128.9, 128.5, 128.4, 126.8, 126.2, 114.0, 55.2, 54.3, 54.0, 44.0, 42.2, 33.2; HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{27}N_4O_2$: 379.21285; found, 379.21230.

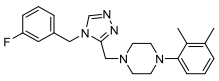
5j) 3-((4-(2,3-Dimethylphenyl)piperazin-1-yl)methyl)-4-(3-fluorobenzyl)-1H-1,2,4-triazole-5(4H)-thione

Compound **5j** (52%, 0.15 g) was synthesized, starting from 1-(2,4-difluorophenyl)piperazine by following 4 steps procedure as described above.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (bs, 1H), 7.26 – 7.21 (m, 1H), 7.07-6.99 (m, 3H), 6.95 – 6.88 (m, 2H), 6.83 (d, *J* = 7.9 Hz, 1H), 5.43 (s, 2H), 3.43 (s, 2H), 2.75 (t, *J* = 4.7 Hz, 4H), 2.50 (bs, 4H), 2.24 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.06, 161.61, 151.13, 138.43 (d, *J* = 7.1 Hz), 137.94, 131.17, 130.33 (d, *J* = 8.6 Hz), 125.8, 125.1, 122.9, 116.6, 114.8 (d, *J* = 21.2 Hz), 114.5, 114.3, 53.5, 53.2, 51.7, 46.7, 20.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.98; HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{27}FN_5S$: 412.19657; found, 412.19672.

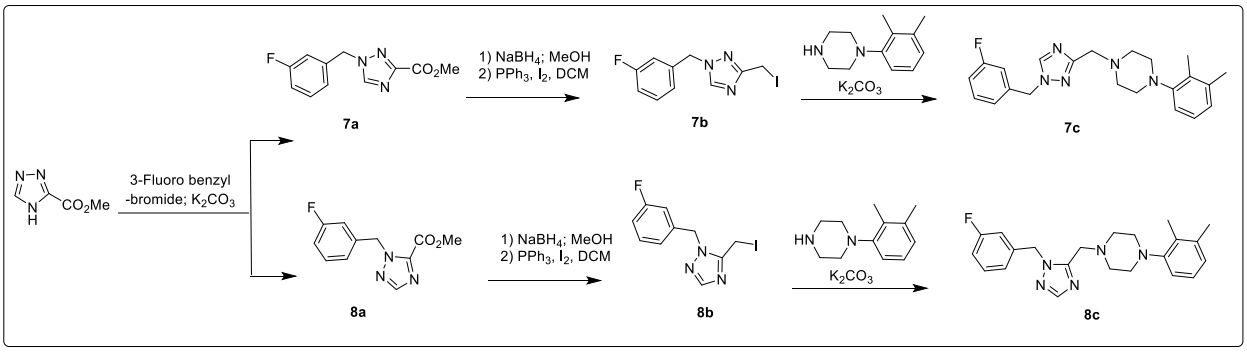
6) 1-(2,3-Dimethylphenyl)-4-((4-(3-fluorobenzyl)-4H-1,2,4-triazol-3-yl)methyl)piperazine



3-Phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (0.127 g, 0.486 mmol) was added to a solution of **5j** (0.1 g, 0.243 mmol) in pyridine. Reaction mixture was stirred for 3 hours at room temperature, then it was concentrated *in vacuo*. The residue was dissolved in EtOAc (15 ml) and washed with water (10ml) once and brine (10 ml) once. Organic layer was dried on sodium sulfate and concentrated *in vacuo*. The crude mixture was purified by Combiflash silica gel column chromatography eluting with DCM:MeOH to afford 75 mg of product with unknown impurities. Impure product was dissolved in diethyl ether (2-3 ml) and triturated at 0 °C and most of impurity crashed out as white solid particles, and the supernatant solution was pipetted out and concentrated to afford 50 mg of product which was further purified by Combiflash silica gel column chromatography eluting with a mixture of DCM and MeOH to afford the product as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.35 (td, *J* = 8.0, 5.8 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.98 – 6.88 (m, 3H), 6.88 – 6.80 (m, 1H), 5.36 (s, 2H), 3.71 (s, 2H), 2.83 (t, *J* = 4.7 Hz, 4H), 2.62 (bs, 4H), 2.26 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.3, 161.8, 154.5, 151.2, 138.0, 137.5 (d, *J* = 7.3 Hz), 131.3, 130.8 (d, *J* = 8.2 Hz), 125.7, 125.1, 122.8 (d, *J* = 3.1 Hz), 116.4, 115.5 (d, *J* = 21.0 Hz), 114.4 (d, *J* = 22.2 Hz), 53.6, 52.57, 51.9, 47.7, 20.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.15 – -111.48 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{27}FN_5$: 380.22450; found, 380.22431.

Scheme 2:

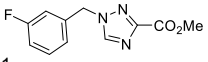


7c: Following 4 steps **7c** was synthesized:

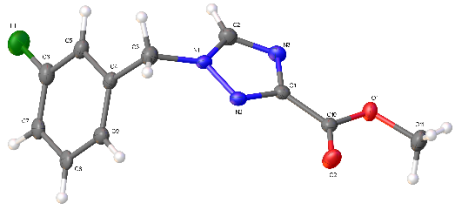
Step-1: Synthesis of **7a** (methyl 1-(3-fluorobenzyl)-1H-1,2,4-triazole-5-carboxylate) and **8a** (methyl 1-(3-fluorobenzyl)-1H-1,2,4-triazole-3-carboxylate) from methyl 4H-1,2,4-triazole-3-carboxylate :

Potassium carbonate (1.414 g, 10.23 mmol) was added to a solution of 1-(bromomethyl)-3-fluorobenzene (0.966 ml, 7.87 mmol) methyl 4H-1,2,4-triazole-3-carboxylate (1 g, 7.87 mmol) in acetone and the reaction mixture was refluxed for 4 hours. Then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with water, dried (Na_2SO_4), concentrated to afford the crude product which was purified by Combiflash silica gel column chromatography eluting with a mixture of EtOAc and hexanes to afford **7a** (38%, 0.7 g) and **8a** (16%, 0.3 g).

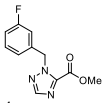
Characterization of **7a**:



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (t, *J* = 0.9 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.12 – 7.02 (m, 2H), 7.00-6.96 (m, 1H), 5.41 (s, 2H), 4.00 (s, 3H); X-Ray analysis: small portion of pure **7a** was crystallized in EtOAc and analyzed by X-Ray crystallography (please see supporting information).

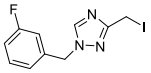


Characterization of **8a**:



^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.34 – 7.24 (m, 1H), 7.15 – 7.09 (m, 1H), 7.07 – 6.94 (m, 2H), 5.79 (s, 2H), 3.99 (s, 3H).

Step-2: Synthesis of **7b** 1-(3-fluorobenzyl)-3-(iodomethyl)-1H-1,2,4-triazole

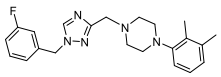


Sodium borohydride (0.45 g, 11.90 mmol) was added to a solution of **7a** (0.7 g, 2.98 mmol) in MeOH, followed by a drop of water. Reaction mixture was stirred at room temperature for 24 hours. Reaction mixture was concentrated, and the residue was dissolved in EtOAc, which was washed with saturated aq. ammonium chloride once and brine once. Organic layer was dried, concentrated *in vacuo* to afford the product which was pure enough to go to the next step (Iodination, see below).

Iodination: (1-(3-fluorobenzyl)-1H-1,2,4-triazol-3-yl)methanol (0.3 g, 1.448 mmol) was added to a solution of Ph_3P (0.380 g, 1.448 mmol), I_2 (0.367 g, 1.448 mmol) and imidazole (0.118 g, 1.737 mmol). Reaction mixture was stirred at room temperature for overnight. Then it was diluted with DCM, washed with water. Organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product, which was purified by Combiflash silica gel column chromatography.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.34 – 7.26 (m, 1H), 7.03-6.98 (m, 2H), 6.93-6.89 (m, 1H), 5.24 (s, 2H), 4.36 (s, 2H).

Step-3: Synthesis of **7c** 1-(2,3-dimethylphenyl)-4-((1-(3-fluorobenzyl)-1H-1,2,4-triazol-3-yl)methyl) piperaz-ine:

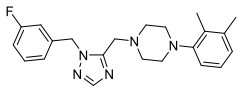


Potassium carbonate (0.17 g, 1.26 mmol) was added to a solution of **7b** (0.2 g, 0.631 mmol) and 1-(2,3-dimethylphenyl)piperazine (0.120 g, 0.631 mmol) in acetone. Reaction mixture was refluxed for 3 hours at 75 ^{o}C. Reaction mixture was concentrated, and the residue was dissolved in ethyl acetate, washed with water. Organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford a crude product which was further purified by Combiflash silica gel column chromatography using a mixture of EtOAc and hexanes to afford the product as a pale yellow liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.45 (s, 1H), 5.72-5.67 (m, 1H), 5.47 – 5.39 (m, 3H), 5.35 – 5.27 (m, 3H), 3.69 (s, 2H), 2.17 (s, 2H), 1.34 (t, *J* = 4.8 Hz, 4H), 1.15 (s, 4H), 0.64 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.1, 161.6, 151.5, 143.7, 137.8, 137.2 (d, *J* = 7.4 Hz), 131.1, 130.6 (d, *J* = 8.2 Hz), 125.8, 124.8, 123.3 (d, *J* = 3.0 Hz), 116.6, 115.5 (d, *J* = 21.0 Hz), 114.8 (d, *J* = 22.2 Hz), 55.3, 53.5, 52.7, 51.8, 20.6, 13.9; ^{19}F NMR (376 MHz) δ -106.65 – -118.54 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{27}FN_5$: 380.22450; found, 380.22425

8c) Synthesis of 1-(2,3-dimethylphenyl)-4-((1-(3-fluorobenzyl)-1H-1,2,4-triazol-5-yl)methyl)piperazine

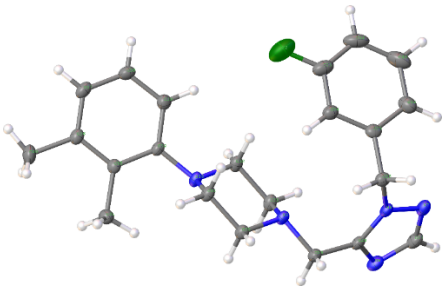
Compound **8c** was synthesized as an off-white solid from methyl 4H-1,2,4-triazole-3-carboxylate using the 3 step procedure described for scheme 2.



Potassium carbonate (0.281 g, 2.031 mmol) was added to a solution of 1-(3-fluorobenzyl)-5-(iodomethyl)-1H-1,2,4-triazole (0.46 g, 1.451 mmol) and 1-(2,3-dimethylphenyl)piperazine (0.276 g, 1.451 mmol) in acetone and reaction was refluxed for 2 hours at 75 °C. Reaction mixture was concentrated *in vacuo.* The residue was dissolved in EtOAc, washed with water. Organic layer was dried (Na_2SO_4), concentrated *in vacuo* to afford the crude product which was purified by Combiflash silica gel column chromatography eluting with a mixture of EtOAc and hexanes to afford **8a** as an off-white solid (0.29 g, 53%).

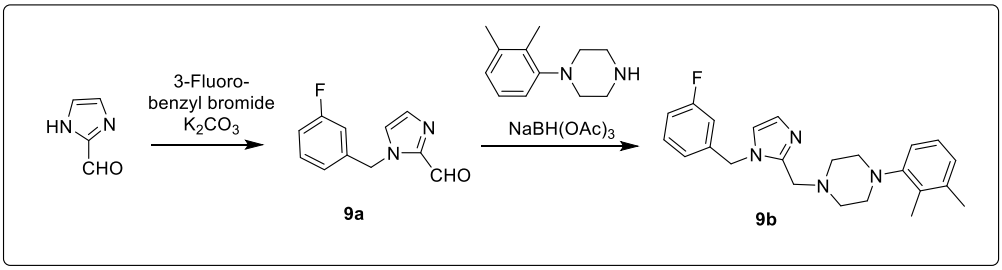
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.35 – 7.29 (m, 1H), 7.10 – 6.98 (m, 4H), 6.90 – 6.86 (m, 2H), 5.53 (s, 2H), 3.70 (s, 2H), 2.82 (t, *J* = 5.2 Hz, 4H), 2.61 (m, 4H), 2.26 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.1, 161.7, 151.2, 150.6, 138.0, 131.2, 130.4, 130.3, 125.8, 125.1, 123.1, 116.5, 115.0 (d, *J* = 21.0 Hz), 114.6 (d, *J* = 22.2 Hz), 53.7, 51.9, 51.8, 51.9, 20.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.14 (td, *J* = 9.0, 5.6 Hz); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{26}FN_5$: 380.22450; found, 380.22444.

X-Ray crystal structure: single colorless prism-shaped crystals of **8c** were recrystallized from a mixture of diethyl ether and hexanes by vapor diffusion (see details in X-Ray supporting information).

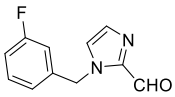


9b) Synthesis of 1-(2,3-dimethylphenyl)-4-((1-(3-fluorobenzyl)-1H-1,2,4-triazol-5-yl)methyl)piperazine

Scheme 3: Compound **9b was** synthesized from 1H-imidazole-2-carbaldehyde in two step procedure as shown below



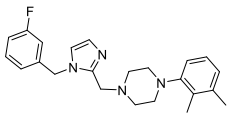
9a) 1-(3-fluorobenzyl)-1H-imidazole-2-carbaldehyde:



Potassium carbonate (1.12 g, 8.12 mmol) was added to a solution of 1-(bromomethyl)-3-fluorobenzene (0.511 g, 2.71 mmol), 1H-imidazole-2-carbaldehyde (0.26 g, 2.71 mmol) in acetone and the reaction mixture was refluxed at 75 °C for 2 hours. Then it was cooled and concentrated *in vacuo*. The residue was dissolved in EtOAc (100 ml), washed with water and brine. Organic layer was dried, concentrated *in vacuo* to afford the product (74%, 0.41 g) as a brown liquid, which was used without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (t, *J* = 9.8 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.02 – 6.95 (m, 2H), 6.88-6.85 (m, 1H), 5.60 (s, 2H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.67 – -118.31 (m).

9b) 1-(2,3-Dimethylphenyl)-4-((1-(3-fluorobenzyl)-1H-imidazol-2-yl)methyl)piperazine

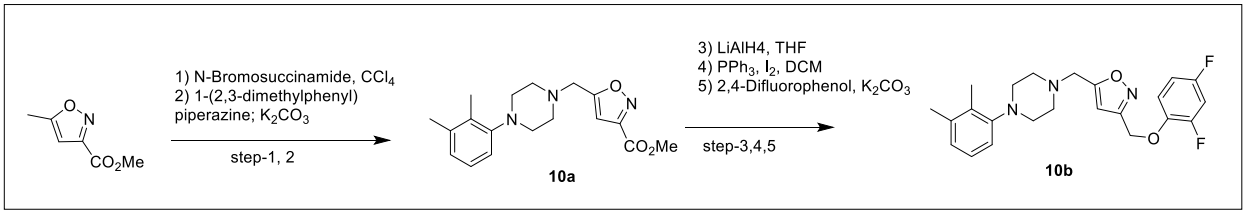


Acetic acid (0.011 ml, 0.201 mmol) was added to a solution of **9a** (0.41 g, 2.00 mmol), and 1-(2,3-dimethylphenyl)piperazine (0.382 g, 2.00 mmol) in CH_2Cl_2. After stirring for 5 minutes,

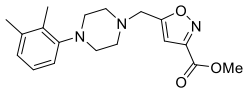
sodium triacetoxy borohydride (0.85 g, 4.02 mmol) was added and the reaction mixture was allowed to stir at 25 °C for 18 hours. LC-MS showed product formation along with unreacted starting materials. Reaction mixture was diluted with DCM, washed with aq. ammonium chloride and brine. Organic layer was dried, concentrated *in vacuo*. The crude residue was purified using Combiflash silica gel chromatography by eluting with a mixture of EtOAc and hexanes to afford the product as a yellow sticky liquid (29%, 0.22g).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34-7.28 (m, 2H), 7.08 – 6.97 (m, 4H), 6.94 – 6.84 (m, 3H), 5.33 (s, 2H), 3.64 (s, 2H), 2.81 (s, 4H), 2.60 (s, 4H), 2.25 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 164.3, 161.8, 151.4, 144.8, 139.5 (d, *J* = 7.2 Hz), 138.0, 131.3, 130.3 (d, *J* = 8.2 Hz), 127.5, 125.7, 124.9, 122.5 (d, *J* = 3.0 Hz), 121.1, 116.4, 114.4 (dd, *J* = 66.4, 21.6 Hz), 55.1, 53.5, 51.9, 49.1, 20.6, 13.9; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.21 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{28}FN_4$: 379.22925; found, 379.22864.

Scheme 4: Syntheisis of 3-((2,4-difluorophenoxy)methyl)-5-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)isoxazole **10b**



10a) Methyl 5-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)isoxazole-3-carboxylate

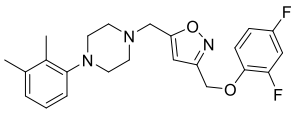


Step-1: To a solution of methyl 5-methylisoxazole-3-carboxylate (5.0 g, 35.4 mmol) in carbon tetrachloride (30 mL) was added N-bromosuccinamide (8.2 g, 46.1 mmol) and benzoyl peroxide (0.858 g, 3.54 mmol) at room temperature. The resulting mixture was stirred at 80°C for 18 hours. Then reaction was cooled, diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. Organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by Combiflash silica gel chromatography using a mixture of EtOAc and hexanes as eluents to afford the product as an off-white solid (52%, 4 g).

Step-2: A solution of 1-(2,3-dimethylphenyl)piperazine (0.432 g, 2.273 mmol), methyl 5-(bromomethyl)isoxazole-3-carboxylate (0.5 g, 2.273 mmol) and potassium carbonate (0.942 g, 6.82 mmol) was refluxed for 4 hours at 75 ^{o}C. Reaction mixture was concentrated *in vacuo*. The residue was dissolved in water and extracted with dichloromethane. Organic layer was dried, concentrated *in vacuo* and purified by Combiflash silica gel column chromatography using a mixture of EtOAc and hexane as eluents to afford the product as a white solid (70%, 0.5 g).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.45 (m, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 4.18 (s, 3H), 4.03 (s, 2H), 3.12 (d, *J* = 4.8 Hz, 4H), 2.90 (s, 4H), 2.45 (d, *J* = 2.3 Hz, 3H), 2.39 (d, *J* = 2.4 Hz, 3H).

10b) 3-((2,4-Difluorophenoxy)methyl)-5-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)isoxazole



Step-3: $LiAlH_4$ (0.118 g, 3.10 mmol) was added in three portions (5 minute intervals) to a solution of **10a** (0.51 g, 1.54 mmol) in THF at room temperature. Reaction was allowed to stir at room temperature for 4 hours. Then it was quenched with 30 ml aq. sodium-potassium tartrate solution and reaction mixture was stirred for overnight. Product was extracted with EtOAc, washed with brine, dried (Na_2SO_4), concentrated *in vacuo* to afford a brown liquid which was used for the next step without further purification.

Step-4: Triphenylphospine (0.480 g, 1.832 mmol), iodine (0.465 g, 1.832 mmol), (5-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)isoxazol-3-yl)methanol (0.46 g, 1.526 mmol), imidazole (0.145 g, 2.137 mmol) were added sequentially to DCM. Then reaction mixture was stirred for 3 hours at room temperature. Then it was diluted with DCM, washed with water and brine. Organic layer was dried, concentrated *in vacuo* to afford the crude product which was used in the next step without further purification (99%, 0.62 g).

Step-5: A solution of 2,4-difluorophenol (0.108 g, 0.827 mmol), 5-((4-(2,3-dimethylphenyl)piperazin-1-yl)methyl)-3-(iodomethyl)isoxazole (0.34 g, 0.827 mmol) and potassium carbonate (0.343 g, 2.48 mmol) was refluxed at 85 °C for 4 hours. Reaction mixture was cooled and concentrated *in vacuo*. The residue was dissolved in DCM. Organic layer was washed with water, dried (Na_2SO_4), concentrated *in vacuo* to afford the crude product which was purified by Combiflash silica gel column chromatography using a mixture of EtOAc and hexanes as eluents to afford the product as a yellow thick liquid (64%, 0.22 g).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 – 7.00 (m, 2H), 6.95 – 6.86 (m, 3H), 6.83-6.77 (m, 1H), 6.42 (d, *J* = 1.4 Hz, 1H), 5.20 (s, 2H), 3.79 (s, 2H), 2.95 (dt, *J* = 4.8, 2.5 Hz, 4H), 2.71 (s, 4H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.3, 160.2, 157.1 (dd, *J* = 243.0, 10.3 Hz), 152.8 (dd, *J* = 249.7, 12.1 Hz), 151.3, 142.4 (m), 138.0, 131.2, 125.8, 125.1, 116.9 (dd, *J* = 9.5, 2.6 Hz), 116.6, 110.6 (dd, *J* = 22.7, 3.9 Hz), 105.1 (dd, *J* = 26.8, 22.1 Hz), 102.8, 63.96, 53.49, 53.41, 51.97, 20.66, 13.96; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -118.17 (dp, *J* = 8.8, 4.5 Hz), -126.24 – -135.89 (m); HR-ESIMS (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{26}F_2N_3O_2$: 414.19876; found, 414.19817.