**Supporting Information**

for

**A Potent, *in vivo* Active Antimalarial Series Based on a Triazolopyrazine Core: Open Source Malaria Series 4**

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# General Experimental Details

All commercially available reagents and solvents were purchased and used as received from Sigma-Aldrich or Alfa-Aesar. Drying of glassware at 115 ˚C overnight and activation of molecular sieves in a microwave was performed when anhydrous conditions were required. Dichloromethane was distilled over calcium hydride. Reflux reactions were performed with a paraffin oil bath. Flash column chromatography was performed with Grace Silica Gel 60 (40 – 63 μm, 230 – 400 mesh), with solvent ratios as specified. All novel compounds listed below are italicised.

Melting points were obtained on an Optimelt Automated Melting Point System and reported in degrees Celsius. Optical rotation was recorded on a Perkin Elmer 341 polarimeter with Na lamp (589 nm).

1H and 13C nuclear magnetic resonance spectroscopy was conducted on a Bruker Avance III 500 (1H at 500.1 MHz, 13C at 125.8 MHz, 19Fat 470.6 MHz), a Bruker Avance III 400 (1H at 400.1 MHz, 13C at 100.6 MHz, 19Fat 376.5 MHz), a Bruker Avance 300 (1H at 300.1 MHz, 13C at 75.5 Hz, 19Fat 282.4 MHz) or a Bruker Avance 200 (1H at 200.1 MHz) with deuterated solvents (CDCl3, *d*-DMSO, MeOD) used without further purification. Signals are reported in the order chemical shift (ppm downfield with respect to the solvent residual), integration, multiplicity, coupling constants *J* (in Hertz) and assignments.

Low-resolution mass spectrometry was performed on a Finnigan LCQ mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode. High-resonance mass spectrometry was performed on a Bruker 7T Fourier Transform Ion Cyclotron Resonance mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode.

Infrared spectroscopy was performed on a Bruker Alpha FT-IR spectrometer under transmission mode, with absorbances reported as wave numbers.

Each experimental entry contains a publicly accessible hyperlink to the representative example from the Open Source Malaria electronic lab notebook (ELN, http://malaria.ourexperiment.org) reported in this experimental section and also to a page where all attempts at the reaction are collated. Raw and processed data is available on the ELN.

# General Synthetic Procedures

## General Procedure X: Hydrazinylpyrazine synthesis

Chloropyrazine (1 equiv.) was stirred in EtOH (0.35 M) and hydrazine monohydrate (2 equiv.) was added. The reaction was stirred at 80 °C until completion as indicated by TLC. The solvent was removed under reduced pressure, and the residue diluted with H2O and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc (3 ×) and the combined organic layers washed with brine, dried (Na2SO4), filtered and concentrated under reduced pressure to give the corresponding hydrazinylpyrazine that was used without further purification unless otherwise stated.

## General Procedure A: Condensation reaction

This procedure was adapted from the CRO method. REF

The product from General Procedure **Hydra** (1 equiv.) was dissolved in MeCN (0.60 M) and glacial acetic acid (1 equiv.) and the appropriate aldehyde (1 equiv.) were added. The reaction mixture was stirred at rt until completion as indicated by TLC. The reaction mixture was concentrated under reduced pressure to give the crude condensation product that was used without further purification unless otherwise stated.

## General Procedure B: Improved condensation reaction

The product from General Procedure **Hydra** (1 equiv.) was suspended in EtOH (0.1 M) and the appropriate aldehyde (1 equiv.) was added. The reaction mixture was stirred at rt until completion as indicated by TLC. The reaction mixture was concentrated under reduced pressure to give the crude condensation product that was used without further purification unless otherwise stated.

## General Procedure C: Oxidative cyclisation

The product from General Procedure **Conden** (1 equiv.) was dissolved in CH­2Cl2 (0.1 M) and (diacetoxyiodo)benzene (1 equiv.) was added. The reaction mixture was stirred at rt until completion as indicated by TLC, then quenched by the addition of a sat. aq. solution of NaHCO3. The aqueous layer was separated and extracted with CH­2Cl2 (3 ×) and the combined organic layers washed with brine, dried (MgSO4), filtered and concentrated under reduced pressure to give the crude material that was purified according to the stated method to give the corresponding cyclisation product.

General Procedure D: Nucleophilic aromatic substitution

The product from General Procedure **Cycle** (1.0 equiv.) was suspended in anhydrous PhMe (0.17 M). Powdered KOH (3.0 equiv.) and 18-crown-6 (~0.1 equiv.) were added and the reaction mixture was stirred at rt under Ar. The appropriate nucleophile (1.0 equiv.) was added and the reaction mixture was stirred at the stated temperature until completion as indicated by TLC. The reaction mixture was quenched by the addition of H2O and diluted with EtOAc. Organic layer was separated and the aqueous layer extracted with EtOAc (3 ×). The combined organic layers were washed with water until the aqueous layer became neutral, followed by brine, dried (MgSO­4), filtered and concentrated under reduced pressure to give the crude material that was purified according to the stated method to give the corresponding substitution product.

General Procedure E: Amide Coupling**[[1]](#endnote-1)**

6-Chloropyrazine-2-carboxlic acid (1.0 equiv.), the appropriate amine (1.0 equiv.) and DIPEA (1.5 equiv.) were dissolved in DMF (~1.0 M) and the reaction mixture cooled to 0 °C. T3P (50% in EtOAc, 1.5 equiv.) was added dropwise with stirring and the reaction mixture stirred at rt for ~18 h. The reaction mixture was diluted with EtOAc and washed with a sat. aq. solution of NaHCO3 (3 ×). The combined organic layers were washed with H2O, brine, dried (MgSO­4), filtered and concentrated under reduced pressure to give the crude material that was purified according to the stated method to give the corresponding amide product.

## General Procedure F: Suzuki Coupling

To a mixture of halogenated triazolopyrazine (0.3 mmol, 1.0 equiv.), Na2CO3 (6.0 equiv.), Pd(PPh3)4 (0.1 equiv.) and the appropriate boronic acid/ester (1.3 equiv.) were successively added H2O (1 mL), EtOH (2 mL) and 1,4-dioxane (4 mL). The reaction mixture was heated at 90 °C under N2 for 8 h. The reaction was cooled to rt, silica was added and the solvent removed under reduced pressure to give the crude material that was purified by flash chromatography on silica to give the corresponding Suzuki product.

## General Procedure G: Buchwald-Hartwig Coupling

A flask was charged with halogenated triazolopyrazine (1.00 mmol, 1.0 equiv.), the appropriate amine (1.3 equiv.), Pd(dba)2 (0.2 equiv.), JohnPhos (0.4 equiv.) and NaO*t*-Bu (1.4 equiv.) then backfilled with N2 (3 ×). PhMe (10 mL) was added and the reaction mixture was heated at 100 °C overnight under N2. The reaction was cooled to rt, diluted with H2O (30 mL) and extracted with CH2Cl2 (3 × 30 mL). The combined organic layers were dried (Na2SO4), filtered and concentrated under reduced to give the crude material that was that was purified by flash chromatography on silica to give the corresponding Buchwald-Hartwig product.

# Intermediates

**2-(Benzylsulfonyl)-6-chloropyrazine ()**

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NaH (60% dispersion in mineral oil, 1.60 g, 67.1 mmol) was added to benzyl mercaptan (8.00 mL, 67.1 mmol) in PhMe (64 mL). The mixture was heated at reﬂux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (10.0 g, 67.1 mmol) in PhMe (64 mL) was added. The mixture was heated at reﬂux for 24 h, cooled to rt, then washed with H2O (80 mL). The organic layer was separated, dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give the crude sulﬁde as a yellow liquid (16.9 g). The crude sulﬁde (4.91 g, 20.7 mmol) in glacial AcOH (50 mL) was added to a solution of KMnO4 (3.50 g) in H2O (28 mL) and the mixture was stirred at rt for 1 h. The mixture was adjusted to pH 7 with sat. aq. NH4OH solution (40 mL) then ﬁltered, extracted with CHCl3 (3 × 100 mL), dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give a cloudy yellow liquid (3.14 g); puriﬁed by automated ﬂash chromatography on silica (6–75% EtOAc in hexanes) to give **X** as large white crystals (1.31 g, 24%); **m.p.** 84–92 °C (lit. [181] 86–87 °C); **1H NMR** (300 MHz, CDCl3) δ: 8.85 (s, 1H), 8.79 (s, 1H), 7.71–6.67 (m, 5H), 4.65 (s, 2H); **13C NMR** (75 MHz, CDCl3) δ: 151.2, 149.3, 148.7, 141.4, 131.2, 129.4, 129.1, 126.4, 59.0; ***m/z*** (ESI+) 291 ([M+Na]+, 100%), 559 ([2M+Na]+, 74%); **HRMS** (ESI+) found 290.9969 ([M+Na]+), C11H9ClN2O2SNa+ requires 290.9965. Compound reported in the literature not fully characterized. [181]

*ClC1=CN=CC(S(CC2=CC=CC=C2)(=O)=O)=N1*

*InChI=1S/C11H9ClN2O2S/c12-10-6-13-7-11(14-10)17(15,16)8-9-4-2-1-3-5-9/h1-7H,8H2*

**2-(Benzylsulfonyl)-6-hydrazinylpyrazine ()**

**

Prepared according to General Procedure **Hydra** from: **X** (503 mg, 1.86 mmol) to give **X** as a yellow powder (483 mg); **1H NMR** (400 MHz, DMSO-d*6*) δ: 8.86 (s, 1H), 8.31 (s, 1H), 7.92 (s, 1H), 7.41–7.10 (m, 3H), 7.26–7.19 (m, 2H), 4.74 (s, 2H), 4.55 (s, 2H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 156.1, 148.4, 131.1, 128.4, 128.26, 128.34, 128.0, 57.1 (1 obscured signal).

*NNC1=CN=CC(S(CC2=CC=CC=C2)(=O)=O)=N1  
InChI=1S/C11H12N4O2S/c12-15-10-6-13-7-11(14-10)18(16,17)8-9-4-2-1-3-5-9/h1-7H,8,12H2,(H,14,15)*

**(*E*)-2-(Benzylsulfonyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine ()**



Prepared according to General Procedure **Conden** from: **X** (100 mg, 0.38 mmol) and 4-(difluoromethoxy)benzaldehyde (50.0 μL, 0.38 mmol); purified by trituration with CH2Cl2 to give **X** as a light brown powder (140 mg, 88%); **m.p.** 238–242 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.99 (br s, 1H), 8.93 (s, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.37–7.32 (m, 3H), 7.31 (t, *J* = 73.9 Hz, 1H), 7.27–7.21 (m, 4H), 4.74 (s, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 152.0, 151.8, 148.5, 142.3, 135.7, 131.9, 131.4, 131.2, 128.6, 128.5, 127.6, 118.9, 118.3, 116.2, 58.0; ***m/z*** (ESI+) 441 ([M+Na]+, 100%); **HRMS** (ESI+) found 441.0807 ([M+Na]+), C19H16F2N4O3SNa+ requires 441.0803.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=CN=CC(S(CC3=CC=CC=C3)(=O)=O)=N2*

*InChI=1S/C19H16F2N4O3S/c20-19(21)28-16-8-6-14(7-9-16)10-23-25-17-11-22-12-18(24-17)29(26,27)13-15-4-2-1-3-5-15/h1-12,19H,13H2,(H,24,25)/b23-10+*

**2-Chloro-6-(phenethylsulfonyl)pyrazine ()**



NaH (60% dispersion in mineral oil, 403 mg, 16.8 mmol) was added to phenylethyl mercaptan (2.25 mL, 16.8 mmol) in PhMe (16 mL). The mixture was heated at reﬂux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (2.50 g, 16.8 mmol) in PhMe (16 mL) was added. The mixture was heated at reﬂux for 24 h, cooled to rt, then washed with H2O (30 mL). The organic layer was separated, dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give the crude sulﬁde as a yellow liquid (3.92 g). The crude sulﬁde (3.92 g, 15.6 mmol) in glacial AcOH (40 mL) was added to a solution of KMnO4 (2.5 g) in H2O (20 mL) and the mixture was stirred at rt for 1 h. The mixture was adjusted to pH 7 with sat. NH4OH solution (40 mL) then ﬁltered, extracted with CHCl3 (3 × 100 mL), dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give an orange semi-solid (1.23 g); puriﬁed by automated ﬂash chromatography on silica (6–50% EtOAc in hexanes) to give **X** as large white crystals (547 mg, 12%); **m.p.** 92–100 °C; **1H NMR** (200 MHz, CDCl3) δ: 9.04 (s, 1H), 8.72 (s, 1H), 7.98–6.81 (m, 5H), 3.90–3.59 (m, 2H), 3.28–3.04 (m, 2H).

*ClC1=CN=CC(S(CCC2=CC=CC=C2)(=O)=O)=N1*

*InChI=1S/C12H11ClN2O2S/c13-11-8-14-9-12(15-11)18(16,17)7-6-10-4-2-1-3-5-10/h1-5,8-9H,6-7H2*

**(*E*)-2-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)-6-(phenethylsulfonyl)pyrazine ()**



Prepared according to General Procedure **Hydra** from: **X** (444 mg, 1.57 mmol) to give 2-hydrazinyl-6-(phenethylsulfonyl)pyrazine as a yellow powder (400 mg); followed by General Procedure **Conden** from: **X** (400 mg, 1.44 mmol) and 4-(difluoromethoxy)benzaldehyde (190 μL, 1.44 mmol); purified by flash chromatography on silica (12–100% EtOAc in hexanes) to give **X** as a yellow powder (275 mg, 44%); **1H NMR** (300 MHz; CDCl3) δ: 8.97 (s, 1H), 8.67 (s, 1H), 8.42 (s, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.42–7.05 (m, 7H), 6.57 (t, *J* = 73.4 Hz, 1H), 3.40–3.69 (m, 2H), 3.33–3.01 (m, 2H).

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=CN=CC(S(CCC3=CC=CC=C3)(=O)=O)=N2*

*InChI=1S/C20H18F2N4O3S/c21-20(22)29-17-8-6-16(7-9-17)12-24-26-18-13-23-14-19(25-18)30(27,28)11-10-15-4-2-1-3-5-15/h1-9,12-14,20H,10-11H2,(H,25,26)/b24-12+*

**6-Chloro-*N*-(3-chlorophenyl)pyrazine-2-carboxamide ()**

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Prepared according to General Procedure **Amide** from: 6-chloropyrazine-2-carboxylic acid (1.50 g, X mmol) and 3-chloroaniline (X); purified by flash chromatography on silica (10–50% EtOAc in hexanes) to give **X** as a light brown powder (1.90 g, 75%); **m.p.** 101–102 °C (lit. [67] 107–108 !); **1H NMR** (400 MHz, DMSO-d*6*) 10.82 (s, 1H), 9.24 (s, 1H), 9.07 (s, 1H), 8.04 (t, *J* = 1.9 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.22 (dd, *J* = 7.9, 1.3 Hz, 1H); **13C NMR** (101 MHz, DMSO-d*6*) 160.9, 147.6, 146.9, 144.8, 142.4, 139.4, 132.9, 130.3, 124.2, 120.3, 119.2; ***m/z*** (EI+) 267 ([M]+, 100%). Compound reported in the literature but not fully characterized. [66,67]

*ClC1=CN=CC(C(NC2=CC=CC(Cl)=C2)=O)=N1*

*InChI=1S/C11H7Cl2N3O/c12-7-2-1-3-8(4-7)15-11(17)9-5-14-6-10(13)16-9/h1-6H,(H,15,17)*

***N*-(3-Chlorophenyl)-6-hydrazinylpyrazine-2-carboxamide ()**



Prepared according to General Procedure **Hydra** from: X (1.80 g, 6.70 mmol) to give **X** as a yellow powder (1.46 g, 82%); **m.p.** 187 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.47 (s, 1H), 8.52 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 8.00 (t, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.64 (s, 2H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 162.6, 155.0, 140.8, 139.6, 135.7, 133.0, 130.4, 129.7, 123.8, 119.7, 118.7; ***m/z*** (ESI+) 264 ([M+H]+, 100%).

*NNC1=CN=CC(C(NC2=CC=CC(Cl)=C2)=O)=N1*

*InChI=1S/C11H10ClN5O/c12-7-2-1-3-8(4-7)15-11(18)9-5-14-6-10(16-9)17-13/h1-6H,13H2,(H,15,18)(H,16,17)*

**(*E*)-*N*-(3-Chlorophenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide ()**



Prepared according to General Procedure **Conden** from: **X** (300 mg, 1.14 mmol) and 4-(difluoromethoxy)benzaldehyde (X); purified by flash chromatography on silica (5–100% EtOAc in hexanes) to give **X** as a pale yellow powder (217 mg, 46%); **m.p.** 229–230 °C; **1H NMR** (400 MHz, DMSO-d*6*) 11.48 (s, 1H), 10.43 (s, 1H), 8.89 (s, 1H), 8.59 (s, 1H), 8.16 (s, 1H), 8.02 (t, *J* = 2.0 Hz, 1H), 7.84 (dapp, *J* = 8.8 Hz, 2H), 7.71 (ddd, *J* = 8.1, 1.7, 0.6 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 73.9 Hz, 1H), 7.24 (dapp, *J* = 8.6 Hz, 2H), 7.21 (ddd, *J* = 8.0, 2.0, 0.8 Hz, 1H); **13C NMR** (101 MHz, DMSO-d*6*) 162.6,151.6 (t, *J* = 3.2 Hz), 151.2, 142.3, 141.1, 139.6, 134.0, 133.4, 133.1, 131.6, 130.5, 128.3 (2C), 123.8, 119.5, 118.8 (2C), 118.4, 116.2 (t, *J* = 257.8 Hz); ***m/z*** (APCI+) 418 ([M+H]+, 100%); **HRMS** (APCI+) found 418.0877 ([M+H]+), C19H15ClF2N5O2+ requires 418.0877.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=CN=CC(C(NC3=CC=CC(Cl)=C3)=O)=N2*

*InChI=1S/C19H14ClF2N5O2/c20-13-2-1-3-14(8-13)25-18(28)16-10-23-11-17(26-16)27-24-9-12-4-6-15(7-5-12)29-19(21)22/h1-11,19H,(H,25,28)(H,26,27)/b24-9+*

**6-Chloro-*N*-(3-chloro-2-methylphenyl)pyrazine-2-carboxamide ()**



Prepared according to general procedure 1 from 1 (530 mg, 3.35 mmol). Crystalline beige solid (580 mg, 2.10 mmol, 62%); mp 155–156 !; ‹ max (ﬁlm)/cm ≠1 3367, 1701, 1579, 1542, 1436; ” H (400 MHz, CDCl 3 ) 9.44 (s, 1 H), 9.40 (s, 1 H), 8.84 (s, 1 H), 7.98 (dd, J = 1.18, 7.97 Hz, 1 H), 7.27 (dd, J = 1.28, 8.24 Hz, 1 H), 7.21 (t, J = 8.02 Hz, 1 H), 2.44 (s, 3 H);re ” C (100 MHz, CDCl 3 ) 159.69, 147.91, 147.69,144.05, 142.41, 136.15, 135.20, 127.93, 127.36, 126.82, 121.29, 14.62; m/z (APCI) 282 ([M+H] + ), (EI) 281 ([M] + ).

*ClC1=CN=CC(C(NC2=CC=CC(Cl)=C2C)=O)=N1*

*InChI=1S/C12H9Cl2N3O/c1-7-8(13)3-2-4-9(7)17-12(18)10-5-15-6-11(14)16-10/h2-6H,1H3,(H,17,18)*

***N*-(3-Chloro-2-methylphenyl)-6-hydrazinylpyrazine-2-carboxamide ()**



Prepared from 3 (525 mg, 1.86 mmol) according to general procedure 2 prior to development of ethyl acetate workup. Yellow solid (525 mg, >100%: residual hydrazine), carried forward without puriﬁcation or full characterisation; ‹ max (ﬁlm)/cm ≠1 2914, 1672, 1579, 1516, 1429; ” H (400 MHz, DMSO≠d 6 ) 10.15 (s, 1 H), 9.83 (s, 1 H), 8.65 (s, 1 H), 8.54 (s, 1 H), 7.69 (d, J = 7.0 Hz, 1 H), 7.34(dd, J = 7.9, 1.4 Hz, 1 H), 7.27 (t, J = 7.8 Hz, 1 H), 4.37 (s, 2 H), 2.33 (s, 3 H); m/z (ESI) 278 ([M+H] + ]).

*O=C(NC1=CC=CC(Cl)=C1C)C2=NC(NN)=CN=C2*

*InChI=1S/C12H12ClN5O/c1-7-8(13)3-2-4-9(7)17-12(19)10-5-15-6-11(16-10)18-14/h2-6H,14H2,1H3,(H,16,18)(H,17,19)*

**(*E*)-*N*-(3-Chloro-2-methylphenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide ()**



Prepared by general procedure 3 from 45 (300 mg, 1.08 mmol). Bright yellow ﬂakes (265 mg, 0.61 mmol, 56%); mp 209 !; ‹ max (ﬁlm)/cm ≠1 2174, 1674, 1577, 1508, 1421, 1226, 1112; ” H (400 MHz, DMSO≠d 6 ) 11.48 (s, 1 H), 10.06 (s, 1 H), 8.87 (s, 1 H), 8.62 (s, 1 H), 8.17 (s, 1 N H), 7.84 (d app , J = 8.8 Hz, 2 H), 7.79 (dd, J = 7.9, 1.6 Hz, 1 H), 7.34 N H (dd, J = 8.1, 1.7 Hz, 1 H), 7.32 (t, J = 73.9 Hz, 1 H), 7.29(t, J = 7.9 Hz, 1 H), 7.24 (d app , J = 8.7 Hz, 2 H), 2.37 (s, 3 H); ” C (100 MHz, DMSO≠d 6 ) 161.91, 151.62 (t, J = 3.1 Hz), 151.02, 141.61, 141.32, 137.26, 134.51, 133.78, 133.20, 131.65, 128.95, 128.32 (2 C), 127.27, 126.07, 122.54, 118.84 (2 C), 116.23 (t, J = 257.8 Hz); m/z (APCI) 432 ([M + H] + ); HRMS (APCI) 432.10329 ([M+H] + ) calcd. for C 20 H 17 ClF 2 N 5 O 2 + 432.10334.

*O=C(NC1=CC=CC(Cl)=C1C)C2=NC(N/N=C/C3=CC=C(OC(F)F)C=C3)=CN=C2*

*InChI=1S/C20H16ClF2N5O2/c1-12-15(21)3-2-4-16(12)27-19(29)17-10-24-11-18(26-17)28-25-9-13-5-7-14(8-6-13)30-20(22)23/h2-11,20H,1H3,(H,26,28)(H,27,29)/b25-9+*

**5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-387)**

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**OSM-S-592** (2.14 g, 13.5 mmol, 1.00 equiv.), 43 (2.09 g, 13.5 mmol, 1.00 equiv.) and 18-crown-6 (0.29 g, 1.08 mmol, 0.08 equiv.) were dissolved in PhMe (100 mL) and cooled in an ice bath. KOH (2.28 g, 40.6 mmol, 3.00 equiv.) was added portionwise within 1 h while stirring and the mixture was allowed to warm to rt and stirred for 3 h. After completion of the reaction as indicated by TLC, H2O (100 mL) was added and the resulting suspension filtered through a sintered funnel, washed with H2O (3 x 100 mL) then acetone (3 x 50 mL) and dried *in vacuo* to give the crude product as a pale violet solid (1.87 g); purified by recrystallisation from MeOH (1 g of crude per 100 mL of MeOH) to give **OSM-S-387** as yellow needles (1.51 g, 40%); **m.p.** 205–207 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.43 (s, 1H), 9.04 (s, 1H), 7.64 (s, 1H), 7.54 (ddd, *J* = 11.9, 7.9, 2.2 Hz, 1H), 7.42–7.31 (m, 1H), 7.31–7.23 (m, 1H), 4.64 (t, *J* = 6.5 Hz, 2H), 3.20 (d, *J* = 6.4 Hz, 2H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 150.0 (dd, *J* = 85.5, 12.7 Hz), 147.6 (dd, *J* = 84.7, 12.6 Hz), 145.8, 142.3, 135.3 (dd, *J* = 6.0, 3.7 Hz), 134.5, 133.1, 126.1 (dd, *J* = 6.3, 3.4 Hz), 118.2 (d, *J* = 16.9 Hz), 117.2 (d, *J* = 16.8 Hz), 108.3, 70.8, 33.5; ***m/z*** (APCI+) 277 ([M+H]+, 100%); **HRMS** (ESI+) found 277.0892 ([M+H]+), C13H11F2N4O+ requires 277.0895.

*FC(C=C1)=C(F)C=C1CCOC2=CN=CC3=NN=CN32*

*InChI=1S/C13H10F2N4O/c14-10-2-1-9(5-11(10)15)3-4-20-13-7-16-6-12-18-17-8-19(12)13/h1-2,5-8H,3-4H2*

**3-Bromo-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-432, MMV1576796)**

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*N*-Bromosuccinimide (1.08 g, 6.07 mmol, 1.5 equiv.) and **OSM-S-387** (1.12 g, 4.05 mmol, 1.0 equiv.) were dissolved in a mixture of CH2Cl2 (147 mL) and THF (3 mL) and heated at refluxed for 6 h. The reaction mixture was cooled to rt, washed with conc. Na2S2O3 solution (20 mL), H2O (2 x 30 mL) and brine (20 mL), then concentrated under reduced pressure and purified by flash chromatography on silica (20–100% EtOAc in hexanes) to give **OSM-S-432** as a pale brown solid (1.10 g, 77%); **m.p.** 171–172 °C (decomp.); **1H NMR** (400 MHz, CDCl3) δ: 8.93 (s, 1H), 7.28 (s, 1H), 7.21–7.08 (m, 2H), 7.05 (ddd, *J* = 8.4, 4.0, 1.9 Hz, 1H), 4.52 (t, *J* = 6.5 Hz, 2H), 3.26 (t, *J* = 6.5 Hz, 2H); **13C NMR** (101 MHz, CDCl3) δ: 151.4 (dd, *J* = 78.1, 12.6 Hz), 148.9 (dd, *J* = 78.1, 12.6 Hz), 148.7, 143.6, 136.5, 133.5 (dd, *J* = 5.7, 4.0 Hz), 125.0 (dd, *J* = 6.3, 3.6 Hz), 118.3–117.5 (m, 3C), 108.8, 71.5, 34.3; ***m/z*** (ESI+) 377 ([M+Na]+, 100%); **HRMS** (ESI+) found 356.9977 ([M+H]+), C13H10BrF2N4O+ requires 356.9980.

*FC(C=C1)=C(F)C=C1CCOC2=CN=CC3=NN=C(Br)N32*

*InChI=1S/C13H9BrF2N4O/c14-13-19-18-11-6-17-7-12(20(11)13)21-4-3-8-1-2-9(15)10(16)5-8/h1-2,5-7H,3-4H2*

**3-(Benzo[*d*][1,3]dioxol-4-yl)-5-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-661)**



Adapted from the literature procedures. 10.1016/j.tetlet.2015.04.076 To a stirred suspension of **X** (308 mg, 2.13 mmol, 1.0 equiv.) in EtOH (10 mL) was added benzo[*d*][1,3]dioxole-4-carbaldehyde (320 mg, 2.13 mmol, 1.0 equiv.) and the mixture heated at reflux overnight. After consumption of starting material as indicated by TLC, the reaction was cooled in an ice bath and chloramine T trihydrate (780 mg, 2.77 mmol, 1.3 equiv.) was added portionwise while stirring over 1 h. After consumption of the intermediate was confirmed by TLC, cold H2O (100 mL) was added. The solution was stirred for 10 min, then filtered through a sintered glass funnel (P3 porosity), washed with H2O (3 x 30 mL) then Et2O (30 mL) and dried *in vacuo* to give **OSM-S-661** as a pale brown solid (320 mg, 1.17 mmol, 55%); **m.p.** 164–167 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.50 (s, 1H), 8.13 (s, 1H), 7.18 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.02 (t, *J* = 7.9 Hz, 1H), 6.08 (s, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 147.1, 147.1, 142.9, 142.4, 129.5, 124.1, 121.7, 121.4, 110.8, 108.9, 101.7 (one carbon signal is overlapping or obscured); ***m/z*** (ESI+) 297 ([M+Na]+, 100%); **HRMS** (ESI+) found 297.0150 ([M+Na]+), C12H7ClN4O2Na+ requires 297.0150.

*ClC1=CN=CC2=NN=C(C3=CC=CC4=C3OCO4)N21*

*InChI=1S/C12H7ClN4O2/c13-9-4-14-5-10-15-16-12(17(9)10)7-2-1-3-8-11(7)19-6-18-8/h1-5H,6H2*

**EGT 190-3 precursors (thesis 98, 95, 94, OCHF2 core)**

**EGT 169-1 precursors (thesis 47, 54, 53, 52, OCHF2 core)**

**EGT 181-3 precursors (thesis 52, 53, 110, 112, OCHF2 core)**

**EGT 119-3 precursors (thesis 104, 103, 102, 101, OCHF2 core)**

**EGT 198-1 precursors (thesis 215, 214, 213, 212, OCHF2 core)**

**EGT 95-3 precursors (thesis 255, 254, 253)**

**EGT 141-1 precursors (thesis 258, 257, 256)**

**EGT 137-1 precursors (thesis 107, 103, Alice core?)**

# Synthesis and Characterization

**3-(4-Chlorophenyl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-272; MMV639565) ALICE**

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*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)Cl)N23*

*InChI=1S/C19H13ClF2N4O/c20-14-4-2-13(3-5-14)19-25-24-17-10-23-11-18(26(17)19)27-8-7-12-1-6-15(21)16(22)9-12/h1-6,9-11H,7-8H2*

**3-(4-Chlorophenyl)-5-(3,4-difluorophenethoxy)imidazo[1,5-*a*]pyrazine (OSM-S-274; MMV670250)**

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Compound **OSM-S-274** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, DMSO-d*6*) δ: 8.76 (s, 1H), 7.92 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 1H), 7.21–7.16 (m, 1H), 6.89–6.83 (m, 1H), 6.72–6.71 (m, 1H), 4.45 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H); ***m/z*** (ESI+) 386 ([M+H]+, 100%).

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=CN=C(C4=CC=C(C=C4)Cl)N23*

*InChI=1S/C20H14ClF2N3O/c21-15-4-2-14(3-5-15)20-25-11-16-10-24-12-19(26(16)20)27-8-7-13-1-6-17(22)18(23)9-13/h1-6,9-12H,7-8H2*

**3-(4-Chlorophenyl)-5-(3,4-difluorophenethoxy)imidazo[1,2-*a*]pyrazine (OSM-S-273; MMV669846)**

**

Compound **OSM-S-273** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 8.80 (s, 1H), 7.63 (s, 1H), 7.37 (s, 4H), 7.34 (s, 1H), 6.98–6.93 (m, 1H), 6.51–6.47 (m, 2H), 4.34 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H); ***m/z*** (ESI+) 386 ([M+H]+, 100%).

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NC=C(C4=CC=C(C=C4)Cl)N23*

*InChI=1S/C20H14ClF2N3O/c21-15-4-2-14(3-5-15)18-10-25-19-11-24-12-20(26(18)19)27-8-7-13-1-6-16(22)17(23)9-13/h1-6,9-12H,7-8H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-260; MMV675960)**

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Prepared according to General Procedure **SNAr** from: **OCHF2 core** (159 mg, 0.54 mmol, 1.0 equiv.) and 2-(3,4-difluorophenyl)ethan-1-ol (98.0 mg, 0.62 mmol, 1.1 equiv.); purified by flash chromatography on silica (20% EtOH in hexanes) followed by recrystallization from EtOAc to give **OSM-S-260** as white needles (43.0 mg, 19%); **m.p.** 111–112 °C; **1H NMR** (200 MHz; DMSO-d*6*) δ: 9.05 (s, 1H), 7.79–7.73 (m, 2H), 7.60 (s, 1H), 7.36 (t, *J* = 73.6 Hz, 1H), 7.30–6.69 (m, 5H), 4.51 (t, *J* = 6.2, 2H), 2.90 (t, *J* = 6.2, 6.0 Hz, 2H); **13C NMR** (75 MHz; DMSO-d*6*) δ: 151.9, 147.4, 146.4, 145.4, 143.8, 135.1, 132.5, 125.3 (2C), 124.7, 117.5, 117.3, 117.0, 116.9, 116.1 (t, *J* = 256.7 Hz), 108.8, 70.6, 32.8; ***m/z*** (APCI+) 419 ([M+H]+, 100%); **HRMS** (APCI+) found 419.1122 ([M+H]+), C20H15F4N4O+ requires 419.1126.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3)F*

*InChI=1S/C20H14F4N4O2/c21-15-6-1-12(9-16(15)22)7-8-29-18-11-25-10-17-26-27-19(28(17)18)13-2-4-14(5-3-13)30-20(23)24/h1-6,9-11,20H,7-8H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3,4-difluorophenethoxy)-8-methyl-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-063; MMV669541)**



Compound **OSM-X-063** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 7.66 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.14 (s, 1H),6.98–6.92 (m, 1H), 6.58 (t, *J* = 73.2 Hz, 1H), 6.51–6.47 (m, 2H), 4.33 (t, *J* = 6.2 Hz, 2H), 2.89 (s, 3H), 2.85 (t, *J* = 6.2 Hz, 2H); ***m/z*** (ESI+) 433 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3C)F*

*InChI=1S/C21H16F4N4O2/c1-12-19-27-28-20(14-3-5-15(6-4-14)31-21(24)25)29(19)18(11-26-12)30-9-8-13-2-7-16(22)17(23)10-13/h2-7,10-11,21H,8-9H2,1H3*

**3-(4-(Difluoromethoxy)phenyl)-6-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-001; MMV670945)**



Compound **OSM-X-001** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 9.03 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.29 (s, 1H), 6.59 (t, *J* = 73.6 Hz, 1H), 6.51–6.46 (m, 2H), 4.40–4.38 (m, 2H), 2.89–2.88 (m, 2H); ***m/z*** (ESI+) 419 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C=C(N=C3)OCCC4=CC=C(C(F)=C4)F)F*

*InChI=1S/C20H14F4N4O2/c21-15-6-1-12(9-16(15)22)7-8-29-18-11-28-17(10-25-18)26-27-19(28)13-2-4-14(5-3-13)30-20(23)24/h1-6,9-11,20H,7-8H2*

**3-(4-(Difluoromethoxy)phenyl)-6-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*b*]pyridazine (OSM-X-061; MMV672939)**



Compound **OSM-X-061** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 8.46 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 9.7 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.15–7.08 (m, 2H), 7.03–7.00 (m, 1H), 6.80 (d, *J* = 9.7 Hz, 1H), 6.61 (t, *J* = 73.3 Hz, 1H), 4.59 (t, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.6 Hz, 2H); ***m/z*** (ESI+) 419 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2N=C(C=C3)OCCC4=CC=C(C(F)=C4)F)F*

*InChI=1S/C20H14F4N4O2/c21-15-6-1-12(11-16(15)22)9-10-29-18-8-7-17-25-26-19(28(17)27-18)13-2-4-14(5-3-13)30-20(23)24/h1-8,11,20H,9-10H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-8(7*H*)-one (OSM-X-055; MMV669025)**



Compound **OSM-X-055** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 7.70 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.98–6.94 (m, 1H), 6.59 (t, *J* = 73.1 Hz, 1H), 6.54–6.52 (m, 2H), 6.25 (s, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 2H); ***m/z*** (ESI+) 435 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CNC3=O)F*

*InChI=1S/C20H14F4N4O3/c21-14-6-1-11(9-15(14)22)7-8-30-16-10-25-19(29)18-27-26-17(28(16)18)12-2-4-13(5-3-12)31-20(23)24/h1-6,9-10,20H,7-8H2,(H,25,29)*

**2-Amino-1-(3-(4-(difluoromethoxy)phenyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)ethan-1-one (OSM-X-077; MMV668962)**



Compound **OSM-X-077** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, DMSO-d*6*) δ: 8.17 (br s, 3H), 7.81 (t, *J* = 8.7 Hz, 2H), 7.38 (t, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 73.7 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 2H), 4.25–3.82 (m, 6H); ***m/z*** (ESI+) 324 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2CCN(C3)C(CN)=O)F*

*InChI=1S/C14H15F2N5O2/c15-14(16)23-10-3-1-9(2-4-10)13-19-18-11-8-20(12(22)7-17)5-6-21(11)13/h1-4,14H,5-8,17H2*

**3-(4-(Difluoromethoxy)phenyl)-5-phenoxy-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-579; MMV1581345)**

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**OSM-S-579** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C18H12F2N4O2/c19-18(20)26-14-8-6-12(7-9-14)17-23-22-15-10-21-11-16(24(15)17)25-13-4-2-1-3-5-13/h1-11,18H*

**5-(Benzyloxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-368; MMV897697)**

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**OSM-S-368** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C19H14F2N4O2/c20-19(21)27-15-8-6-14(7-9-15)18-24-23-16-10-22-11-17(25(16)18)26-12-13-4-2-1-3-5-13/h1-11,19H,12H2*

**3-(4-(Difluoromethoxy)phenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-369; MMV897698)**

****

**OSM-S-369** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C20H16F2N4O2/c21-20(22)28-16-8-6-15(7-9-16)19-25-24-17-12-23-13-18(26(17)19)27-11-10-14-4-2-1-3-5-14/h1-9,12-13,20H,10-11H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3-phenylpropoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-578; MMV1581344)**



**OSM-S-578** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C21H18F2N4O2/c22-21(23)29-17-10-8-16(9-11-17)20-26-25-18-13-24-14-19(27(18)20)28-12-4-7-15-5-2-1-3-6-15/h1-3,5-6,8-11,13-14,21H,4,7,12H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3-phenylpropyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-011; MMV669304)**



Compound **OSM-X-011** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 9.27 (s, 1H), 7.64 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.29–7.14 (m, 5H), 6.88 (d, *J* = 7.0 Hz, 2H), 6.63 (t, *J* = 72.8 Hz, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.72–1.65 (m, 2H); ***m/z*** (ESI+) 381 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(CCCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C21H18F2N4O/c22-21(23)28-18-11-9-16(10-12-18)20-26-25-19-14-24-13-17(27(19)20)8-4-7-15-5-2-1-3-6-15/h1-3,5-6,9-14,21H,4,7-8H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(phenethylthio)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-571; MMV1581336) TELE?**

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*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(SCCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C20H16F2N4OS/c21-20(22)27-16-8-6-15(7-9-16)19-25-24-17-12-23-13-18(26(17)19)28-11-10-14-4-2-1-3-5-14/h1-9,12-13,20H,10-11H2*

**5-(Benzylsulfonyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-361; MMV693163)**

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Prepared according to General Procedure **Cycle** from: **X** (100 mg, 0.24 mmol); purified by flash chromatography on silica (12–100% EtOAc in hexanes) to give **OSM-S-361** as a pale yellow powder (24.9 mg, 25%); **m.p.** 222–224 °C; **1H NMR** (300 MHz, CDCl3) δ: 9.56 (s, 1H), 8.41 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.44–7.18 (m, 3H), 6.88 (d, *J* = 7.4 Hz, 2H), 6.69 (t, *J* = 72.7 Hz, 1H), 4.02 (s, 2H); ***m/z*** (ESI–) 415 ([M–H]–, 100%); **HRMS** (ESI+) found 417.0831 ([M+H]+), C19H15F2N4O3S+ requires 417.0828.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(S(CC4=CC=CC=C4)(=O)=O)=CN=C3)F*

*InChI=1S/C19H14F2N4O3S/c20-19(21)28-15-8-6-14(7-9-15)18-24-23-16-10-22-11-17(25(16)18)29(26,27)12-13-4-2-1-3-5-13/h1-11,19H,12H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(phenethylsulfonyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-365; MMV693166)**

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Prepared according to General Procedure **Cycle** from: **X** (275 mg, 0.64 mmol); purified by flash chromatography on silica (12–100% EtOAc in hexanes) to give **OSM-S-365** as a white powder (179 mg, 65%); **m.p.** 142–143 °C; **1H NMR** (300 MHz, CDCl3) δ: 9.50 (s, 1H), 8.62 (s, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.39–7.11 (m, 6H), 6.89 (m, 1H), 6.61 (t, *J* = 72.8 Hz, 1H), 3.03 (ddd, *J* = 8.4, 6.1, 1.8 Hz, 2H), 2.88 (ddd, *J* = 8.3, 6.1, 1.8 Hz, 2H); **13C NMR** (75 MHz, CDCl3) δ: 153.4, 150.4, 147.3, 144.4, 141.5, 136.5, 130.2, 129.3, 128.8, 128.3, 126.8, 120.8, 118.9, 115.5 (t, *J* = 262.6 Hz), 54.6, 28.9; ***m/z*** (ESI+) 453 ([M+Na]+, 100%); **HRMS** (ESI+) found 431.0986 ([M+H]+), C20H17F2N4O3S+ requires 431.0984.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(S(CCC4=CC=CC=C4)(=O)=O)=CN=C3)F*

*InChI=1S/C20H16F2N4O3S/c21-20(22)29-16-8-6-15(7-9-16)19-25-24-17-12-23-13-18(26(17)19)30(27,28)11-10-14-4-2-1-3-5-14/h1-9,12-13,20H,10-11H2*

***N*-Benzyl-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-amine (OSM-S-638; MMV1634424) DAVID**



(200 mg, 66%); **1H NMR** (500 MHz , CDCl3) δ: 8.82 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.34–7.29 (m, 3H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.14–7.08 (m, 3H), 6.49 (t, *J* = 72.8 Hz, 1H), 4.34–4.31 (br m, 3H); **13C NMR** (126 MHz, CDCl3) δ: 153.1 (t, *J* = 2.8 Hz), 147.0, 144.3, 135.73, 135.66, 132.6, 132.1, 129.1, 128.5, 127.4, 124.2, 119.3, 115.4 (t, *J* = 262.2 Hz), 108.5, 47.8.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(NCC4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C19H15F2N5O/c20-19(21)27-15-8-6-14(7-9-15)18-25-24-17-12-22-11-16(26(17)18)23-10-13-4-2-1-3-5-13/h1-9,11-12,19,23H,10H2*

***N*-(3-Chlorophenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-202; MMV669542)**



Prepared according to General Procedure **Cycle** from: **X** (150 mg, 0.36 mmol); purified by flash chromatography on silica (20–100% EtOAc in hexanes) to give **OSM-S-202** as a pearlescent white powder (60.0 mg, 39%); **m.p.** 257–258 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.88 (br s, 1H), 9.66 (s, 1H), 8.30 (s, 1H), 7.63 (dapp, *J* = 8.7 Hz, 2H), 7.40 (t, *J* = 1.9 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H) 7.17 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.11 (t, *J* = 73.6 Hz, 1H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 157.4, 152.11 (t, *J* = 3.2 Hz), 146.8, 146.1, 145.7, 138.6, 132.8, 130.31, 130.25, 130.2, 124.33, 124.28, 124.0, 119.2, 118.2, 118.1, 115.9 (t, *J* = 258 Hz); ***m/z*** (ESI+) 438 ([M+Na]+, 100%); **HRMS** (APCI+) found 416.0718 ([M+H]+), C19H13ClF2N5O2+ requires 416.0720.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC4=CC=CC(Cl)=C4)=O)=CN=C3)F*

*InChI=1S/C19H12ClF2N5O2/c20-12-2-1-3-13(8-12)24-18(28)15-9-23-10-16-25-26-17(27(15)16)11-4-6-14(7-5-11)29-19(21)22/h1-10,19H,(H,24,28)*

***N*-(3-Chloro-2-methylphenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-201; MMV675718)**



Prepared according to General Procedure **Cycle** from: **X** (200 mg, 0.46 mmol); purified by flash chromatography on silica (20–100% EtOAc in hexanes) to give **OSM-S-201** as a fine pearly white powder (140 mg, 71%); **m.p.** 211–212 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 10.63 (br s, 1H), 9.66 (s, 1H), 8.38 (s, 1H), 7.70 (dapp, *J* = 8.7 Hz, 2H), 7.32 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.32 (t, *J* = 73.6 Hz, 1H), 7.30 (dapp, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 1.2, 8.3 Hz, 1H), 2.22 (s, 3H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 158.0, 152.1 (t, *J* = 3.5 Hz), 146.8, 146.1, 145.9, 136.1, 133.8, 130.50, 130.47, 130.3 (2C), 126.9, 126.7, 124.36, 124.31, 123.9, 118.5 (2C), 115.9 (t, *J* = 256.9 Hz), 14.9; ***m/z*** (ESI−) 428 ([M−H]−, 100%); **HRMS** (APCI+) found 430.0872 ([M+H]+), C20H15ClF2N5O2+ requires 430.0877.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC4=CC=CC(Cl)=C4C)=O)=CN=C3)F*

*InChI=1S/C20H14ClF2N5O2/c1-11-14(21)3-2-4-15(11)25-19(29)16-9-24-10-17-26-27-18(28(16)17)12-5-7-13(8-6-12)30-20(22)23/h2-10,20H,1H3,(H,25,29)*

**3-(4-(Difluoromethoxy)phenyl)-*N*-(3,4-difluorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-X-031; MMV669850)**

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Compound **OSM-X-031** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.92 (s, 1H), 9.66 (s, 1H), 8.29 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.39–7.29 (m, 2H), 7.17–7.14 (m, 2H), 7.02–6.99 (m, 1H); ***m/z*** (ESI+) 418 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC4=CC(F)=C(C=C4)F)=O)=CN=C3)F*

*InChI=1S/C19H11F4N5O2/c20-13-6-3-11(7-14(13)21)25-18(29)15-8-24-9-16-26-27-17(28(15)16)10-1-4-12(5-2-10)30-19(22)23/h1-9,19H,(H,25,29)*

***N*-(3-Chlorobenzyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-176, MMV668958)**



Compound **OSM-S-176** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.59 (s, 1H), 9.45 (t, *J* = 5.7 Hz, 1H), 8.19 (s, 1H), 7.62 (d, J = 8.6Hz, 2H), 7.52–7.15 (m, 7H), 4.09 (d, *J* = 5.7 Hz, 2H); ***m/z*** (ESI+) 430 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NCC4=CC=CC(Cl)=C4)=O)=CN=C3)F*

*InChI=1S/C20H14ClF2N5O2/c21-14-3-1-2-12(8-14)9-25-19(29)16-10-24-11-17-26-27-18(28(16)17)13-4-6-15(7-5-13)30-20(22)23/h1-8,10-11,20H,9H2,(H,25,29)*

***N*-(3,4-Difluorobenzyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-X-012; MMV669543)**



Compound **OSM-X-012** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 9.40 (s, 1H), 8.06 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.17–7.10 (m, 1H), 7.02–6.97 (m, 1H), 6.92–6.89 (m, 1H), 6.61 (t, *J* = 72.9 Hz, 1H), 6.59–6.58 (m, 1H), 4.23 (d, *J* = 5.8 Hz, 2H); ***m/z*** (ESI+) 432 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NCC4=CC=C(C(F)=C4)F)=O)=CN=C3)F*

*InChI=1S/C20H13F4N5O2/c21-14-6-1-11(7-15(14)22)8-26-19(30)16-9-25-10-17-27-28-18(29(16)17)12-2-4-13(5-3-12)31-20(23)24/h1-7,9-10,20H,8H2,(H,26,30)*

**3-(4-(Difluoromethoxy)phenyl)-*N*-phenethyl-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-X-051; MMV669027)**

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Compound **OSM-X-051** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ: 9.42 (s, 1H), 7.87 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.37–7.22 (m, 5H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.59 (t, *J* = 73.2 Hz, 1H), 6.03–6.02 (m, 1H), 3.44 (q, *J* = 6.5 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, 2H); ***m/z*** (ESI) 410 ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NCCC4=CC=CC=C4)=O)=CN=C3)F*

*InChI=1S/C21H17F2N5O2/c22-21(23)30-16-8-6-15(7-9-16)19-27-26-18-13-24-12-17(28(18)19)20(29)25-11-10-14-4-2-1-3-5-14/h1-9,12-13,21H,10-11H2,(H,25,29)*

***N*-(3-Chlorobenzyl)-3-(4-(difluoromethoxy)phenyl)-*N*-methyl-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-X-036; MMV669105) INHERITED**



Compound **OSM-X-036** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(N(C)CC4=CC=CC(Cl)=C4)=O)=CN=C3)F*

*InChI=1S/C21H16ClF2N5O2/c1-28(12-13-3-2-4-15(22)9-13)20(30)17-10-25-11-18-26-27-19(29(17)18)14-5-7-16(8-6-14)31-21(23)24/h2-11,21H,12H2,1H3*

***N*-(3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)-1-(4-(trifluoromethyl)phenyl)methanesulfonamide (OSM-X-092; MMV669103) INHERITED**



Compound **OSM-X-092** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(NS(CC4=CC=C(C(F)(F)F)C=C4)(=O)=O)=CN=C3)F*

*InChI=1S/C20H14F5N5O3S/c21-19(22)33-15-7-3-13(4-8-15)18-28-27-16-9-26-10-17(30(16)18)29-34(31,32)11-12-1-5-14(6-2-12)20(23,24)25/h1-10,19,29H,11H2*

***N*-(3-(4-Cyanophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)-2-(3,4-difluorophenyl)acetamide (OSM-W-6)**



To a 25mL RBF was added 100.0 of 4-(5-chloro-[1,2,4]triazol[4,3-a]pyrazin-3-yl)benzonitrile (0.39mmol, 1.0eq.), 80.4mg of 2-(3,4-difluorophenyl)acetamide (0.47mmol, 1.2eq.), 72.0mg of Pd2(dba)3 (0.08mmol, 0.2eq.), 46.0mg of Xantphos (0.08mmol, 0.2eq.) and 381.2mg of Cs2CO3 (1.17mmol, 3 eq.) were mixed as solids and the flask was flushed with nitrogen. Anhydrous Dioxane (10mL) that had been degassed was then added and the mixture heated to 105 °C and the reaction monitored by TLC. The reaction was then cooled and concentrated under reduced pressure and purified directly via silica gel column chromatography eluting with 10% methanol / dichloromethane to yield of 15.7mg of product (10% Yield).: 1H NMR (500 MHz, CDCl3)  9.36 (s, 1H), 8.03 (s, 1H), 7.88-7.81 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.20-7.11 (m, 2H), 6.80 (ddd, *J* = 10.1, 7.3, 2.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 3.25 (s, 2H); 13C NMR (125 MHz, CDCI3)  170.05, 148.52 (dd, *J* = 245.2Hz, 12.8Hz), 147.33 (dd, *J* = 244.9Hz, 12.7Hz), 147.14, 145.93,142.13, 131.57, 131.25, 130.95, 126.92 (dd, *J* = 6.5Hz, 3.4Hz), 126.76, 125.38, 118.11, 117.97 (d, J=17.3Hz), 116.78 (d, *J* = 17.0Hz), 112.39, 39.51; LCMS (ESI) m/z: [M+1] 391 (100.0%).

*O=C(CC1=CC=C(C(F)=C1)F)NC2=CN=CC3=NN=C(C(C=C4)=CC=C4C#N)N32*

*InChI=1S/C20H12F2N6O/c21-15-6-3-13(7-16(15)22)8-19(29)25-17-10-24-11-18-26-27-20(28(17)18)14-4-1-12(9-23)2-5-14/h1-7,10-11H,8H2,(H,25,29)*

**3-(4-(Difluoromethoxy)phenyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-175; MMV670944)**



*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC4=CC(C(F)(F)F)=NC=C4)=O)=CN=C3)F*

*InChI=1S/C19H11F5N6O2/c20-18(21)32-12-3-1-10(2-4-12)16-29-28-15-9-25-8-13(30(15)16)17(31)27-11-5-6-26-14(7-11)19(22,23)24/h1-9,18H,(H,26,27,31)*

**3-(4-Chlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-293; MMV663915)**

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*ClC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=CC=C4)=CN=C3*

*InChI=1S/C19H15ClN4O/c20-16-8-6-15(7-9-16)19-23-22-17-12-21-13-18(24(17)19)25-11-10-14-4-2-1-3-5-14/h1-9,12-13H,10-11H2*

**3-(4-Chlorophenyl)-5-(4-fluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-W-10)**

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A dry, clean 100 mL RBF equipped with a magnetic stir-bar was charged with 265.1mg (1.0mmoles; 1.0eq.) of 5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 32.2 mg of 18-crown-6 (0.1mmoles; 0.1 eq.) and 8.5mL of anhydrous toluene. To the stirred solution was then added 0.15mL of 2-(4-fluorophenyl)ethan-1-ol (1.2mmoles; 1.2 eq.) and 168.33mg of potassium hydroxide (3.0mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 459.0mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 186.0mg of pure product (50% yield). m.p. 128-130 °C; 1H NMR (500 MHz, DMSO-d6) δ: 9.05 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.61 (s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.00 (t, J = 8.9 Hz, 2H), 6.93 (dd, J = 8.8, 5.7 Hz, 2H), 4.50 (t, J = 6.4 Hz, 2H), 2.89 (t, J = 6.3 Hz, 2H); 13C NMR (126 MHz, DMSO-d6) δ: 160.43, 147.91, 145.76, 144.30, 135.49, 135.21, 133.85, 132.94, 130.88 (d, J = 7.9 Hz), 128.12, 115.31 (d, J = 20.9 Hz), 109.40, 71.54, 33.40.

*FC(C=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)Cl)N23*

*InChI=1S/C19H14ClFN4O/c20-15-5-3-14(4-6-15)19-24-23-17-11-22-12-18(25(17)19)26-10-9-13-1-7-16(21)8-2-13/h1-8,11-12H,9-10H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(3-methoxyphenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-383; MMV897711)**



*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=CC(OC)=C4)=CN=C3)F*

*InChI=1S/C21H18F2N4O3/c1-28-17-4-2-3-14(11-17)9-10-29-19-13-24-12-18-25-26-20(27(18)19)15-5-7-16(8-6-15)30-21(22)23/h2-8,11-13,21H,9-10H2,1H3*

**3-(4-(Difluoromethoxy)phenyl)-5-(4-methoxyphenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-384; MMV897712)**



*COC(C=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N23*

*InChI=1S/C21H18F2N4O3/c1-28-16-6-2-14(3-7-16)10-11-29-19-13-24-12-18-25-26-20(27(18)19)15-4-8-17(9-5-15)30-21(22)23/h2-9,12-13,21H,10-11H2,1H3*

**5-(2-(Cuban-1-yl)ethoxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-371; MMV897700)**



**OSM-S-371** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC45C6C7C4C8C5C6C87)N32*

*InChI=1S/C22H18F2N4O2/c23-21(24)30-10-3-1-9(2-4-10)20-27-26-11-7-25-8-12(28(11)20)29-6-5-22-17-14-13-15(17)19(22)16(13)18(14)22/h1-4,7-8,13-19,21H,5-6H2*

**4-(2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)ethyl)morpholine (OSM-S-498; MMV1577575)**



**OSM-S-498** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCN4CCOCC4)=CN=C3)F*

*InChI=1S/C18H19F2N5O3/c19-18(20)28-14-3-1-13(2-4-14)17-23-22-15-11-21-12-16(25(15)17)27-10-7-24-5-8-26-9-6-24/h1-4,11-12,18H,5-10H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(2-(piperidin-1-yl)ethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-499; MMV1577576)**



**OSM-S-499** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCCN4CCCCC4)=CN=C3)F*

*InChI=1S/C19H21F2N5O2/c20-19(21)28-15-6-4-14(5-7-15)18-24-23-16-12-22-13-17(26(16)18)27-11-10-25-8-2-1-3-9-25/h4-7,12-13,19H,1-3,8-11H2*

**5-(3,4-Difluorophenethoxy)-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-415; MMV1557949)**

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*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC=C4)N23*

*InChI=1S/C19H14F2N4O/c20-15-7-6-13(10-16(15)21)8-9-26-18-12-22-11-17-23-24-19(25(17)18)14-4-2-1-3-5-14/h1-7,10-12H,8-9H2*

**2-Chloro-5-(5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)aniline (OSM-S-548; MMV1580433)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (107 mg, 0.30 mmol) and (3-amino-4-chlorophenyl)boronic acid (67.0 mg, 0.39 mmol) to give **OSM-S-548** as an off-white solid (110 mg, 91%); **m.p.** 165–168 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.02 (s, 1H), 7.55 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.18 (dt, *J* = 10.8, 8.5 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 6.96 (ddd, *J* = 12.0, 7.9, 2.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.74–6.68 (m, 1H), 5.60 (s, 2H), 4.49 (t, *J* = 6.2 Hz, 2H), 2.95 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.6 (dd, *J* = 109.1, 12.4 Hz), 147.6 (dd, *J* = 107.7, 12.5 Hz), 147.3, 146.0, 144.0, 143.7, 135.3–135.2 (m), 135.1, 128.1, 127.1, 125.5 (dd, *J* = 6.3, 3.3 Hz), 119.1, 118.5, 117.5, 117.5 (d, *J* = 17.0 Hz), 116.8 (d, *J* = 16.7 Hz), 108.7, 70.7, 33.0; ***m/z*** (ESI+) 424 ([M+Na]+, 100%); **HRMS** (ESI+) found 402.0926 ([M+H]+), C19H15ClF2N5O+ requires 402.0928.

*ClC1=CC=C(C=C1N)C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3 InChI=1S/C19H14ClF2N5O/c20-13-3-2-12(8-16(13)23)19-26-25-17-9-24-10-18(27(17)19)28-6-5-11-1-4-14(21)15(22)7-11/h1-4,7-10H,5-6,23H2*

**5-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)-2-fluoroaniline (OSM-S-585; MMV1581334)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (83.0 mg, 0.23 mmol) and 3-amino-4-fluorophenylboronic acid (47.0 mg, 0.31 mmol) to give **OSM-S-585** as an off-white solid (27.0 mg, 30%, contains 0.8% DMA); **m.p.** 161–164 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.01 (s, 1H), 7.54 (s, 1H), 7.20 (dt, *J* = 10.7, 8.5 Hz, 1H), 7.15–7.09 (m, 1H), 7.13–7.05 (m, 1H), 6.97 (ddd, *J* = 11.9, 7.9, 2.1 Hz, 1H), 6.84 (ddd, *J* = 8.3, 4.4, 2.2 Hz, 1H), 6.73 (ddd, *J* = 9.1, 4.2, 2.1 Hz, 1H), 5.39 (s, 2H), 4.47 (t, *J* = 6.2 Hz, 2H), 2.94 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 152.3, 150.4, 149.6 (dd, *J* = 104.8, 12.6 Hz), 148.4–146.9 (m), 147.2, 146.1, 143.7, 135.7 (d, *J* = 13.5 Hz), 135.2 (dd, *J* = 5.9, 3.6 Hz), 135.2, 125.5 (dd, *J* = 6.4, 3.3 Hz), 124.1 (d, *J* = 3.1 Hz), 118.8–118.6 (m), 117.6 (d, *J* = 17.0 Hz), 116.9 (d, *J* = 16.7 Hz), 114.1 (d, *J* = 19.2 Hz), 108.6, 70.7, 33.0; ***m/z*** (ESI+) 408 ([M+Na]+, 100%); **HRMS** (ESI+) found 386.1217 ([M+H]+), C19H15F3N5O+ requires 386.1223.

*FC1=CC=C(C=C1N)C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3*

*InChI=1S/C19H14F3N5O/c20-13-3-1-11(7-15(13)22)5-6-28-18-10-24-9-17-25-26-19(27(17)18)12-2-4-14(21)16(23)8-12/h1-4,7-10H,5-6,23H2*

**3-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)aniline (OSM-S-549; MMV1580434)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (89.0 mg, 0.25 mmol) and (3-aminophenyl)boronic acid (45.0 mg, 0.33 mmol) to give **OSM-S-549** as an off-white solid (92 mg, 93%); **m.p.** 150–152 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.00 (s, 1H), 7.51 (s, 1H), 7.23–7.12 (m, 2H), 6.97–6.89 (m, 2H), 6.85–6.80 (m, 1H), 6.76 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.69–6.62 (m, 1H), 5.33 (s, 2H), 4.45 (t, *J* = 6.1 Hz, 2H), 2.91 (t, *J* = 6.1 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.5 (dd, *J* = 99.2, 12.5 Hz), 148.0, 147.6 (dd, *J* = 98.0, 12.6 Hz), 147.2, 146.9, 143.7, 135.3 (dd, *J* = 6.0, 3.7 Hz), 135.2, 128.3, 128.0, 125.7 (dd, *J* = 6.3, 3.3 Hz), 118.3, 117.7 (d, *J* = 16.8 Hz), 116.9 (d, *J* = 16.7 Hz), 116.2, 115.0, 108.6, 70.9, 33.1; ***m/z*** (ESI+) 390 ([M+Na]+, 100%); **HRMS** (ESI+) found 368.1313 ([M+H]+), C19H16F2N5O+ requires 368.1317.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC(N)=C4)N23*

*InChI=1S/C19H15F2N5O/c20-15-5-4-12(8-16(15)21)6-7-27-18-11-23-10-17-24-25-19(26(17)18)13-2-1-3-14(22)9-13/h1-5,8-11H,6-7,22H2*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)aniline (OSM-S-526; MMV1579342)**

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Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (105 mg, 0.30 mmol) and 4-aminophenylboronic acid hydrochloride (66.7 mg, 0.39 mmol) to give **OSM-S-526** as an off-white foam (63.0 mg, 58%); **m.p.** 161–164 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 8.95 (s, 1H), 7.46 (s, 1H), 7.40–7.34 (m, 2H), 7.19 (dt, *J* = 10.8, 8.5 Hz, 1H), 6.95 (ddd, *J* = 11.9, 7.9, 2.1 Hz, 1H), 6.81–6.72 (m, 1H), 6.70–6.64 (m, 2H), 5.54 (s, 2H), 4.46 (t, *J* = 6.2 Hz, 2H), 2.93 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.6 (dd, *J* = 100.3, 12.5 Hz), 147.6 (dd, *J* = 99.3, 12.6 Hz), 147.3, 147.1, 143.9, 135.3 (dd, *J* = 6.0, 3.7 Hz), 135.2, 131.7, 125.7 (dd, *J* = 6.2, 3.3 Hz), 117.7 (d, *J* = 16.9 Hz), 116.9 (d, *J* = 16.6 Hz), 114.3, 112.4, 108.3, 70.8, 33.1; ***m/z*** (ESI+) 390 ([M+Na]+, 100%); **HRMS** (ESI+) found 368.1313 ([M+H]+), C19H16F2N5O+ requires 368.1317.

*NC(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3*

*InChI=1S/C19H15F2N5O/c20-15-6-1-12(9-16(15)21)7-8-27-18-11-23-10-17-24-25-19(26(17)18)13-2-4-14(22)5-3-13/h1-6,9-11H,7-8,22H2*

**3-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)-*N*,*N*-dimethylaniline (OSM-S-545; MMV1580430)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (101 mg, 0.28 mmol) and 3-(dimethylamino)phenylboronic acid (60.9 mg, 0.37 mmol) to give **OSM-S-545** as a grey solid (108 mg, 96%); **m.p.** 137–140 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.02 (s, 1H), 7.53 (s, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.13 (dt, *J* = 11.0, 8.5 Hz, 1H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.93 (ddd, *J* = 23.8, 8.1, 2.1 Hz, 3H), 6.73 (ddd, *J* = 11.8, 7.9, 2.2 Hz, 1H), 6.67–6.60 (m, 1H), 4.46 (t, *J* = 6.0 Hz, 2H), 2.96 (s, 6H), 2.83 (t, *J* = 5.9 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.6, 149.5 (dd, *J* = 99.1, 12.6 Hz), 148.0–147.0 (m), 147.2, 146.9, 143.8, 135.3 (dd, *J* = 6.0, 3.7 Hz), 135.0, 128.5, 128.0, 125.4 (dd, *J* = 6.5, 3.3 Hz), 118.6, 117.6 (d, *J* = 16.8 Hz), 116.8 (d, *J* = 16.7 Hz), 114.6, 113.4, 108.7, 70.7, 40.1, 33.1; ***m/z*** (ESI+) 418 ([M+Na]+, 100%); **HRMS** (ESI+) found 396.1627 ([M+H]+), C21H20F2N5O+ requires 396.1630.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC(N(C)C)=C4)N23*

*InChI=1S/C21H19F2N5O/c1-27(2)16-5-3-4-15(11-16)21-26-25-19-12-24-13-20(28(19)21)29-9-8-14-6-7-17(22)18(23)10-14/h3-7,10-13H,8-9H2,1-2H3*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)-*N*,*N*-dimethylaniline (OSM-S-531; MMV1579351)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (98.0 mg, 0.28 mmol) and 4-(dimethylamino)phenylboronic acid hydrochloride (74.0 mg, 0.36 mmol) to give **OSM-S-531** as an off-white solid (85.0 mg, 77%); **m.p.** 177–179 °C; **1H NMR** (300 MHz, CDCl3) δ: 8.97 (s, 1H), 7.59–7.49 (m, 2H), 7.21 (s, 1H), 6.93 (dt, *J* = 10.4, 8.1 Hz, 1H), 6.82–6.71 (m, 2H), 6.56–6.44 (m, 2H), 4.37 (t, *J* = 6.0 Hz, 2H), 3.04 (s, 6H), 2.94 (t, *J* = 6.0 Hz, 2H); **13C NMR** (126 MHz, CDCl3) δ: 151.4, 150.8 (dd, *J* = 90.4, 12.6 Hz), 148.8 (dd, *J* = 89.4, 12.6 Hz), 148.1, 147.8, 144.2, 136.9, 133.9 (dd, *J* = 5.7, 4.0 Hz), 131.9, 124.7 (dd, *J* = 6.2, 3.6 Hz), 117.9 (d, *J* = 17.1 Hz), 117.3 (d, *J* = 17.0 Hz), 111.3, 108.0, 70.9, 40.6, 34.0 (one carbon signal is overlapping or obscured); ***m/z*** (ESI+) 418 ([M+Na]+, 100%); **HRMS** (ESI+) found 396.16240 ([M+H]+), C21H20F2N5O+ requires 396.1630.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)N(C)C)N23*

*InChI=1S/C21H19F2N5O/c1-27(2)16-6-4-15(5-7-16)21-26-25-19-12-24-13-20(28(19)21)29-10-9-14-3-8-17(22)18(23)11-14/h3-8,11-13H,9-10H2,1-2H3*

**3-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzoic acid (OSM-S-552; MMV1580437)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (88.0 mg, 0.25 mmol) and 3-boronobenzoic acid (54.0 mg, 0.32 mmol); purified by flash chromatography on silica (0–5% MeOH in EtOAc, then 0.2% formic acid in 5% MeOH in EtOAc) to give **OSM-S-552** as an off-white solid (67.0 mg, 68%, contains 1.2% EtOAc); **m.p.** 223–225 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 13.16 (s, 1H), 9.06 (s, 1H), 8.30 (t, *J* = 1.7 Hz, 1H), 8.08 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.96 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.65–7.58 (m, 2H), 7.14 (dt, *J* = 10.8, 8.5 Hz, 1H), 6.78 (ddd, *J* = 11.9, 7.9, 2.2 Hz, 1H), 6.69 (ddd, *J* = 8.8, 4.3, 1.9 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 2H), 2.87 (t, *J* = 6.3 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 166.8, 149.5 (dd, *J* = 104.0, 12.4 Hz), 147.6 (dd, *J* = 103.1, 12.4 Hz), 147.5, 145.6, 143.8, 135.1, 134.9 (dd, *J* = 6.1, 3.6 Hz), 134.8, 131.5, 130.3, 130.3, 128.3, 128.0, 125.2 (dd, *J* = 6.4, 3.3 Hz), 117.4 (d, *J* = 16.9 Hz), 116.9 (d, *J* = 16.7 Hz), 109.0, 70.6, 32.7; ***m/z*** (ESI+) 419 ([M+Na]+, 100%); **HRMS** (ESI+) found 397.1100 ([M+H]+), C20H15F2N4O3+ requires 397.1107.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC(C(O)=O)=C4)N23*

*InChI=1S/C20H14F2N4O3/c21-15-5-4-12(8-16(15)22)6-7-29-18-11-23-10-17-24-25-19(26(17)18)13-2-1-3-14(9-13)20(27)28/h1-5,8-11H,6-7H2,(H,27,28)*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzoic acid (OSM-S-551; MMV1580436)**

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Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (83.0 mg, 0.23 mmol) and 4-boronobenzoic acid (50.0 mg, 0.30 mmol); purified by flash chromatography on silica (0–5% MeOH in EtOAc, then 0.2% formic acid in 5% MeOH in EtOAc) to give **OSM-S-551** as an off-white solid (63.0 mg, 68%); **m.p.** 223–225 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 13.19 (s, 1H), 9.08 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.63 (s, 1H), 7.15 (q, *J* = 9.2 Hz, 1H), 6.88 (t, *J* = 10.0 Hz, 1H), 6.72 (s, 1H), 4.53 (t, *J* = 6.2 Hz, 2H), 2.89 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 166.9, 149.5 (dd, *J* = 109.2, 12.5 Hz), 147.6 (dd, *J* = 108.2, 12.5 Hz), 147.5, 145.6, 143.7, 135.0, 135.0 (d, *J* = 3.7 Hz), 131.8, 131.7, 130.8, 128.3, 125.2 (dd, *J* = 6.3, 3.3 Hz), 117.4 (d, *J* = 17.0 Hz), 116.9 (d, *J* = 16.7 Hz), 109.1, 70.6, 32.7; ***m/z*** (ESI–) 396 ([M–H]–, 100%); **HRMS** (ESI+) found 419.0929 ([M+Na]+), C20H14F2N4O3Na+ requires 419.0929.

*O=C(C(C=C1)=CC=C1C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3)O*

*InChI=1S/C20H14F2N4O3/c21-15-6-1-12(9-16(15)22)7-8-29-18-11-23-10-17-24-25-19(26(17)18)13-2-4-14(5-3-13)20(27)28/h1-6,9-11H,7-8H2,(H,27,28)*

**3-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzamide (OSM-S-495; MMV1576794)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (101 mg, 0.28 mmol) and (3-carbamoylphenyl)boronic acid (61.0 mg, 0.37 mmol) to give **OSM-S-495** as an off-white solid (81.0 mg, 72%); **m.p.** 186–188 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.06 (s, 1H), 8.29 (t, *J* = 1.8 Hz, 1H), 8.11 (s, 1H), 8.07 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.88 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.66–7.56 (m, 2H), 7.52 (s, 1H), 7.14 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.81 (ddd, *J* = 11.9, 7.8, 2.2 Hz, 1H), 6.68–6.57 (m, 1H), 4.49 (t, *J* = 6.3 Hz, 2H), 2.86 (t, *J* = 6.3 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 167.1, 149.5 (dd, *J* = 103.2, 12.6 Hz), 147.6 (dd, *J* = 102.0, 12.9 Hz), 147.4, 145.8, 143.8, 135.1, 135.0–134.9 (m), 133.5, 133.2, 130.0, 128.6, 127.9, 127.6, 125.4 (dd, *J* = 6.2, 3.3 Hz), 117.4 (d, *J* = 16.8 Hz), 116.9 (d, *J* = 16.8 Hz), 108.9, 70.7, 32.8; ***m/z*** (ESI+) 418 ([M+Na]+, 100%); **HRMS** (ESI+) found 396.1263 ([M+H]+), C20H16F2N5O2+ requires 396.1267.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC(C(N)=O)=C4)N23*

*InChI=1S/C20H15F2N5O2/c21-15-5-4-12(8-16(15)22)6-7-29-18-11-24-10-17-25-26-20(27(17)18)14-3-1-2-13(9-14)19(23)28/h1-5,8-11H,6-7H2,(H2,23,28)*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzamide (OSM-S-494; MMV1576793)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (100 mg, 0.28 mmol) and (4-carbamoylphenyl)boronic acid (60.5 mg, 0.37 mmol) to give **OSM-S-494** as an off-white solid (67.0 mg, 60%); **m.p.** 217–220 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.06 (s, 1H), 8.11 (s, 1H), 8.02–7.97 (m, 2H), 7.86–7.77 (m, 2H), 7.61 (s, 1H), 7.50 (s, 1H), 7.15 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.88 (ddd, *J* = 12.0, 7.9, 2.2 Hz, 1H), 6.68–6.61 (m, 1H), 4.51 (t, *J* = 6.2 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 167.3, 149.5 (dd, *J* = 106.3, 12.5 Hz), 147.6 (dd, *J* = 105.2, 12.6 Hz), 147.5, 145.7, 143.8, 135.1, 135.1, 135.0–134.9 (m), 130.6, 130.4, 126.6, 125.4 (dd, *J* = 6.3, 3.4 Hz), 117.5 (d, *J* = 16.9 Hz), 116.9 (d, *J* = 16.7 Hz), 109.0, 70.8, 32.9; ***m/z*** (ESI+) 418 ([M+Na]+, 100%); **HRMS** (ESI+) found 396.1263 ([M+H]+), requires C20H16F2N5O2+ 396.1272.

*O=C(C1=CC=C(C=C1)C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3)N*

*InChI=1S/C20H15F2N5O2/c21-15-6-1-12(9-16(15)22)7-8-29-18-11-24-10-17-25-26-20(27(17)18)14-4-2-13(3-5-14)19(23)28/h1-6,9-11H,7-8H2,(H2,23,28)*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzenesulfonamide (OSM-S-506; MMV1577569)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (94.9 mg, 0.27 mmol) and (4-sulfamoylphenyl)boronic acid (69.8 mg, 0.35 mmol) to give **OSM-S-506** as an off-white solid (58.0 mg, 50%); **m.p.** 166–167 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.08 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.64 (s, 1H), 7.53 (s, 2H), 7.19 (dt, *J* = 10.8, 8.5 Hz, 1H), 7.01 (ddd, *J* = 11.8, 7.8, 2.1 Hz, 1H), 6.67 (ddd, *J* = 9.2, 4.0, 2.2 Hz, 1H), 4.52 (t, *J* = 6.4 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.6 (dd, *J* = 113.8, 12.4 Hz), 147.6 (dd, *J* = 112.5, 12.4 Hz), 147.5, 145.2, 145.0, 143.7, 135.1, 134.9 (dd, *J* = 5.9, 3.7 Hz), 131.2, 131.0, 125.5 (dd, *J* = 6.5, 3.3 Hz), 124.8, 117.4 (d, *J* = 16.8 Hz), 117.0 (d, *J* = 16.9 Hz), 109.1, 70.9, 32.9; ***m/z*** (ESI+) 454 ([M+Na]+, 100%); **HRMS** (ESI+) found 432.0934 ([M+H]+), C19H16F2N5O3S+ requires 432.0936.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)S(N)(=O)=O)N23*

*InChI=1S/C19H15F2N5O3S/c20-15-6-1-12(9-16(15)21)7-8-29-18-11-23-10-17-24-25-19(26(17)18)13-2-4-14(5-3-13)30(22,27)28/h1-6,9-11H,7-8H2,(H2,22,27,28)*

**5-(3,4-Difluorophenethoxy)-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-W-5)**



A dry, clean 25mL RBF equipped with a magnetic stir-bar was charged with 130.0mg (0.42mmoles; 1.0eq.) of 5-chloro-3-(4-(methylsulfonyl)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, 13.6mg of 18-crown-6 (0.04mmoles; 0.1eq.) and 5mL of anhydrous toluene. To the stirred solution was then added 0.015 mL of 2-(3,4-diflourophenyl)ethan-1-ol (0.5mmoles; 1.2eq.) and 70.9mg of potassium hydroxide (1.26mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief top with split-seal septa and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50 mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50mL of saturated, aqueous sodium bicarbonate and 50 mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 290.9mg of crude product. The material was then purified by silica gel column chromatography eluting with 25% of ethyl acetate / hexanes, then 100% of ethyl acetate, to afford 87.5mg of pure product (48% Yield). m.p. 67-69 °C; 1H NMR (500 MHz, CDCl3)  9.08 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 7.39 (s, 1H), 7.01 (dt, J = 10.2, 8.4 Hz, 1H), 6.57-6.47 (m, 2H), 4.45 (t, J = 6.3 Hz, 2H), 3.11 (s, 3H), 2.91 (t, J = 6.2 Hz, 2H); 13C NMR (126 MHz, CDCl3)  148.06, 145.41, 143.65, 142.12, 136.88, 133.25, 131.77, 127.01, 124.68 (dd, J = 6.1, 3.7 Hz), 117.83 (d, J = 17.3 Hz), 117.13 (d, J = 17.3 Hz), 108.88, 71.09, 44.56, 33.79; LCMS (ESI) m/z: [M+1] 431 (100.0%).

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)S(C)(=O)=O)N23*

*InChI=1S/C20H16F2N4O3S/c1-30(27,28)15-5-3-14(4-6-15)20-25-24-18-11-23-12-19(26(18)20)29-9-8-13-2-7-16(21)17(22)10-13/h2-7,10-12H,8-9H2,1H3*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzonitrile (OSM-W-9)**



A dry, clean 100 mL RBF equipped with a magnetic stir-bar was charged with 255.0mg (1.0mmoles; 1.0eq.) of 4-(5-chloro-[1,2,4]triazol[4,3-a]pyrazin-3-yl)benzonitrile, 32.2mg of 18-crown-6 (0.1mmoles; 0.1eq.) and 8.5mL of anhydrous toluene. To the stirred solution was then added 0.02mL of 2-(3,4-diflourophenyl)ethan-1-ol (1.2mmoles; 1.2eq.) and 168.33mg of potassium hydroxide (3.0mmoles; 3.0eq.). The resulting mixture was then sealed with a pressure relief cap and heated to 40 °C for 3 hours and monitored by TLC. Once complete, the reaction was diluted with 50mL of ethyl acetate and poured into a separatory funnel. The organic layer was then washed with 50mL of saturated, aqueous sodium bicarbonate and 50mL of brine solution. The organic layer was then separated, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 280.0mg of crude product. The material was then purified by silica gel column chromatography starting with 25% of ethyl acetate / hexanes, eluting to 100% of ethyl acetate / hexanes, to afford 118.0mg of product (31% Yield).: m.p. 164-166 °C; 1H NMR (500 MHz, DMSO-d6)  9.10 (s, 1H), 7.92 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 8.6 Hz, 2H), 7.67 (s, 1H), 7.26-7.17 (m, 1H), 6.98-6.89 (m, 1H), 6.76 (s, 1H), 4.55 (t, J = 6.3 Hz, 2H), 2.92 (t, J = 6.2 Hz, 2H); LCMS (ESI) m/z: [M+1] 378 (100.0%).

*FC1=CC=C(C=C1F)CCOC2=CN=CC3=NN=C(C(C=C4)=CC=C4C#N)N23*

*InChI=1S/C20H13F2N5O/c21-16-6-3-13(9-17(16)22)7-8-28-19-12-24-11-18-25-26-20(27(18)19)15-4-1-14(10-23)2-5-15/h1-6,9,11-12H,7-8H2*

**5-(3,4-Difluorophenethoxy)-3-(4-ethylphenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-550; MMV1580435)**

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Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (104 mg, 0.29 mmol) and (4-ethylphenyl)boronic acid (57.2 mg, 0.38 mmol) to give **OSM-S-550** as a brown solid (97.8 mg, 88%); **m.p.** 130–132 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.02 (s, 1H), 7.67–7.59 (m, 2H), 7.55 (s, 1H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.17 (dt, *J* = 10.8, 8.5 Hz, 1H), 6.77 (ddd, *J* = 11.9, 7.9, 2.1 Hz, 1H), 6.65 (ddd, *J* = 9.0, 4.4, 2.2 Hz, 1H), 4.49 (t, *J* = 6.0 Hz, 2H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.69 (q, *J* = 7.6 Hz, 2H), 1.20 (d, *J* = 7.6 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.5 (dd, *J* = 103.5, 12.6 Hz), 147.6 (dd, *J* = 102.4, 12.5 Hz), 147.3, 146.3, 145.6, 143.8, 135.3 (dd, *J* = 6.1, 3.6 Hz), 135.1, 130.7, 126.9, 125.4 (dd, *J* = 6.3, 3.3 Hz), 125.3, 117.5 (d, *J* = 16.8 Hz), 116.9 (d, *J* = 16.7 Hz), 108.6, 70.7, 32.9, 28.0, 15.4; ***m/z*** (ESI+) 403 ([M+Na]+, 100%); **HRMS** (ESI+) found 381.1519 ([M+H]+), C21H19F2N4O+ requires 381.1521.

*CCC1=CC=C(C=C1)C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3*

*InChI=1S/C21H18F2N4O/c1-2-14-3-6-16(7-4-14)21-26-25-19-12-24-13-20(27(19)21)28-10-9-15-5-8-17(22)18(23)11-15/h3-8,11-13H,2,9-10H2,1H3*

**5-(3,4-Difluorophenethoxy)-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-553; MMV1580438)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (98.0 mg, 0.28 mmol) and (4-nitrophenyl)boronic acid (60.0 mg, 0.36 mmol) to give **OSM-S-553** as a yellow solid (82.0 mg, 75%, contains 0.5% Et2O); **m.p.** 173–177 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.11 (s, 1H), 8.28–8.22 (m, 2H), 7.99–7.92 (m, 2H), 7.70 (s, 1H), 7.15 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.95 (ddd, *J* = 12.0, 7.9, 2.2 Hz, 1H), 6.83–6.76 (m, 1H), 4.59 (t, *J* = 6.2 Hz, 2H), 2.94 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.4 (dd, *J* = 119.0, 12.6 Hz), 147.8, 147.6, 147.5 (dd, *J* = 118.1, 12.5 Hz), 144.6, 143.8, 135.0–134.9 (m), 134.9, 134.0, 131.9, 125.1 (dd, *J* = 6.3, 3.4 Hz), 122.5, 117.2 (d, *J* = 17.0 Hz), 116.9 (d, *J* = 16.8 Hz), 109.4, 70.2, 32.5; ***m/z*** (APCI+) ([M+H]+) 398; **HRMS** (ESI+) found 398.1056 ([M+H]+), C19H14F2N5O3+ requires 398.1059.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)[N+]([O-])=O)N23*

*InChI=1S/C19H13F2N5O3/c20-15-6-1-12(9-16(15)21)7-8-29-18-11-22-10-17-23-24-19(25(17)18)13-2-4-14(5-3-13)26(27)28/h1-6,9-11H,7-8H2*

**5-(3,4-Difluorophenethoxy)-3-(1*H*-indol-6-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-525; MMV1579341)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (80.0 mg, 0.23 mmol) and indole-6-boronic acid (47.0 mg, 0.29 mmol) to give **OSM-S-525** as an off-white solid (51.0 mg, 58%, contains 0.8% EtOAc); **m.p.** 210–213 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.42 (s, 1H), 9.02 (s, 1H), 7.79 (dt, *J* = 1.6, 0.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.57–7.47 (m, 2H), 7.33 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.92 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.60 (ddd, *J* = 11.9, 7.9, 2.2 Hz, 1H), 6.54 (ddd, *J* = 3.0, 1.9, 0.9 Hz, 1H), 6.36 (dq, *J* = 6.5, 2.6, 2.0 Hz, 1H), 4.44 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.1 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.4 (dd, *J* = 100.6, 12.5 Hz), 147.7, 147.4 (dd, *J* = 99.2, 12.5 Hz), 147.3, 144.0, 135.2, 135.0 (dd, *J* = 6.0, 3.8 Hz), 134.9, 128.5, 127.4, 125.3 (dd, *J* = 6.3, 3.3 Hz), 121.7, 120.0, 118.8, 117.4 (d, *J* = 16.9 Hz), 116.5 (d, *J* = 16.6 Hz), 114.4, 108.5, 101.2, 70.7, 33.0; ***m/z*** (ESI+) 392 ([M+H]+); **HRMS** (ESI+) found 392.1311 ([M+H]+), C21H16F2N5O+ requires 392.1317.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=CN5)C5=C4)N23*

*InChI=1S/C21H15F2N5O/c22-16-4-1-13(9-17(16)23)6-8-29-20-12-24-11-19-26-27-21(28(19)20)15-3-2-14-5-7-25-18(14)10-15/h1-5,7,9-12,25H,6,8H2*

**5-(3,4-Difluorophenethoxy)-3-(1*H*-indol-4-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-547; MMV1580432)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (101 mg, 0.28 mmol) and (1*H*-indol-4-yl)boronic acid (59.5 mg, 0.37 mmol) to give **OSM-S-547** as an off-white solid (72.0 mg, 65%); **m.p.** 199–201 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.37 (s, 1H), 9.06 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.51–7.44 (m, 2H), 7.31–7.25 (m, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 6.94 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.48 (ddd, *J* = 11.8, 7.9, 2.1 Hz, 1H), 6.27–6.19 (m, 2H), 4.27 (t, *J* = 5.9 Hz, 2H), 2.35 (t, *J* = 5.9 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.4 (dd, *J* = 93.6, 12.5 Hz), 147.4 (dd, *J* = 92.3, 12.6 Hz), 147.2, 145.7, 143.8, 135.6, 135.3, 135.1 (dd, *J* = 6.0, 3.9 Hz), 128.3, 126.5, 125.4 (dd, *J* = 6.4, 3.3 Hz), 122.1, 120.1, 119.4, 117.4 (d, *J* = 16.9 Hz), 116.6 (d, *J* = 16.7 Hz), 113.2, 108.7, 100.7, 70.8, 32.8; ***m/z*** (ESI+) 414 ([M+Na]+, 100%); **HRMS** (ESI+) found 392.1313 ([M+H]+), C21H16F2N5O+ requires 392.1317.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC5=C4C=CN5)N23*

*InChI=1S/C21H15F2N5O/c22-16-5-4-13(10-17(16)23)7-9-29-20-12-24-11-19-26-27-21(28(19)20)15-2-1-3-18-14(15)6-8-25-18/h1-6,8,10-12,25H,7,9H2*

**5-(3,4-Difluorophenethoxy)-3-(1-methyl-1*H*-indol-6-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-582; MMV1581331)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (84.0 mg, 0.24 mmol) and 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (79.0 mg, 0.31 mmol) to give **OSM-S-582** as an off-white solid (51.0 mg, 53%); **m.p.** 172–175 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*)δ: 9.03 (s, 1H), 7.83 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.49 (d, *J* = 3.1 Hz, 1H), 7.35 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.92 (dt, *J* = 10.7, 8.5 Hz, 1H), 6.53 (d, *J* = 3.1 Hz, 1H), 6.48 (ddd, *J* = 11.9, 7.9, 2.1 Hz, 1H), 6.42–6.35 (m, 1H), 4.45 (t, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 2.74 (t, *J* = 6.0 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.3 (dd, *J* = 100.1, 12.5 Hz), 147.6, 147.4 (dd, *J* = 98.9, 12.6 Hz), 147.3, 144.0, 135.4, 135.2, 135.0 (dd, *J* = 5.8, 4.0 Hz), 131.6, 128.8, 125.2 (dd, *J* = 6.4, 3.4 Hz), 121.7, 120.3, 119.1, 117.3 (d, *J* = 16.8 Hz), 116.5 (d, *J* = 16.7 Hz), 112.6, 108.5, 100.5, 70.6, 33.0, 32.6; ***m/z*** (ESI+) 428 ([M+Na]+, 100%); **HRMS** (ESI+) found 406.1472 ([M+H]+), C22H18F2N5O+ requires 406.14740.

*CN1C=CC2=CC=C(C=C21)C3=NN=C4N3C(OCCC5=CC=C(C(F)=C5)F)=CN=C4*

*InChI=1S/C22H17F2N5O/c1-28-8-6-15-3-4-16(11-19(15)28)22-27-26-20-12-25-13-21(29(20)22)30-9-7-14-2-5-17(23)18(24)10-14/h2-6,8,10-13H,7,9H2,1H3*

**3-(Benzo[*d*][1,3]dioxol-4-yl)-5-(3,4-difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-662; MMV1794874)**



Prepared according to General Procedure **SNAr** from: **OSM-S-661** (99.0 mg, 0.36 mmol) and 2-(3,4-difluorophenyl)ethanol (57.0 mg, 0.36 mmol) to give **OSM-S-662** as a yellow solid (79.0 mg, 55%); **m.p.** 162–165 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.06 (s, 1H), 7.60 (s, 1H), 7.21 (dt, *J* = 10.9, 8.5 Hz, 1H), 7.10 (ddd, *J* = 13.9, 7.9, 1.2 Hz, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.88 (ddd, *J* = 12.0, 7.9, 2.2 Hz, 1H), 6.71 (ddt, *J* = 8.4, 3.9, 1.7 Hz, 1H), 6.06 (s, 2H), 4.49 (t, *J* = 6.1 Hz, 2H), 2.83 (t, *J* = 6.1 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.6 (dd, *J* = 101.9, 12.5 Hz), 147.6 (dd, *J* = 100.8, 12.5 Hz), 147.2, 147.0, 146.5, 143.6, 140.9, 135.1, 135.0 (dd, *J* = 5.9, 3.8 Hz), 125.3 (dd, *J* = 6.5, 3.4 Hz), 123.6, 121.1, 117.5 (d, *J* = 17.1 Hz), 117.0 (d, *J* = 16.8 Hz), 110.1, 110.0, 109.1, 101.5, 70.7, 33.1; ***m/z*** (ESI+) 419 ([M+Na]+, 100%); **HRMS** (ESI+) found 419.0926 ([M+Na]+), C20H14F2N4O3Na+ requires 419.0926.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=CC5=C4OCO5)N23*

*InChI=1S/C20H14F2N4O3/c21-14-5-4-12(8-15(14)22)6-7-27-18-10-23-9-17-24-25-20(26(17)18)13-2-1-3-16-19(13)29-11-28-16/h1-5,8-10H,6-7,11H2*

**5-(3,4-Difluorophenethoxy)-3-(2*H*-indazol-6-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-546; MMV1580431)**



Prepared according to General Procedure **Suzuki** from: **OSM-S-432** (95.0 mg, 0.27 mmol) and (1*H*-indazol-6-yl)boronic acid (56.0 mg, 0.35 mmol) to give **OSM-S-546** as an off-white solid (24.0 mg, 23%, contains 0.5% CH2Cl2); **m.p.** 184–188 °C (decomp.); **1H NMR** (500 MHz, DMSO-d*6*) δ: 13.36 (s, 1H), 9.06 (s, 1H), 8.19 (s, 1H), 7.92 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.44 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.95 (dt, *J* = 10.9, 8.5 Hz, 1H), 6.63 (ddd, *J* = 12.0, 7.9, 2.2 Hz, 1H), 6.44 (ddt, *J* = 7.1, 5.0, 2.3 Hz, 1H), 4.47 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.2 Hz, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 149.9 (dd, *J* = 103.9, 12.6 Hz), 147.9, 147.9 (dd, *J* = 102.8, 12.5 Hz), 147.1, 144.4, 139.4, 135.6, 135.4 (dd, *J* = 6.1, 3.6 Hz), 134.1, 125.7, 125.6 (dd, *J* = 6.3, 3.3 Hz), 123.6, 123.4, 119.9, 117.7 (d, *J* = 16.9 Hz), 117.1 (d, *J* = 16.8 Hz), 113.4, 109.3, 71.1, 33.4; ***m/z*** (ESI+) 415 ([M+Na]+, 100%); **HRMS** (ESI+) found 393.1267 ([M+H]+), C20H15F2N6O+ requires 393.1270.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C5C=NNC5=C4)N23*

*InChI=1S/C20H14F2N6O/c21-15-4-1-12(7-16(15)22)5-6-29-19-11-23-10-18-26-27-20(28(18)19)13-2-3-14-9-24-25-17(14)8-13/h1-4,7-11H,5-6H2,(H,24,25)*

**5-(3,4-Difluorophenethoxy)-3-(6-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-366; MMV670936) ALICE**



*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C(F)(F)F)N=C4)N23*

*InChI=1S/C19H12F5N5O/c20-13-3-1-11(7-14(13)21)5-6-30-17-10-25-9-16-27-28-18(29(16)17)12-2-4-15(26-8-12)19(22,23)24/h1-4,7-10H,5-6H2*

**5-(3,4-Difluorophenethoxy)-3-(piperidin-1-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-049; MMV669009) INHERITED HAVEN’T GOT DATA YET**



*FC1=CC=C(C=C1F)CCOC2=CN=CC3=NN=C(N4CCCCC4)N23*

*InChI=1S/C18H19F2N5O/c19-14-5-4-13(10-15(14)20)6-9-26-17-12-21-11-16-22-23-18(25(16)17)24-7-2-1-3-8-24/h4-5,10-12H,1-3,6-9H2*

**5-(3,4-Difluorophenethoxy)-3-(4,4-difluoropiperidin-1-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-S-518; MMV1579347)**



Prepared according to General Procedure **Buch** from: **OSM-S-432** (305 mg, 0.86 mmol) and 4,4-difluoropiperidine hydrochloride (176 mg, 1.12 mmol) to give **OSM-S-518** as a yellow solid (8.10 mg, 2%); **1H NMR** (500 MHz, CDCl3) δ: 8.80 (s, 1H), 7.21–7.09 (m, 3H), 7.01 (ddd, *J* = 8.5, 4.1, 1.9 Hz, 1H), 4.47 (t, *J* = 6.8 Hz, 2H), 3.53–3.47 (m, 4H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.13 (tt, *J* = 13.8, 5.9 Hz, 4H); **13C NMR** (126 MHz, CDCl3) δ: 151.2 (dd, *J* = 98.1, 12.5 Hz), 149.2 (dd, *J* = 97.2, 12.6 Hz), 144.0, 137.5, 133.1 (dd, *J* = 5.9, 4.0 Hz), 130.4 (d, *J* = 8.6 Hz), 129.0 (d, *J* = 9.9 Hz), 124.9 (dd, *J* = 6.2, 3.6 Hz), 121.3 (t, *J* = 242.0 Hz), 118.0 (d, *J* = 2.3 Hz), 117.8 (d, *J* = 2.5 Hz), 107.8, 70.9, 49.3 (t, *J* = 5.3 Hz), 34.3, 33.4 (t, *J* = 23.3 Hz); ***m/z*** (ESI+) 418 ([M+Na]+, 100%); **HRMS** (ESI+) found 396.1435 ([M+H]+), C18H18F4N5O+ requires 396.1442.

*FC1(CCN(CC1)C2=NN=C3N2C(OCCC4=CC=C(C(F)=C4)F)=CN=C3)F*

*InChI=1S/C18H17F4N5O/c19-13-2-1-12(9-14(13)20)3-8-28-16-11-23-10-15-24-25-17(27(15)16)26-6-4-18(21,22)5-7-26/h1-2,9-11H,3-8H2*

**4-(5-(3,4-Difluorophenethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)morpholine (OSM-S-517; MMV1579337)**



Prepared according to General Procedure **Buch** from: **OSM-S-432** (101 mg, 0.28 mmol) and morpholine (34.0 mg, 0.37 mmol) to give **OSM-S-517** as a yellow solid (5.00 mg, 5%); **m.p.** 137–140 °C (decomp.); **1H NMR** (500 MHz, CDCl3) δ: 8.78 (s, 1H), 7.22 (ddd, *J* = 11.1, 7.4, 2.2 Hz, 1H), 7.18–7.09 (m, 2H), 7.03 (ddt, *J* = 6.5, 4.3, 1.9 Hz, 1H), 4.47 (t, *J* = 6.7 Hz, 2H), 3.83–3.78 (m, 4H), 3.41–3.35 (m, 4H), 3.21 (t, *J* = 6.8 Hz, 2H); **13C NMR** (126 MHz, CDCl3) δ: 152.5, 151.2 (dd, *J* = 100.5, 12.4 Hz), 149.2 (dd, *J* = 99.8, 12.6 Hz), 146.6, 143.9, 137.6, 133.2 (dd, *J* = 5.6, 4.1 Hz), 124.9 (dd, *J* = 6.2, 3.6 Hz), 117.9 (d, *J* = 3.7 Hz), 117.8 (d, *J* = 3.5 Hz), 107.8, 70.8, 66.3, 52.4, 34.2; ***m/z*** (ESI+) 384 ([M+Na]+, 100%); **HRMS** (ESI+) found 362.1420 ([M+H]+), C17H18F2N5O2+ requires 362.1423.

*FC(C(F)=C1)=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=C(C=C4)N5CCOCC5)N23*

*InChI=1S/C23H21F2N5O2/c24-19-6-1-16(13-20(19)25)7-10-32-22-15-26-14-21-27-28-23(30(21)22)17-2-4-18(5-3-17)29-8-11-31-12-9-29/h1-6,13-15H,7-12H2*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-(3,4-difluorophenyl)ethan-1-ol (OSM-S-390; MMV672687) HAVE SAMPLE, NO DATA?**



*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=C(C(F)=C4)F)O)=CN=C3)F*

*InChI=1S/C20H14F4N4O3/c21-14-6-3-12(7-15(14)22)16(29)10-30-18-9-25-8-17-26-27-19(28(17)18)11-1-4-13(5-2-11)31-20(23)24/h1-9,16,20,29H,10H2*

**1-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-(3,4-difluorophenyl)propan-2-ol (OSM-X-004; MMV672723) INHERITED**



Compound **OSM-X-004** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=C(C(F)=C4)F)(C)O)=CN=C3)F*

*InChI=1S/C21H16F4N4O3/c1-21(30,13-4-7-15(22)16(23)8-13)11-31-18-10-26-9-17-27-28-19(29(17)18)12-2-5-14(6-3-12)32-20(24)25/h2-10,20,30H,11H2,1H3*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-(3,4-difluorophenyl)ethan-1-one (OSM-S-392; MMV1557932)**



Compound **X** (100 mg, 0.21 mmol, 1 equiv.) was dissolved in 3:1 THF:H2O (10 mL) and *p*-TsOH (72.0 mg, 0.42 mmol, 2 equiv.) was added. The mixture was stirred at reﬂux. The condenser was removed and the THF allowed to boil off to give a mixture of black sludge and H2O. The reaction was quenched with H2O and extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give the crude product as a brown solid (94.1 mg); puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give a light brown powder (50.4 mg, 56%); repuriﬁed by preparative TLC (5% MeOH in CH2Cl2) to give **OSM-S-392** as an off-white powder (24.0 mg, 27%); **m.p.** 192–200 °C; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.11 (s, 1H), 8.06–7.98 (m, 1H), 7.90–7.78 (m, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.71 (s, 1H), 7.63 (dt, *J* = 10.1, 8.4 Hz, 1H), 7.34 (t, *J* = 73.7 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 5.85 (s, 2H); **13C NMR** (126 MHz, DMSO-d*6*) δ: 190.2, 153.1 (dd, *J* = 254.9, 12.8 Hz), 152.0 (t, *J*

= 2.9 Hz), 149.4 (dd, *J* = 247.9, 13.0 Hz), 147.5, 145.8, 143.5, 135.7, 132.5, 131.3–130.5 (m), 126.2 (dd, *J* = 7.9, 3.2 Hz), 124.4, 118.2 (d, *J* = 17.9 Hz), 117.7 (d, *J* = 18.1 Hz), 117.4, 115.1 (d, *J* = 257.8 Hz), 109.9, 72.3; ***m/z*** (ESI+) 455 ([M+Na]+, 100%); **HRMS** (ESI+) found 455.0730 ([M+Na]+), C20H12F4N4O3Na+ requires 455.0738.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C(C=C4F)=CC=C4F)=O)=CN=C3)F*

*InChI=1S/C20H12F4N4O3/c21-14-6-3-12(7-15(14)22)16(29)10-30-18-9-25-8-17-26-27-19(28(17)18)11-1-4-13(5-2-11)31-20(23)24/h1-9,20H,10H2*

**3-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-(3,4-difluorophenyl)propan-1-ol (OSM-S-381; MMV670947) INHERITED**



Compound **OSM-S-381** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC(CO)C4=CC(F)=C(F)C=C4)N32*

*InChI=1S/C21H16F4N4O3/c22-16-6-3-13(7-17(16)23)14(10-30)11-31-19-9-26-8-18-27-28-20(29(18)19)12-1-4-15(5-2-12)32-21(24)25/h1-9,14,21,30H,10-11H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(2-(3,4-difluorophenyl)-2-fluoroethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-003; MMV672936) INHERITED**



Compound **OSM-X-003** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=C(C(F)=C4)F)F)=CN=C3)F*

*InChI=1S/C20H13F5N4O2/c21-14-6-3-12(7-15(14)22)16(23)10-30-18-9-26-8-17-27-28-19(29(17)18)11-1-4-13(5-2-11)31-20(24)25/h1-9,16,20H,10H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(2-(3,4-difluorophenyl)-2-fluoropropoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-006; MMV672727) INHERITED**

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Compound **OSM-X-006** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=C(C(F)=C4)F)(C)F)=CN=C3)F*

*InChI=1S/C21H15F5N4O2/c1-21(26,13-4-7-15(22)16(23)8-13)11-31-18-10-27-9-17-28-29-19(30(17)18)12-2-5-14(6-3-12)32-20(24)25/h2-10,20H,11H2,1H3*

**(*R*)-2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-(3,4-difluorophenyl)ethan-1-amine (OSM-X-010; MMV671651) INHERITED**



Compound **OSM-X-010** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OC[C@@H](C4=CC=C(C(F)=C4)F)N)=CN=C3)F*

*InChI=1S/C20H15F4N5O2/c21-14-6-3-12(7-15(14)22)16(25)10-30-18-9-26-8-17-27-28-19(29(17)18)11-1-4-13(5-2-11)31-20(23)24/h1-9,16,20H,10,25H2/t16-/m0/s1*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-(3,4-difluorophenyl)-*N*,*N*-dimethylethan-1-amine (OSM-S-389; MMV897763)**



Prepared according to General Procedure **SNAr** from: **X** (200 mg, 0.99 mmol) and **X** (295 mg, 0.99 mmol) to give the crude product as a dark brown solid (372 mg); puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give **OSM-S-389** a brown powder (169 mg, 37%); **m.p.** 132–135 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.04 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.65 (s, 1H), 7.37 (t, *J* = 73.7 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.31–7.20 (m, 1H), 7.03 (ddd, *J* = 11.7, 8.0, 1.8 Hz, 1H), 6.91–6.79 (m, 1H), 4.95–4.46 (m, 2H), 3.55 (t, *J* = 5.9 Hz, 1H), 2.00 (s, 6H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 151.8 (t, *J* = 3.3 Hz), 147.4, 147.3, 145.5, 143.7, 134.9 (dt, *J* = 39.2, 4.5 Hz), 132.4, 125.0 (dd, *J* = 6.1, 3.3 Hz), 124.5, 117.6, 117.0 (d, *J* = 17.0 Hz), 116.6 (d, *J* = 17.0 Hz), 116.1 (t, *J* = 258.4 Hz), 109.0, 70.6, 65.7, 41.8 (two phenyl C–F signals expected between 155 and 148 ppm; observed for **OSM-S-392**; too weak to be seen); ***m/z*** (ESI+) 462 ([M+H]+, 100%); **HRMS** (ESI+) found 462.1560 ([M+H]+), C22H20F4N5O2+ requires 462.1548.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(N(C)C)C4=CC(F)=C(F)C=C4)=CN=C3*

*InChI=1S/C22H19F4N5O2/c1-30(2)18(14-5-8-16(23)17(24)9-14)12-32-20-11-27-10-19-28-29-21(31(19)20)13-3-6-15(7-4-13)33-22(25)26/h3-11,18,22H,12H2,1-2H3*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-(3,4-difluorophenyl)-*N*,*N*-diethylethan-1-amine (OSM-S-430; MMV1576791)**



Prepared according to General Procedure **SNAr** from: **X** (30.0 mg, 131 µmol) and **X** (38.8 mg, 131 µmol) to give the crude product as a brown solid; puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give **OSM-S-430** as a yellow powder (40.1 mg, 63%); insuﬃcient material remaining for complete characterisation; **1H NMR** (200 MHz, CDCl3) δ: 9.04 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.34 (s, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.08–6.88 (m, 1H), 6.83–6.62 (m, 2H), 6.41 (t, *J* = 73.1 Hz, 1H), 4.64–4.25 (m, 2H), 3.85 (t, *J* = 5.7 Hz, 1H), 2.68–2.19 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 6H); ***m/z*** (ESI+) 512 ([M+Na]+, 100%); **HRMS** (ESI+) found 512.1677 ([M+Na]+), C24H23F4N5O2Na+ requires 512.1680.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(N(CC)CC)C4=CC(F)=C(F)C=C4)=CN=C3*

*InChI=1S/C24H23F4N5O2/c1-3-32(4-2)20(16-7-10-18(25)19(26)11-16)14-34-22-13-29-12-21-30-31-23(33(21)22)15-5-8-17(9-6-15)35-24(27)28/h5-13,20,24H,3-4,14H2,1-2H3*

**3-(4-(Difluoromethoxy)phenyl)-5-((3-(3,4-difluorophenyl)oxetan-3-yl)methoxy)-[1,2,4]triazolo[4,3-*a*]pyrazine (OSM-X-022; MMV670438) INHERITED**



Compound **OSM-X-022** was synthesized by TCG using analogous procedures and the following characterization data have been provided; **1H NMR** (400 MHz, CDCl3) δ:–; ***m/z*** (ESI) ([M+H]+, 100%).

*FC(F)OC(C=C1)=CC=C1C2=NN=C3N2C(OCC4(COC4)C5=CC(F)=C(F)C=C5)=CN=C3*

*InChI=1S/C22H16F4N4O3/c23-16-6-3-14(7-17(16)24)22(10-31-11-22)12-32-19-9-27-8-18-28-29-20(30(18)19)13-1-4-15(5-2-13)33-21(25)26/h1-9,21H,10-12H2*

**3-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-(3,4-difluorophenyl)propane-1,2-diol (OSM-S-560; MMV1581298) DAVID**



*FC(F)OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(CO)(O)C4=CC(F)=C(F)C=C4)=CN=C3*

*InChI=1S/C21H16F4N4O4/c22-15-6-3-13(7-16(15)23)21(31,10-30)11-32-18-9-26-8-17-27-28-19(29(17)18)12-1-4-14(5-2-12)33-20(24)25/h1-9,20,30-31H,10-11H2*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-phenylethan-1-ol (OSM-S-279; MMV688896)**

**

Compound **X** (100 mg, 0.21 mmol, 1 equiv.) was dissolved in EtOH (2 mL). CuCl2·2H2O (1.77 mg, 0.01 mmol, 5 mol%) was added and the mixture heated at reﬂux for 3 h. The solvent was removed and the residue dissolved in EtOAc, washed with H2O, brine, dried (MgSO4), ﬁltered and concentrated under reduced pressure to give the crude product as a dark brown liquid (90.0 mg); puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give **OSM-S-279** as a brown powder (65.2 mg, 79%); **m.p.** 85–90 °C; **1H NMR** (300 MHz, CDCl3) δ: 8.92 (br s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.27 (dapp, *J* = 28.7 Hz, 8H), 6.62 (t, *J* = 73.3 Hz, 1H), 4.91 (br s, 1H), 4.31 (d, *J* = 5.0 Hz, 2H), 3.26 (br s, 1H); **13C NMR** (75 MHz, CDCl3) δ: 152.5, 147.7, 146.4, 144.0, 139.0, 136.5, 132.6, 128.9, 128.7, 126.2, 124.8, 118.8, 115.7 (t, *J* = 261.4 Hz), 108.8, 75.2, 71.5; ***m/z*** (ESI+) 399 ([M+H]+, 100%); **HRMS** (ESI+) 399.1260 ([M+H]+), C20H17F2N4O3+ requires 399.1263.

*FC(F)OC1=CC=C(C2=NN=C3N2C(OCC(O)C4=CC=CC=C4)=CN=C3)C=C1*

*InChI=1S/C20H16F2N4O3/c21-20(22)29-15-8-6-14(7-9-15)19-25-24-17-10-23-11-18(26(17)19)28-12-16(27)13-4-2-1-3-5-13/h1-11,16,20,27H,12H2*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-1-phenylethan-1-one (OSM-S-400; MMV1557940)**



**OSM-S-279** (2.00 g, 5.02 mmol, 1.0 equiv.) was dissolved in anhydrous CH2Cl2 (30 mL) and MnO2 (21.8 g, 251 mmol, 50 equiv.) was added and the reaction stirred at reﬂux. The mixture was ﬁltered through celite and the celite washed with EtOAc. The ﬁltrate was concentrated under reduced pressure to give the crude product as a brown solid (1.65 g); puriﬁed by ﬂash chromatograph on silica (25–100% EtOAc in hexanes) to give **OSM-S-400** as a brown powder (741 mg, 37%); **m.p.** 120–128 °C; **1H NMR** (400 MHz, CDCl3) δ: 8.99 (s, 1H), 7.84 (ddapp, *J* = 8.3, 1.1 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.22 (s, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.57 (t, *J* = 73.4 Hz, 1H), 5.49 (s, 2H); **13C NMR** (101 MHz, CDCl3) δ: 190.4, 152.5, 147.9, 146.6, 143.5, 137.1, 134.9, 133.4, 132.5, 129.3, 128.0, 124.7, 118.5, 115.7 (t, *J* = 260.6 Hz), 109.2, 71.3; ***m/z*** (ESI+) 419 ([M+Na]+, 100%), 815 ([2M+Na]+, 13%); **HRMS** (ESI+) found 419.0927 ([M+Na]+), C20H14F2N4O3Na+ requires 419.0926.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=CC=C4)=O)=CN=C3)F*

*InChI=1S/C20H14F2N4O3/c21-20(22)29-15-8-6-14(7-9-15)19-25-24-17-10-23-11-18(26(17)19)28-12-16(27)13-4-2-1-3-5-13/h1-11,20H,12H2*

**3-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-phenylpropan-1-ol (OSM-S-353; OSM-LO-13; MMV693155)**



Compound **X** (1.50 g, 2.82 mmol, 1 equiv.) was dissolved in EtOH (30 mL). CuCl2·2H2O (24.0 mg, 0.14 mmol, 5 mol%) was added and the mixture heated at reﬂux for 1 h. The solvent was removed and CH2Cl2 was added to the residue. The solid was ﬁltered, washed with CH2Cl2 and dried *in vacuo* to give **OSM-S-353** as a light brown powder (683 mg, 54%); **m.p.** 154–160 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.05 (br s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.63 (br s, 1H), 7.35 (t, *J* = 73.7 Hz, 1H), 7.26–7.12 (m, 5H), 6.98 (dd, *J* = 7.4, 2.0 Hz, 2H), 4.80 (t, *J* = 5.3 Hz, 1H), 4.68–4.38 (m, 2H), 3.39 (t, *J* = 5.8 Hz, 2H), 2.99 (p, *J* = 6.3 Hz, 1H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 151.9, 146.2, 145.2, 139.6, 135.0, 132.4, 128.1, 127.9, 126.6, 124.8, 117.7, 116.2 (t, *J* = 258.1 Hz), 108.8, 71.7, 61.8, 46.6; ***m/z*** (ESI+) 435 ([M+Na]+, 100%); **HRMS** (ESI+) found 435.1245 ([M+Na]+), C21H18F2N4O3Na+ requires 435.1239.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=CC=C4)CO)=CN=C3)F*

*InChI=1S/C21H18F2N4O3/c22-21(23)30-17-8-6-15(7-9-17)20-26-25-18-10-24-11-19(27(18)20)29-13-16(12-28)14-4-2-1-3-5-14/h1-11,16,21,28H,12-13H2*

**3-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-phenylpropane-1,2-diol (OSM-S-556; MMV1581295) DAVID**



*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C4=CC=CC=C4)(O)CO)=CN=C3)F*

*InChI=1S/C21H18F2N4O4/c22-20(23)31-16-8-6-14(7-9-16)19-26-25-17-10-24-11-18(27(17)19)30-13-21(29,12-28)15-4-2-1-3-5-15/h1-11,20,28-29H,12-13H2*

**3-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-2-phenylpropanoic acid (OSM-S-515; MMV1579336)**



**OSM-S-353** (100 mg, 0.24 mmol, 1 equiv.) was dissolved in acetone (4.33 mL) and cooled to 0 °C. Jones reagent (2.5 M, 194 µL, 0.48 mmol, 2 equiv.) was added in 3 portions (64.7 µL each) with 20 min intervals between additions. After stirring for 20 min, the reaction was quenched with excess isopropanol and stirred for a further 10 min. The mixture was diluted with H2O and the organic solvents removed. The aqueous phase was diluted with H2O and extracted with EtOAc (4 ×), washed with brine, dried (Na2SO4), ﬁltered and concentrated under reduced pressure to give the crude product as a brownish-yellow solid (97.7 mg); puriﬁed by flash chromatograph on silica (75–100% EtOAc in hexanes) to give **OSM-S-515** as an oﬀ-white powder (25.7 mg, 25%); **m.p.** 115–120 °C; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.06 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.33 (t, *J* = 73.6 Hz, 1H), 7.31–7.26 (m, 5H), 7.14–7.10 (m, 2H), 4.79 (t, *J* = 9.0 Hz, 1H), 4.64–4.36 (m, 1H), 3.80 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.38 (ddapp , *J* = 14.1, 7.1 Hz, 1H); **13C NMR** (101 MHz, DMSO-d*6*) δ: 171.9, 152.0, 147.4, 145.5, 143.6, 135.4, 135.1, 132.3, 128.6, 128.0, 127.7, 124.5, 117.7, 116.3, 109.0, 71.1, 49.6; ***m/z*** (ESI+) 449 ([M+Na]+, 41%), 471 ([M-H+2Na]+, 100%); **HRMS** (ESI+) found 427.1216 ([M+H]+), C21H17F2N4O4+ requires 427.1212.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(OCC(C(O)=O)C4=CC=CC=C4)=CN=C3)F*

*InChI=1S/C21H16F2N4O4/c22-21(23)31-15-8-6-14(7-9-15)19-26-25-17-10-24-11-18(27(17)19)30-12-16(20(28)29)13-4-2-1-3-5-13/h1-11,16,21H,12H2,(H,28,29)*

**4-(5-(2-(3,4-Difluorophenyl)-2-methoxyethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzonitrile (OSM-S-218; MMV897709) ALICE**



*COC(C1=CC(F)=C(F)C=C1)COC2=CN=CC3=NN=C(C4=CC=C(C=C4)C#N)N23*

*InChI=1S/C21H15F2N5O2/c1-29-18(15-6-7-16(22)17(23)8-15)12-30-20-11-25-10-19-26-27-21(28(19)20)14-4-2-13(9-24)3-5-14/h2-8,10-11,18H,12H2,1H3*

**5-((1,2-Dicarba-*closo*-decaborane-1-yl)ethoxy)-3-(4-(diﬂuoromethoxy)phenyl)-[1,2,4] triazolo[4,3-*a*]pyrazine (OSM-S-418; MMV1576784)**

**

**OSM-S-418** was previously synthesized and characterized according to literature procedures.[bioisostere]

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4567[BH]89%10[CH]%11%124[BH]8%13%14[BH]%11%15%16[BH]%13%17%18[BH]%149%19[BH]%105%20[BH]%21%226[BH]%17%15([BH]%22%12%167)[BH]%18%19%20%21)N32*

*InChI=1S/C16H22B10F2N4O2/c27-14(28)34-10-3-1-9(2-4-10)13-31-30-11-7-29-8-12(32(11)13)33-6-5-16-15-17(16)19(15)20(15)18(15,16)22(16)21(16,17)23(17,19)25(19,20)24(18,20,22)26(21,22,23)25/h1-4,7-8,14-15,17-26H,5-6H2*

***N*-(4-Chlorophenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-367; MMV670246)**



Prepared according to General Procedure **Cycle** from: **X** (111 mg, 0.27 mmol) to give the crude product as an orange solid (1.16 g); puriﬁed by trituration with MeOH to give **OSM-S-367** as a white powder (398 mg, 49%); **m.p.** >300 °C; **1H NMR** (300 MHz, DMSO-d*6*) δ: 10.85 (s, 1H), 9.65 (s, 1H), 8.30 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.54–6.69 (m, 7H); **13C NMR** (75 MHz, DMSO-d*6*) δ: 157.2, 152.0, 146.8, 146.0, 145.7, 136.3, 130.3, 130.2, 128.4, 128.2, 124.5, 124.0, 121.1, 118.3, 115.9 (t, *J* = 258.3 Hz); ***m/z*** (ESI+) 438 ([M+Na]+, 100%); **HRMS** (ESI+) found 438.0540 ([M+Na]+), C19H12ClF2N5O2Na+ requires 438.0540.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC(C=C4)=CC=C4Cl)=O)=CN=C3)F*

*InChI=1S/C19H12ClF2N5O2/c20-12-3-5-13(6-4-12)24-18(28)15-9-23-10-16-25-26-17(27(15)16)11-1-7-14(8-2-11)29-19(21)22/h1-10,19H,(H,24,28)*

***N*-(3-Chloro-4-fluorophenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine-5-carboxamide (OSM-S-379; MMV670767)**



Prepared according to General Procedure **Cycle** from: **X** (500 mg, 1.15 mmol) to give the crude product as an orange solid (663 mg); puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give **OSM-S-379** as an oﬀ-white powder (191 mg, 38%); **m.p.** 266–269 °C; **1H NMR** (300 MHz, DMSO-d*6*) δ: 10.93 (s, 1H), 9.66 (s, 1H), 8.30 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 6.5 Hz, 1H), 7.31 (t, *J* = 9.0 Hz, 1H), 7.43–6.82 (m, 4H); **13C NMR** (75 MHz, DMSO-d*6*) δ: 157.3, 155.5, 152.1, 146.8, 146.2, 145.7, 134.4, 130.4, 130.3, 124.3, 124.0, 121.1, 120.0 (d, *J* = 6.9 Hz), 119.1 (d, *J* = 18.4 Hz), 118.2, 116.8 (d, *J* = 22.0 Hz), 115.8; ***m/z*** (ESI+) 434 ([M+H]+, 27%), 466 ([M+CH3OH+H]+, 100%); **HRMS** (ESI+) found 434.0631 ([M+H]+), C19H12ClF3N5O2+ requires 434.0626.

*FC(OC(C=C1)=CC=C1C2=NN=C3N2C(C(NC4=CC(Cl)=C(C=C4)F)=O)=CN=C3)F*

*InChI=1S/C19H11ClF3N5O2/c20-13-7-11(3-6-14(13)21)25-18(29)15-8-24-9-16-26-27-17(28(15)16)10-1-4-12(5-2-10)30-19(22)23/h1-9,19H,(H,25,29)*

**1-Phenyl-2-((3-(6-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)ethan-1-ol (OSM-S-278; MMV688895)**



Compound **X** (200 mg, 0.41 mmol, 1 equiv.) was dissolved in EtOH (5 mL). CuCl2·2H2O (3.51 mg, 0.02 mmol, 5 mol%) was added and the mixture heated at reﬂux for 2 h. The solvent was removed and the residue directly puriﬁed by ﬂash chromatography on silica (25–100% EtOAc in hexanes) to give **OSM-S-278** as an olive green powder (145 mg, 88%); **m.p.** 145–148 °C; **1H NMR** (300 MHz, CDCl3) δ: 9.13 (s, 1H), 8.98 (br s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.31 (br s, 5H), 4.92 (br s, 1H), 4.44–4.21 (m, 2H), 3.59 (s, 1H); **13C NMR** (75 MHz, CDCl3) δ: 151.3, 148.9, 148.5, 143.8, 143.5, 139.8, 139.0, 136.5, 129.0, 127.0, 126.1, 123.3, 119.8, 119.6, 109.3, 75.4, 71.6; ***m/z*** (ESI+) 402 ([M+H]+, 100%); **HRMS** (ESI+) found 402.1181 ([M+H]+), C19H15F3N5O2+ requires 402.1172.

*OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(C4=CC=C(C(F)(F)F)N=C4)N23*

*InChI=1S/C19H14F3N5O2/c20-19(21,22)15-7-6-13(8-24-15)18-26-25-16-9-23-10-17(27(16)18)29-11-14(28)12-4-2-1-3-5-12/h1-10,14,28H,11H2*

# NMR Spectra

# References

1. Dunetz JR, Xiang Y, Baldwin A, Ringling J (2011) General and scalable amide bond formation with epimerization-prone substrates using T3P and pyridine. *Org. Lett.*, 13:5048– 5051. (10.1021/ol201875q) [↑](#endnote-ref-1)