***Supporting Information***

**Open Source Drug Discovery – Series Four Triazolopyrazines**

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***I. 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 publically 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.

***II. Experimental Procedures and Characterisation Data***

***1. General Procedures***

**General Procedure A: Condensation reaction**

This procedure was adapted from the CRO method. REF

To a stirred solution of **OSM-S-302** (crude, 1 equiv.) in acetonitrile (0.60 M) was added acetic acid (glacial, 1 equiv.) and the appropriate aldehyde (1 equiv.). The reaction mixture was stirred at rt for 2.5–36 h. The reaction mixture was concentrated under reduced pressure and dried *in vacuo* and the crude product submitted to General Procedure **C** without further purification unless otherwise stated.

**General Procedure B: Improved condensation reaction**

**OSM-S-302** (1 equiv.) was suspended in EtOH (~0.1 M) and the appropriate aldehyde (1 equiv.) was added. The reaction mixture was stirred at rt for the stated time and then volatiles were removed *in vacuo* and the crude product submitted to General Procedure **C** without further purification unless otherwise stated.

**General Procedure C: Oxidative cyclisation**

Crude condensation product (1 equiv.) was dissolved in CH­2Cl2 (~0.1 M) and (diacetoxyiodo)benzene (1 equiv.) was added. The reaction mixture was stirred at rt for the stated time and then quenched by the addition of a saturated aqueous solution of sodium hydrogen carbonate. Aqueous layers were separated and then extracted with CH­2Cl2 and then organic layers were combined and washed with brine (× 1), dried (MgSO4), filtered and evaporated. The crude mixture was then purified according to the stated method.

**General Procedure D: Nucleophilic aromatic substitution JO**

Chlorotrizaolopyrazine (1.0 equiv.) was suspended in anhydrous toluene (~0.4 or ~0.1 M) and then powdered KOH (1.3–3.3 equiv.) and 18-crown-6 (0.05–0.10 equiv.) were added and the reaction mixture was stirred at rt under Ar. The appropriate nucleophile (1.0-1.2 equiv.) was added and the reaction mixture was stirred at the stated temperature for the stated time under Ar. On completion, the reaction mixture was quenched by the addition of water and diluted with EtOAc. Organic layers were separated and the aqueous layer extracted with EtOAc (× 2/3). Combined organic layers were washed with water, brine, dried (MgSO­4), filtered and evaporated to give a crude product that was purified by flash column chromatography over silica.

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

6-Chloropyrazine-2-carboxlic acid (1 equiv.), the appropriate amine (1 equiv.) and DIPEA (1.5 equiv.) were dissolved in DMF (~1.0 M) and the reaction mixture cooled to 0 ˚C over ice. T3P (1.5 equiv., 50% solution in EtOAc) was added dropwise with stirring and the reaction mixture stirred for ~18 h at rt. On completion, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO3 (× 3). Combined organic layers were washed with water, brine, dried (MgSO­4), filtered and evaporated to five a crude product that was purified by flash chromatography over silica (10-50% EtOAc in hexanes, λ*max* ~260 nm).

**General Procedure F: Oxidative Cyclisation of Amides**

This procedure was adapted from the literature.[[2]](#endnote-2) An appropriate hydrazone (1 equiv.) was suspended in CH2Cl2 (~50 mM), and phenyliodine diacetate (PIDA) (1 equiv.) added. The reaction mixture was stirred at rt for 12 h, then neutralised with an aqueous solution of saturated NaHCO3. The mixture was extracted with CH2Cl2, the combined organic portions dried with brine, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica (20-100% EtOAc in hexanes; λ*max* ≥230 nm) to give the desired [1,2,4]triazolo[4,3-a]pyrazine.

***2. Ether Synthesis***

***2.1 Hydrazine Displacement***

**2-Chloro-6-hydrazinylpyrazine, OSM-S-302**



Representative example: <http://malaria.ourexperiment.org/uri/864>

2,6-dichloropyrazine (21.0 g, 141 mmol, 1.0 equiv.) was dissolved in EtOH (282 mL, 0.50 M) and hydrazine hydrate (13.5 mL, 270 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at reflux for 16 h. The solvent was removed under reduced pressure to give a pale yellow solid. Water (~200 mL) and EtOAc (~300 mL) were added, and the mixture was shaken in an attempt to dissolve all solid. The organic layer was removed and the aqueous layer extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (~30 mL) and then concentrated under reduced pressure to give the crude title compound as a yellow solid (18.1 g, 125 mmol, 89% yield); **m.p.** 130–131 ˚C; **IR** νmax (film) /cm-1 3210, 3075, 1566, 1544; **­­1H NMR** (200 MHz, DMSO-d*6*) δ: 8.04 (1H, s), 7.72 (1H, s), 6.74 (1H, bs), 4.39 (2H, s); **m/z** (APCI+) 145 [M+H]+.

*ClC1=CN=CC(NN)=N1*

*InChI=1S/C4H5ClN4/c5-3-1-7-2-4(8-3)9-6/h1-2H,6H2,(H,8,9)*

Data consistent with the literature.[[3]](#endnote-3) (although NMR in dmso so prob should compare or get more data)

***2.2 Condensation Reactions***

**(E)-4-((2-(6-Chloropyrazin-2-yl)hydrazono)methyl)benzonitrile, OSM-S-303**



# Representative Example: http://malaria.ourexperiment.org/uri/4de

# Prepared according to General Procedure A from: OSM-S-302 (crude, 1.68 g, ~12.0 mmol) and 4-formylbenzonitrile (1.52 g, 11.6 mmol) to give the crude title compound as a pale orange powder (3.04 g, quant. yield); m.p 191–193 ˚C; 1H NMR (200 MHz, DMSO-d*6*) δ: 11.91 (1H, s), 8.64 (1H, s), 8.12 (1H, s), 8.11 (1H, s), 7.96–7.84 (4H, m); 13C NMR (101 MHz, DMSO-d*6*) δ: 152.0, 145.5, 140.6, 139.0, 133.1, 132.6, 129.1, 127.1, 118.8, 111.1; m/z (APCI+) 258 [M+H]+;HRMS (ESI+) found 258.05406 [M+H]+, C12H9N5Cl requires 258.05410.

*ClC1=CN=CC(N/N=C/C2=CC=C(C#N)C=C2)=N1*

*InChI=1S/C12H8ClN5/c13-11-7-15-8-12(17-11)18-16-6-10-3-1-9(5-14)2-4-10/h1-4,6-8H,(H,17,18)/b16-6-*

# 2-Chloro-6-(2-(pyridin-4-ylmethylene)hydrazinyl)pyrazine, OSM-S-318

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# Representative Example: http://malaria.ourexperiment.org/uri/62d

Prepared according to General Procedure **A** from: **OSM-S-302** (crude, 1.0 g, ~7.0 mmol) and 4-pyridinecarboxaldehyde (0.65 mL, 0.74 g, 6.9 mmol) to yield the crude title compound as a bright yellow powder (1.97 g, quant. yield). A small quantity was purified for characterisation purposes by automated flash column chromatography over silica (Biotage Isolera, 1% TEA in 40–90% EtOAc in hexanes) to give the title compound as a pale yellow powder; **m.p** 254–256 ˚C; **IR** νmax (film) /cm-1 3188, 3035, 2971, 1586, 1561, 1417; **1H NMR** (200 MHz, DMSO-d*6*) δ: 11.89 (1H, bs), 8.66 (1H, s), 8.62–8.59 (2H, m), 8.13 (1H, s), 8.03 (1H, s) 7.71–7.68 (2H, m); **13C NMR** (76 MHz, DMSO-d*6*) δ: 153.0, 151.1, 146.5, 142.5, 140.8, 134.3, 130.1, 121.5; **m/z** (APCI+) 234 [M+H]+;**HRMS** (ESI+) found234.05414 [M+H]+, C10H9ClN5 requires234.05410.

ClC1=NC(N/N=C/C2=CC=NC=C2)=CN=C1

*InChI=1S/C10H8ClN5/c11-9-6-13-7-10(15-9)16-14-5-8-1-3-12-4-2-8/h1-7H,(H,15,16)/b14-5+*

**(E)-2-Chloro-6-(2-(4-(trifluoromethoxy)benzylidene)hydrazinyl)pyrazine, OSM-S-304**



Representative example:

Prepared according to General Procedure **X** from: **OSM-S-302** (X g, X mmol) and \_\_\_ (X g, X mmol) to give the crude title compound as \_\_\_ (X g, X yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;  **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(OC(F)(F)F)C=C2)=N1*

*InChI=1S/C12H8ClF3N4O/c13-10-6-17-7-11(19-10)20-18-5-8-1-3-9(4-2-8)21-12(14,15)16/h1-7H,(H,19,20)/b18-5+*

**(E)-2-Chloro-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine, OSM-S-305**



Representative example: http://malaria.ourexperiment.org/uri/6b1

Prepared according to General Procedure **A** from: **OSM-S-302** (crude, 1.0 g, ~7.0 mmol) and 4-(difluoromethoxy)benzaldehyde (0.9 mL, 1.2 mg, 7.0 mmol) to give the crude title compound as \_\_\_ (2.18 g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(OC(F)F)C=C2)=N1*

*InChI=1S/C12H9ClF2N4O/c13-10-6-16-7-11(18-10)19-17-5-8-1-3-9(4-2-8)20-12(14)15/h1-7,12H,(H,18,19)/b17-5+*

**(E)-2-(2-Benzylidenehydrazinyl)-6-chloropyrazine, OSM-S-306**



Representative example: http://malaria.ourexperiment.org/uri/7bf

Prepared according to General Procedure **A** from: **OSM-S-302** (1.5 g, 10.4 mmol) and benzaldeyde (1.78 mL, 1.85 g, 10.4 mmol) to give the crude title compound as \_\_\_ (X g, X yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=CC=C2)=N1*

*InChI=1S/C11H9ClN4/c12-10-7-13-8-11(15-10)16-14-6-9-4-2-1-3-5-9/h1-8H,(H,15,16)/b14-6*

**(E)-2-Chloro-6-(2-(2-chlorobenzylidene)hydrazinyl)pyrazine, OSM-S-307**



Representative example: Nothing much on page http://malaria.ourexperiment.org/uri/7e5

Prepared according to General Procedure **B** from: **OSM-S-302** (1.5 g, 10.4 mmol) and 2-chlorobenzaldehyde (X g, 10.4 mmol) to give the crude title compound as \_\_\_ (X g, X yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=C(Cl)C=CC=C2)=N1*

*InChI=1S/C11H8Cl2N4/c12-9-4-2-1-3-8(9)5-15-17-11-7-14-6-10(13)16-11/h1-7H,(H,16,17)/b15-5+*

**(E)-2-Chloro-6-(2-(3-chlorobenzylidene)hydrazinyl)pyrazine, OSM-S-308**



Representative example: Nothing much on page http://malaria.ourexperiment.org/uri/7e6

Prepared according to General Procedure **B** from: **OSM-S-302** (1.5 g, 10.4 mmol) and 3-chlorobenzaldehyde (X g, 10.4 mmol) to give the crude title compound as \_\_\_ (X g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC(Cl)=CC=C2)=N1*

*InChI=1S/C11H8Cl2N4/c12-9-3-1-2-8(4-9)5-15-17-11-7-14-6-10(13)16-11/h1-7H,(H,16,17)/b15-5+*

**(E)-2-Chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)pyrazine, OSM-S-309**



Representative Example: http://malaria.ourexperiment.org/uri/56b

Prepared according to General Procedure **A** from: **OSM-S-302** (crude, 2.51 g, ~17.0 mmol, 1.0 equiv.) and 4-chlorobenzaldehyde (1.95 g, 13.9 mmol, 0.8 equiv.) to give the crude title compound as a pale yellow powder (3.89 g, quant. yield); **m.p.** 224–226 ˚C; **IR** νmax (neat) /cm-1 3026, 1582; **1H NMR** (300 MHz, DMSO-d*6*) δ: 11.63 (1H, s), 8.58 (1H, s), 8.06 (1H, s), 8.05 (1H, s), 7.77 (2H, d, *J* 8.7), 7.48 (2H, d, *J* 8.4); **13C NMR** (76 MHz, DMSO-d*6*) δ: 152.2, 145.5, 141.3, 133.8, 133.4, 132.6, 131.0, 128.8, 128.2; **HRMS** (ESI+) found 267.01999 [M+H]+, C11H9Cl2N4 requires 267.01988.

*ClC1=CN=CC(N/N=C/C2=CC=C(Cl)C=C2)=N1*

*InChI=1S/C11H8Cl2N4/c12-9-3-1-8(2-4-9)5-15-17-11-7-14-6-10(13)16-11/h1-7H,(H,16,17)/b15-5+*

**(*E*)-2-Chloro-6-(2-(4-fluorobenzylidene)hydrazinyl)pyrazine, OSM-S-XXX**

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# Representative Example: http://malaria.ourexperiment.org/uri/8ba

**Procedure**

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(F)C=C2)=N1*

*InChI=1S/C11H8ClFN4/c12-10-6-14-7-11(16-10)17-15-5-8-1-3-9(13)4-2-8/h1-7H,(H,16,17)/b15-5+*

**(*E*)-2-Chloro-6-(2-(2,4-dichlorobenzylidene)hydrazinyl)pyrazine, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/8b9

Prepared according to General Procedure **A** from: **OSM-S-302** (1.50 g, 10.4 mmol, 1.0 equiv.) and 2,4-dichlorobenzaldehyde (1.82 g, 10.4 mmol, 1.0 equiv.) to give the crude title compound as a pale brown solid (3.4 g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=C(Cl)C=C(Cl)C=C2)=N1*

*InChI=1S/C11H7Cl3N4/c12-8-2-1-7(9(13)3-8)4-16-18-11-6-15-5-10(14)17-11/h1-6H,(H,17,18)/b16-4+*

**(E)-2-Chloro-6-(2-(3,4-dichlorobenzylidene)hydrazinyl)pyrazine, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/8b8

Prepared according to General Procedure **A** from: **OSM-S-302** (1.50 g, 10.4 mmol, 1.0 equiv.) and 3,4-dichlorobenzaldehyde (1.82 g, 10.4 mmol, 1.0 equiv.) to give the crude title compound as pale brown powder (3.7 g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC(Cl)=C(Cl)C=C2)=N1*

*InChI=1S/C11H7Cl3N4/c12-8-2-1-7(3-9(8)13)4-16-18-11-6-15-5-10(14)17-11/h1-6H,(H,17,18)/b16-4+*

**(E)-2-Chloro-6-(2-(3,4-difluorobenzylidene)hydrazinyl)pyrazine, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/8b7

Prepared according to General Procedure **A** from: **OSM-S-302** (1.50 g, 10.4 mmol, 1.0 equiv.) and 3,4-difluorobenzaldehyde (1.14 mL, 1.47 g, 10.4 mmol, 1.0 equiv.) to give the crude title compound as a pale brown powder (3.1 g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC(F)=C(F)C=C2)=N1*

*InChI=1S/C11H7ClF2N4/c12-10-5-15-6-11(17-10)18-16-4-7-1-2-8(13)9(14)3-7/h1-6H,(H,17,18)/b16-4+*

**(E)-2-Chloro-6-(2-(3,5-difluorobenzylidene)hydrazinyl)pyrazine, OSM-S-310**



Representative Example: http://malaria.ourexperiment.org/uri/84b

Prepared according to General Procedure **B** from: **OSM-S-302** (4.0 g, 27.7 mmol) and 3,5-difluorobenzaldehyde (3.93 g, 27.7 mmol) to give the crude title compound as \_\_\_ (7.12 g, 96%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC(F)=CC(F)=C2)=N1*

*InChI=1S/C11H7ClF2N4/c12-10-5-15-6-11(17-10)18-16-4-7-1-8(13)3-9(14)2-7/h1-6H,(H,17,18)/b16-4+*

**(E)-2-(2-(Benzo[d][1,3]dioxol-5-ylmethylene)hydrazinyl)-6-chloropyrazine, OSM-S-311**



Representative Example: http://malaria.ourexperiment.org/uri/844

Prepared according to General Procedure **B** from: **OSM-S-302** (4.00 g, 27.7 mmol) and piperonal (4.15 g, 27.7 mmol) to give the crude title compound as a yellow powder (3.67 g, 43%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(OCO3)C3=C2)=N1*

*InChI=1S/C12H9ClN4O2/c13-11-5-14-6-12(16-11)17-15-4-8-1-2-9-10(3-8)19-7-18-9/h1-6H,7H2,(H,16,17)/b15-4+*

**(E)-2-Chloro-6-(2-(naphthalen-2-ylmethylene)hydrazinyl)pyrazine, OSM-S-312**



Representative Example: http://malaria.ourexperiment.org/uri/83e

Prepared according to General Procedure **B** from: **OSM-S-302** (4.00 g, 27.7 mmol) and 2-napthaldehyde (4.32 g, 27.7 mmol) to give the crude title compound as \_\_\_ (7.28 g, 93 yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(C=CC=C3)C3=C2)=N1*

*InChI=1S/C15H11ClN4/c16-14-9-17-10-15(19-14)20-18-8-11-5-6-12-3-1-2-4-13(12)7-11/h1-10H,(H,19,20)/b18-8+*

**(E)-2-Chloro-6-(2-((6-(trifluoromethyl)pyridin-3-yl)methylene)hydrazinyl)pyrazine, OSM-S-313**



Representative Example: http://malaria.ourexperiment.org/uri/7c6

Prepared according to General Procedure **B** from: **OSM-S-302** (150 mg, 1.04 mmol) and 6-(trifluoromethyl)nicotinaldehyde (182 mg, 1.04 mmol) to give the crude title compound as \_\_\_ (X g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 8.94 (1H, s), 8.67 (1H, s), 8.54 (1H, s), 8.24 (1H, d, *J* 7.7), 8.14 (1H, s), 7.85 (1H, s), 7.74 (1H, d, *J* 8.24); **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2=CC=C(C(F)(F)F)N=C2)=N1*

*InChI=1S/C11H7ClF3N5/c12-9-5-16-6-10(19-9)20-18-4-7-1-2-8(17-3-7)11(13,14)15/h1-6H,(H,19,20)/b18-4+*

**tert-Butyl (E)-3-((2-(6-chloropyrazin-2-yl)hydrazono)methyl)piperidine-1-carboxylate, OSM-S-314**



Representative Example: http://malaria.ourexperiment.org/uri/806

Prepared according to General Procedure **B** from: **OSM-S-302** (340 mg, 2.35 mmol) and 1-boc-piperidine-3-carboxaldehyde (500 mg, 2.35 mmol) to give the crude title compound as a yellow-orange solid (779 mg, 98%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2CCCN(C2)C(OC(C)(C)C)=O)=N1*

*InChI=1S/C15H22ClN5O2/c1-15(2,3)23-14(22)21-6-4-5-11(10-21)7-18-20-13-9-17-8-12(16)19-13/h7-9,11H,4-6,10H2,1-3H3,(H,19,20)/b18-7+*

**(E)-2-Chloro-6-(2-(cyclohexylmethylene)hydrazinyl)pyrazine, OSM-S-315**



Representative Example: http://malaria.ourexperiment.org/uri/7ca

Prepared according to General Procedure **B** from: **OSM-S-302** (1.5 g, 10.4 mmol) and cyclohexane carboxaldehyde (1.26 mL, 1.17 g, 10.4 mmol) to give the crude title compound as \_\_\_ (X g, X yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C2CCCCC2)=N1*

*InChI=1S/C11H15ClN4/c12-10-7-13-8-11(15-10)16-14-6-9-4-2-1-3-5-9/h6-9H,1-5H2,(H,15,16)/b14-6+*

**(E)-2-Chloro-6-(2-propylidenehydrazinyl)pyrazine, OSM-S-316**



Representative Example: http://malaria.ourexperiment.org/uri/795

Prepared according to General Procedure **A** from: **OSM-S-302** (1.0 g, 6.92 mmol) and propionaldehyde (0.50 mL, 0.40 g, 6.92 mmol) to give the crude title compound as a brown-orange solid (X g, quant. yield); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/CC)=N1*

*InChI=1S/C7H9ClN4/c1-2-3-10-12-7-5-9-4-6(8)11-7/h3-5H,2H2,1H3,(H,11,12)/b10-3+*

**(E)-2-Chloro-6-(2-((4-iodocuban-1-yl)methylene)hydrazinyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2jS7vMf

# Prepared according to General Procedure B from: OSM-S-302 (33.6 mg, 0.23 mmol) and OSM-S-XXX (60.0 mg, 0.23 mmol) to give the crude title compound as an off-white powder (90 mg, quant. yield); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N/N=C/C23C4C5C2C6C3C4C65I)=N1*

*InChI=1S/C13H10ClIN4/c14-4-1-16-2-5(18-4)19-17-3-12-6-9-7(12)11-8(12)10(6)13(9,11)15/h1-3,6-11H,(H,18,19)/b17-3+*

***2.3 Oxidative Cyclisation***

**5-Chloro-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-324**



Representative example: <http://malaria.ourexperiment.org/uri/74f> check if NMR from Jo

Prepared according to General Procedure **C** from: **OSM-S-305** (crude, 1.0 g, ~7.0 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 30–100% EtOAc in hexanes) to give the title compound as brown plates (829 mg, 40%); **m.p** 122–123 ˚C; **IR** νmax (film) /cm-1 3086, 1612, 1467, 1235, 1122, 1045; **1H NMR** (400MHz, DMSO-d*6*) δ: 9.49 (1H, s), 8.09 (1H, s), 7.81–7.77 (2H, m), 7.41 (1H, t, *J* 73.6), 7.37–7.33 (2H, m); **13C NMR** (101MHz, DMSO-d*6*) δ: 152.6, 147.1, 146.7, 142.8, 133.4, 129.2, 124.0, 121.9, 117.4, 116.2 (t, *J*259); **m/z** (APCI+) 297 [M+H]+; **HRMS** (APCI+) found 297.03505 [M+H]+, C­­­­12H8ClF2N­4Orequires297.03492.

*ClC1=CN=CC2=NN=C(C3=CC=C(OC(F)F)C=C3)N21*

*InChI=1S/C12H7ClF2N4O/c13-9-5-16-6-10-17-18-11(19(9)10)7-1-3-8(4-2-7)20-12(14)15/h1-6,12H*

**

**HRMS** (ESI+) found 301.05075 [M+Na]+, C12H8F2N4O2Narequires301.05084.

**5-Chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-220**



# Representative Example: http://malaria.ourexperiment.org/uri/57a

# Prepared according to General Procedure C from: OSM-S-309 (250 mg, 0.94 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 7-85% EtOAc in hexanes) to give the title compound as pale yellow crystals (207 mg, 83%); m.p. 172–173 ˚C; IR νmax (film) /cm-1 3089, 1601, 1465; 1H NMR (200 MHz, CDCl3) δ: 9.35 (1H, s), 7.89 (1H, s), 7.56–7.49 (4H, m); 13C NMR (101 MHz, DMSO-d*6*) δ: 147.1, 146.5, 142.7, 135.5, 133.2, 129.3, 127.9, 126.2, 121.9; m/z (APCI+) 265 [M+H]+; HRMS (ESI+) 265.00440 [M+H]+, C11H7Cl2N4 requires 265.00423.

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

*InChI=1S/C11H6Cl2N4/c12-8-3-1-7(2-4-8)11-16-15-10-6-14-5-9(13)17(10)11/h1-6H*

**5-Chloro-3-(3-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-333**

# 

# Representative Example:

# m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

# *ClC(N12)=CN=CC1=NN=C2C3=CC(Cl)=CC=C3*

# *InChI=1S/C11H6Cl2N4/c12-8-3-1-2-7(4-8)11-16-15-10-6-14-5-9(13)17(10)11/h1-6H*

# 5-Chloro-3-(2-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-334

# 

# Representative Example:

# m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

# *ClC(N12)=CN=CC1=NN=C2C3=C(Cl)C=CC=C3*

# *InChI=1S/C11H6Cl2N4/c12-8-4-2-1-3-7(8)11-16-15-10-6-14-5-9(13)17(10)11/h1-6H*

# 5-Chloro-3-(4-fluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX

# 

# Representative Example:

# Procedure

# m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

# *FC(C=C1)=CC=C1C2=NN=C3C=NC=C(Cl)N32*

# *InChI=1S/C11H6ClFN4/c12-9-5-14-6-10-15-16-11(17(9)10)7-1-3-8(13)4-2-7/h1-6H*

# 5-Chloro-3-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-317

# 

Representative example: http://malaria.ourexperiment.org/uri/866

Prepared according to General Procedure **C** from: **OSM-S-304** (crude, ~26.3 mmol);purified by automated flash chromatography over silica (Biotage Isolera, XX-XX% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

# *ClC1=CN=CC2=NN=C(C3=CC=C(OC(F)(F)F)C=C3)N21*

# *InChI=1S/C12H6ClF3N4O/c13-9-5-17-6-10-18-19-11(20(9)10)7-1-3-8(4-2-7)21-12(14,15)16/h1-6H*

# 4-(5-Chloro-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile , OSM-S-219

# 

# Representative Example: http://malaria.ourexperiment.org/uri/4f0

# Prepared according to General Procedure C from: OSM-S-303 (crude, 2.0 g, ~8.0 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 50-100% EtOAc in hexanes) to give the title compound as an orange powder (1.14 g, 56%); m.p. 226–227 ˚C; IR νmax (film) /cm-1 3089, 2228, 1597; 1H NMR (200 MHz, DMSO-d*6*) δ: 9.53 (1H, s), 8.14 (1H, s), 8.08–7.93 (4H, m); 13C NMR (75 MHz, DMSO-d*6*) δ: 147.1, 146.1, 142.7, 132.3, 132.0, 131.6, 129.4, 121.9, 118.4, 113.1; m/z (APCI+) 256 [M+H]+; HRMS (ESI+) 256.03845 [M+H]+, C12H7N5Cl requires 256.03845.

# *ClC1=CN=CC2=NN=C(C3=CC=C(C#N)C=C3)N21*

# *InChI=1S/C12H6ClN5/c13-10-6-15-7-11-16-17-12(18(10)11)9-3-1-8(5-14)2-4-9/h1-4,6-7H*

# 5-Chloro-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-332

# 

# Representative Example: http://malaria.ourexperiment.org/uri/643

# Prepared according to General Procedure C from: OSM-S-318 (550 mg, 2.4 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 60-100% EtOAc in hexanes) to give the title compound as a pale yellow solid (406 mg, 75%); m.p. 165–167 °C; IR νmax (film)/cm-1 3036, 3003, 1593; 1H NMR (200 MHz; DMSO-d*6*) δ: 9.54 (1H, s), 8.81–8.78 (2H, m), 8.16 (1H, s), 7.79–7.76 (2H, m); 13C NMR (101 MHz; DMSO-d*6*) δ: 149.1, 147.2, 145.4, 142.7, 135.3, 129.5, 125.8, 121.9; m/z (APCI+) 232 [M+H]+; HRMS (APCI+) 232.03834 [M+H]+, C10H7ClN5 requires 232.03845.

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

*InChI=1S/C10H6ClN5/c11-8-5-13-6-9-14-15-10(16(8)9)7-1-3-12-4-2-7/h1-6H*

**5-Chloro-3-(3,4-dichlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX**

**

Representative Example: http://malaria.ourexperiment.org/uri/8c2

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 3.27 g, 10.8 mmol); 3 h; purified by automated flash chromatography over silica (Biotage Isolera, XX-XX% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

*InChI=1S/C11H5Cl3N4/c12-7-2-1-6(3-8(7)13)11-17-16-10-5-15-4-9(14)18(10)11/h1-5H*

**5-Chloro-3-(2,4-dichlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX**

**

Representative Example: http://malaria.ourexperiment.org/uri/8c3

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 1.35 g, 4.48 mmol); 3 h; purified by automated flash chromatography over silica (Biotage Isolera, XX-XX% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC2=NN=C(C3=C(Cl)C=C(Cl)C=C3)N21*

*InChI=1S/C11H5Cl3N4/c12-6-1-2-7(8(13)3-6)11-17-16-10-5-15-4-9(14)18(10)11/h1-5H*

**5-Chloro-3-(3,4-difluorophenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX**

**

Representative Example: http://malaria.ourexperiment.org/uri/8c0

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 1.79 g, 6.66 mmol); 3 h; purified by automated flash chromatography over silica (Biotage Isolera, XX-XX% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

*InChI=1S/C11H5ClF2N4/c12-9-4-15-5-10-16-17-11(18(9)10)6-1-2-7(13)8(14)3-6/h1-5H*

**5-Chloro-3-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-319**



Representative Example: <http://malaria.ourexperiment.org/uri/84c>

Prepared according to General Procedure **C** from: **OSM-S-310** (3.68 g, 13.7 mmol); 1 h; purified by recrystallisation from \_\_\_ to give the title compound as a pale yellow solid (2.42 g, 66%); **m.p.** 210–212 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.37 (1H, s), 7.94 (1H, d, *J* 2.8), 7.27 (1H, d, *J* 2.8), 7.19-1.02 (3H, m); **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 267.02431 [M+H]+, C­­­­11H6ClF2N4 requires267.02436.

*ClC(N12)=CN=CC1=NN=C2C3=CC(F)=CC(F)=C3*

*InChI=1S/C11H5ClF2N4/c12-9-4-15-5-10-16-17-11(18(9)10)6-1-7(13)3-8(14)2-6/h1-5H*

**5-Chloro-3-(6-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-320**

**

Representative Example: http://malaria.ourexperiment.org/uri/7ce

Prepared according to General Procedure **C** from: **OSM-S-313** (crude, X g, ~10.4 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 15–100% EtOAc in hexanes) to give the title compound as a yellow powder (2.65 g, 96%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (APCI+) found 300.02583 [M+H]+, C11H6ClF3N5 requires300.02594.

*ClC(N12)=CN=CC1=NN=C2C3=CN=C(C(F)(F)F)C=C3*

*InChI=1S/C11H5ClF3N5/c12-8-4-16-5-9-18-19-10(20(8)9)6-1-2-7(17-3-6)11(13,14)15/h1-5H*

**5-Chloro-3-cyclohexyl-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-321**

**

Representative Example: http://malaria.ourexperiment.org/uri/7cc

Prepared according to General Procedure **C** from: **OSM-S-315** (crude, X g, ~10.4 mmol); purified by automated flash chromatography over silica (Biotage Isolera, 15–100% EtOAc in hexanes) to give the title compound as an orange solid (2.02 g, 82%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (APCI+) 237 [M+H]+. **HRMS**

*ClC(N12)=CN=CC1=NN=C2C3CCCCC3*

*InChI=1S/C11H13ClN4/c12-9-6-13-7-10-14-15-11(16(9)10)8-4-2-1-3-5-8/h6-8H,1-5H2*

**5-Chloro-3-ethyl-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-322**

**

Representative Example: <http://malaria.ourexperiment.org/uri/799>

Prepared according to General Procedure **C** from: **OSM-S-316** (crude, X g, ~6.92 mmol); 2 h; purified by automated flash chromatography over silica (Biotage Isolera, X-X% EtOAc in hexanes) to give the title compound as \_\_\_ (X g, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (APCI+) 183 [M+H]+; **HRMS** not found. *related dimers AEW 218-2*

*CCC1=NN=C2C=NC=C(N21)Cl*

*InChI=1S/C7H7ClN4/c1-2-6-10-11-7-4-9-3-5(8)12(6)7/h3-4H,2H2,1H3*

***tert*-Butyl 3-(5-chloro-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)piperidine-1-carboxylate, OSM-S-323**

**

Representative Example: http://malaria.ourexperiment.org/uri/81a

Prepared according to General Procedure **C** from: **OSM-S-314** (crude, X g, ~2.35 mmol); X h; purified by automated flash chromatography over silica (Biotage Isolera, 15–100% EtOAc in hexanes) to give the title compound as a brown/orange oil (X g, X%); **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 360.11986 [M+Na]+, C­­­­15H20ClN5O2Narequires360.11977.

*ClC(N12)=CN=CC1=NN=C2C3CCCN(C3)C(OC(C)(C)C)=O*

*InChI=1S/C15H20ClN5O2/c1-15(2,3)23-14(22)20-6-4-5-10(9-20)13-19-18-12-8-17-7-11(16)21(12)13/h7-8,10H,4-6,9H2,1-3H3*

**5-Chloro-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-325**

**

Representative Example: http://malaria.ourexperiment.org/uri/7c2

Prepared according to General Procedure **C** from: **OSM-S-306** (crude, X g, ~10.4 mmol); 15 h; purified by automated flash chromatography over silica (Biotage Isolera, 15-–100% EtOAc in hexanes) to give the title compound as a yellow solid (2.09 g, 87%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.89 (1H, s), 7.87 (1H, s), 7.56–7.47 (5H, m); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (APCI+) 231 [M+H]+; **HRMS**.

*ClC(N12)=CN=CC1=NN=C2C3=CC=CC=C3*

*InChI=1S/C11H7ClN4/c12-9-6-13-7-10-14-15-11(16(9)10)8-4-2-1-3-5-8/h1-7H*

**5-Chloro-3-(naphthalen-2-yl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-326**

******

Representative Example: http://malaria.ourexperiment.org/uri/875

Prepared according to General Procedure **C** from: **OSM-S-312** (3.7 g, 13.0 mmol); X h; purified by recrystallisation from EtOAc to give the title compound as \_\_\_ (2.69 g, 76%); **m.p.** 196–197 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.38 (1H, s), 8.18 (1H, s), 8.05–7.85 (5H, m) 7.76–7.50 (4H, m), 7.27 (1H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 303.04075 [M+Na]+, C15H20ClN5O2Narequires303.04080.

*ClC(N12)=CN=CC1=NN=C2C3=CC(C=CC=C4)=C4C=C3*

*InChI=1S/C15H9ClN4/c16-13-8-17-9-14-18-19-15(20(13)14)12-6-5-10-3-1-2-4-11(10)7-12/h1-9H*

**3-(Benzo[*d*][1,3]dioxol-5-yl)-5-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-327**

******

Representative Example: http://malaria.ourexperiment.org/uri/849

Prepared according to General Procedure **C** from: **OSM-S-311** (3.67 g, 13.3 mmol); X h; purified by recrystallisation from EtOAc to give the title compound as \_\_\_ (2.83 g, 78%); **m.p.** 189–190 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.31 (1H, s), 7.86 (1H, s), 7.12 (1H, s), 7.12–7.06 (2H, t, *J* 12), 6.94 (1H, d, *J* 7.8), 6.10 (2H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 297.01487 [M+Na]+, C­­­­12H7ClN4O2Narequires297.01497.

*ClC(N12)=CN=CC1=NN=C2C3=CC(OCO4)=C4C=C3*

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

**5-Chloro-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-XXX**

****

# Representative Example:

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC2=NN=CN21*

*InChI=1S/C5H3ClN4/c6-4-1-7-2-5-9-8-3-10(4)5/h1-3H*

**5-Azido-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kIK7QE

# OSM-S-XXX (2.00 g, 6.74 mmol, 1 equiv.) and sodium azide (1.75 g, 27.0 mmol, 4 equiv.) were stirred in anhydrous DMF (40 mL) at rt for 3 h. The mixture was diluted with EtOAc (50 mL) and the organic layer was washed with water (5 x 50 mL), brine (2 x 50 mL), dried (MgSO4), filtered and concentrated under reduced pressure to give a very viscous black liquid (2.05 g, quant. yield); purified by automated flash chromatography on silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a sticky black solid (1.40 g, 69%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(N=[N+]=[N-])N32*

*InChI=1S/C12H7F2N7O/c13-12(14)22-8-3-1-7(2-4-8)11-19-17-9-5-16-6-10(18-20-15)21(9)11/h1-6,12H*

**5-Chloro-3-(4-iodocuban-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kINgQc

# Prepared according to General Procedure C from: OSM-S-XXX (crude, 80.0 mg, 0.21 mmol); 2 h; purified by automated flash chromatography over silica (Biotage Isolera, 0–10% MeOH in DCM) to give the title compound as a brown powder (62.2 mg, 78%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC2=NN=C(C34C5C6C3C7C6(I)C5C74)N21*

*InChI=1S/C13H8ClIN4/c14-3-1-16-2-4-17-18-11(19(3)4)12-5-8-6(12)10-7(12)9(5)13(8,10)15/h1-2,5-10H*

**2-(Benzylsulfinyl)-6-chloropyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2jRYX8k

# Sodium hydride (1.60 g, 67.1 mmol) was added to benzyl mercaptan (8 mL, 67.1 mmol) in toluene (64 mL). The mixture was heated to reflux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (10.0 g, 67.1 mmol) in toluene (64 mL) was added. The mixture was heated to reflux for 24 h, cooled to rt, then washed with water (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, >100%). Hydrogen peroxide (30%, 1.04 mL, 33.8 mmol, 4 equiv.) was slowly added to the crude product (2.00 g, 8.45 mmol, 1 equiv.) in glacial acetic acid (10 mL). The reaction mixture was stirred at rt until completion as indicated by TLC (25% ethyl acetate in hexanes). The solution was neutralised with aqueous 4M NaOH and extracted with DCM. The organic layer was dried (Na2SO4), filtered and concentrated under reduced pressure to give a cloudy orange liquid (2.00 g, 93%); purified by automated flash chromatography on silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a large yellow crystals (628 mg, 29%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(S(CC2=CC=CC=C2)=O)=CN=C1*

*InChI=1S/C11H9ClN2OS/c12-10-6-13-7-11(14-10)16(15)8-9-4-2-1-3-5-9/h1-7H,8H2*

**2-(Benzylsulfinyl)-6-hydrazinylpyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khvCCR

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=S(CC1=CC=CC=C1)C2=CN=CC(NN)=N2*

*InChI=1S/C11H12N4OS/c12-15-10-6-13-7-11(14-10)17(16)8-9-4-2-1-3-5-9/h1-7H,8,12H2,(H,14,15)*

**(*E*)-2-(Benzylsulfinyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khEacN

# Prepared according to General Procedure B from: OSM-S-XXX (200 mg, 0.81 mmol) and 4-(difluoromethoxy)benzaldehyde (107 μL, 0.81 mmol) to give the crude title compound as a pale yellow powder (348 mg, >100%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*O=S(CC1=CC=CC=C1)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=N2*

*InChI=1S/C19H16F2N4O2S/c20-19(21)27-16-8-6-14(7-9-16)10-23-25-17-11-22-12-18(24-17)28(26)13-15-4-2-1-3-5-15/h1-12,19H,13H2,(H,24,25)/b23-10+*

**2-(Benzylsulfonyl)-6-chloropyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kxy3zm

# Sodium hydride (1.60 g, 67.1 mmol) was added to benzyl mercaptan (8 mL, 67.1 mmol) in toluene (64 mL). The mixture was heated to reflux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (10.0 g, 67.1 mmol) in toluene (64 mL) was added. The mixture was heated to reflux for 24 h, cooled to rt, then washed with water (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, >100%). The crude product (4.91 g, 20.7 mmol) in acetic acid (50 mL) was added to a solution of potassium permanganate (3.5 g) in water (28 mL) and the mixture was stirred at rt for 1 h. The mixture was adjusted to pH 7 with NH4OH solution (40 mL) then filtered, extracted with CHCl3 (3 x 100 mL), dried (Na2SO4), filtered and concentrated under reduced pressure to give a cloudy yellow liquid (3.14 g, 56%); purified by automated flash chromatography on silica (Biotage Isolera, 6–75% ethyl acetate in hexanes) to give the title compound as a large white crystals (1.31 g, 24%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 1334, 1119; 1H NMR (300 MHz, CDCl3) δ: 8.85 (1H, s), 8.79 (1H, s), 7.54–7.05 (5H, m), 4,65 (2H, s); 13C NMR (75 MHz, CDCl3) δ: 151.20, 149.31, 148.73, 141.40, 131.18, 129.41, 129.11, 126.39, 58.98; m/z (ESI+) 290.97 [M+Na]+ 100%, 558.93 [2M+Na]+ 74%; HRMS (ESI+) found 290.99692 [M+Na]+, C11H9ClN2O2SNarequires290.99652.

*ClC1=NC(S(CC2=CC=CC=C2)(=O)=O)=CN=C1*

*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, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2l9HhoU

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(S(CC2=CC=CC=C2)(=O)=O)=CN=C1*

*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, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2leCqiT

Prepared according to General Procedure **B** from: **OSM-S-XXX** (100 mg, 0.38 mmol) and 4-(difluoromethoxy)benzaldehyde (50 μL, 0.38 mmol) to give the crude title compound as a pale yellow powder (157 mg, 99%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(S(CC3=CC=CC=C3)(=O)=O)=CN=C2*

*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-(phenethylsulfinyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khu0ZC

# Sodium hydride (403 mg, 16.8 mmol) was added to phenylethyl mercaptan (2.25 mL, 16.8 mmol) in toluene (16 mL). The mixture was heated to reflux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (2.50 g, 16.8 mmol) in toluene (16 mL) was added. The mixture was heated to reflux for 24 h, cooled to rt, then washed with water (30 mL). The organic layer was separated, dried (Na2SO4), filtered and concentrated under reduced pressure to give the crude sulfide as a yellow liquid (3.56 g, 85%). Hydrogen peroxide (30%, 2.18 mL, 71.0 mmol, 5 equiv.) was slowly added to the crude product (3.56 g, 14.2 mmol, 1 equiv.) in glacial acetic acid (15 mL). The reaction mixture was stirred at rt until completion as indicated by TLC (25% ethyl acetate in hexanes). The solution was neutralised with aqueous 4M NaOH and extracted with DCM. The organic layer was dried (Na2SO4), filtered and concentrated under reduced pressure to give a cloudy yellow liquid (3.50 g, 92%); purified by automated flash chromatography on silica (Biotage Isolera, 6–50% ethyl acetate in hexanes) to give the title compound as a viscous orange liquid (888 mg, 23%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(S(CCC2=CC=CC=C2)=O)=CN=C1*

*InChI=1S/C12H11ClN2OS/c13-11-8-14-9-12(15-11)17(16)7-6-10-4-2-1-3-5-10/h1-5,8-9H,6-7H2*

**2-Hydrazinyl-6-(phenethylsulfinyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kIX0u6

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(S(CCC2=CC=CC=C2)=O)=CN=C1*

*InChI=1S/C12H14N4OS/c13-16-11-8-14-9-12(15-11)18(17)7-6-10-4-2-1-3-5-10/h1-5,8-9H,6-7,13H2,(H,15,16)*

**(*E*)-2-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)-6-(phenethylsulfinyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2le8H91

Prepared according to General Procedure **B** from: **OSM-S-XXX** (480 mg, 1.83 mmol) and 4-(difluoromethoxy)benzaldehyde (242 μL, 1.83 mmol) to give a yellow solid (752 mg, 99%); purified by automated flash chromatography on silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a yellow powder (327 mg, 43%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XX requires XX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(S(CCC3=CC=CC=C3)=O)=CN=C2*

*InChI=1S/C20H18F2N4O2S/c21-20(22)28-17-8-6-16(7-9-17)12-24-26-18-13-23-14-19(25-18)29(27)11-10-15-4-2-1-3-5-15/h1-9,12-14,20H,10-11H2,(H,25,26)/b24-12+*

**2-Chloro-6-(phenethylsulfonyl)pyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khElot

# Sodium hydride (403 mg, 16.8 mmol) was added to phenylethyl mercaptan (2.25 mL, 16.8 mmol) in toluene (16 mL). The mixture was heated to reflux for 1 h, then cooled to rt and a solution of 2,6-dichloropyrazine (2.50 g, 16.8 mmol) in toluene (16 mL) was added. The mixture was heated to reflux for 24 h, cooled to rt, then washed with water (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, 93%). The crude product (3.92 g, 15.6 mmol) in acetic acid (40 mL) was added to a solution of potassium permanganate (2.5 g) in water (20 mL) and the mixture was stirred at rt for 1 h. The mixture was adjusted to pH 7 with NH4OH solution (40 mL) then filtered, extracted with CHCl3 (3 x 100 mL), dried (Na2SO4), filtered and concentrated under reduced pressure to give an orange semi-solid (1.23 g, 28%); purified by automated flash chromatography on silica (Biotage Isolera, 6–50% ethyl acetate in hexanes) to give the title compound as a large white crystals (547 mg, 12%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(S(CCC2=CC=CC=C2)(=O)=O)=CN=C1*

*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*

**2-Hydrazinyl-6-(phenethylsulfonyl)pyrazine, OSM-S-XXX**



# Representative Example: http://bit.ly/2lem353

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(S(CCC2=CC=CC=C2)(=O)=O)=CN=C1*

*InChI=1S/C12H14N4O2S/c13-16-11-8-14-9-12(15-11)19(17,18)7-6-10-4-2-1-3-5-10/h1-5,8-9H,6-7,13H2,(H,15,16)*

**(*E*)-2-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)-6-(phenethylsulfonyl)pyrazine, OSM-S-XXX**

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# Representative Example: http://bit.ly/2jRZbMm

Prepared according to General Procedure **B** from: **OSM-S-XXX** (400 mg, 1.44 mmol) and 4-(difluoromethoxy)benzaldehyde (190 μL, 1.44 mmol) to give a yellow solid (620 mg, 100%); purified by automated flash chromatography on silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a yellow powder (275 mg, 44%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XX requires XX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(S(CCC3=CC=CC=C3)(=O)=O)=CN=C2*

*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+*

***2.4 Side Chain Synthesis***

**2-(3,4-Difluorophenyl)-2-((trimethylsilyl)oxy)acetonitrile, OSM-S-226**



Representative Example: http://malaria.ourexperiment.org/uri/486

Freshly dried zinc chloride (0.96 g, 7.00 mmol) was weighed into an oven-dried flask under Ar and 3,4-difluorobenzaldehyde (1.00 g, 7.00 mmol) in CH2Cl2 (6 mL) was added at 0 ˚C. Trimethylsilyl cyanide (0.70 g, 0.90 mL, 7.00 mmol) was added at 0 ˚C and the reaction mixture stirred in an ice bath for 30 min before being allowed to warm to rt whilst stirring overnight. The reaction mixture was poured over water (12 mL), extracted with EtOAc (3 × 20 mL), dried (MgSO4), filtered and evaporated to give the crude title compound as a straw coloured oil (1.38 g, X%) containing a 0.1:1:0.4 mixture of starting material: 2-(3,4-difluorophenyl)-2-hydroxyacetonitrile: **OSM-S-266**. The oil was used as crude in the next reaction; **1H NMR** (200 MHz, CDCl3) δ: 7.44–7.18 (3H, m), 5.54 (1H, s), 0.25 (3H, s).

*FC1=C(F)C=C(C(C#N)O[Si](C)(C)C)C=C1*

*InChI=1S/C11H13F2NOSi/c1-16(2,3)15-11(7-14)8-4-5-9(12)10(13)6-8/h4-6,11H,1-3H3*

Data in accordance with CRO briefing document.[[4]](#endnote-4) Procedure adapted from the literature.[[5]](#endnote-5)

**2-(3,4-Difluorophenyl)-2-hydroxyacetic acid, OSM-S-329**



Representative Example: http://malaria.ourexperiment.org/uri/489

Crude **OSM-S-226** (1.38 g) was stirred in dioxane (5 mL) and 50% aq. H2SO4 (20 mL) was added and the reaction mixture was heated to 90 ˚C for 1h. The reaction mixture removed from the heat, allowed to cool to rt and then poured into water (20 mL), extracted with EtOAc (3 × 20 mL). Combined organic layers were dried (MgSO4), filtered and evaporated to give an amber oil (1.42 g), used as crude in the next reaction; **1H NMR** (300 MHz, CDCl3) δ: 7.35–7.12 (3H, m), 5.20 (1H, s).

*FC1=C(F)C=C(C(C(O)=O)O)C=C1*

*InChI=1S/C8H6F2O3/c9-5-2-1-4(3-6(5)10)7(11)8(12)13/h1-3,7,11H,(H,12,13)*

**Methyl 2-(3,4-difluorophenyl)-2-hydroxyacetate, OSM-S-222**



Representative Example: <http://malaria.ourexperiment.org/uri/48d>

Crude **OSM-S-329** (1.42 g) was dissolved in MeOH (10 mL), a few drops of H2SO4 were added and the reaction mixture stirred at 80 ˚C for 14 h. The reaction mixture was poured over water (20 mL) and extracted into EtOAc (3 × 20 mL). Combined organic layers were dried (MgSO4­­­­), filtered and evaporated to give an amber oil (1.27 g). The crude material was filtered over a pad of silica (EtOAc) to give the title compound as a yellow oil (1.12 g, 79% yield over three steps from **OSM-S-226**); **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl­3) δ: 7.30–7.24 (1H, m), 7.16–7.10 (2H, m), 5.14 (1H, s), 3.79 (3H, s); **13C NMR** (76 MHz, CDCl­3) δ: 173.4, 150.4 (d, *J* 248.4), 150.3 (d, *J* 248.8), 135.0 (m), 122.6, 17.4 (d, *J* 17.8), 115.7 (d, *J* 18.7), 71.7. 53.3; **19F{1H} NMR** (282 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=C(C(C(OC)=O)O)C=C1*

*InChI=1S/C9H8F2O3/c1-14-9(13)8(12)5-2-3-6(10)7(11)4-5/h2-4,8,12H,1H3*

Data and preparation in accordance with CRO briefing document.[[6]](#endnote-6)

All approaches: <http://malaria.ourexperiment.org/uri/5e2>

**Methyl 2-(3,4-difluorophenyl)-2-methoxyacetate, OSM-S-330**



Representative Example: <http://malaria.ourexperiment.org/uri/548>

**OSM-S-222** (300 mg, 1.48 mmol, 1.00 equiv.) was dissolved in DMF (1.5 mL) under Ar. Cs2CO3 (532 mg, 1.63 mmol, 1.10 equiv.) was added and the reaction mixture was stirred at room temperature for 10 min. Methyl iodide (100 μL, 1.56 mmol, 1.10 equiv.) was then added and the reaction stirred at rt for 16 h. The reaction was quenched by addition of water (5 mL) extraction with EtOAc (3 × 5 mL) washed with water (5 × 5 mL), washed with brine (5 mL), dried (MgSO4), filtered and evaporated to give a pale green oil. The crude oil was purified by automated flash chromatography over silica (details of method required) to provide the title compound as a pale yellow oil (108 mg, 34%) and starting material xx mg; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=C(C(C(OC)=O)OC)C=C1*

*InChI=1S/C10H10F2O3/c1-14-9(10(13)15-2)6-3-4-7(11)8(12)5-6/h3-5,9H,1-2H3*

**2-(3,4-Difluorophenyl)-2-methoxyethanol, OSM-S-331**



Representative Example: [http://malaria.ourexperiment.org/uri/5a1](http://malaria.ourexperiment.org/uri/5a1" \t "_blank)

Lithium aluminium hydride (28 mg, 0.75 mmol, 1.5 equiv.) was dissolved in anhydrous THF (2 mL) and then stirred at 0 ˚C. **OSM-S-330** (108 mg, 0.50 mmol, 1.0 equiv.) was dissolved in anhydrous THF (1 mL) and added dropwise to the solution at 0 ˚C and then stirred whilst reaching rt for 1.5 h. On completion, the reaction mixture was quenched by the dropwise addition of HCl (2M aq. soln., 2 mL) and then extracted with EtOAc (2 × 12 mL), washed with brine (6 mL), dried (MgSO4), filtered and evaporated to give a pale yellow oil (81 mg, 0.43 mmol, 86%) that was used as crude in the subsequent reaction; **1H NMR** (300 MHz, CDCl­3) δ: 7.20–6.97 (3H, m), 4.18 (1H, t, *J* 6.0), 3.53 (2H, d, *J* 6.0), 3.23 (3H, s), **HRMS** (ESI+) found 211.05422 [M+Na]+, C9H10F2O2Na requires211.05411.

*FC1=C(F)C=C(C(CO)OC)C=C1*

*InChI=1S/C9H10F2O2/c1-13-9(5-12)6-2-3-7(10)8(11)4-6/h2-4,9,12H,5H2,1H3*

**Methyl 2-(3,4-difluorophenyl)-2-((tetrahydro-2H-pyran-2-yl)oxy)acetate, OSM-S-XXX**

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# Representative Example: http://malaria.ourexperiment.org/uri/933

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(OC)C(OC1OCCCC1)C2=CC(F)=C(F)C=C2*

*InChI=1S/C14H16F2O4/c1-18-14(17)13(20-12-4-2-3-7-19-12)9-5-6-10(15)11(16)8-9/h5-6,8,12-13H,2-4,7H2,1H3*

**2-(3,4-Difluorophenyl)-2-((tetrahydro-2H-pyran-2-yl)oxy)ethan-1-ol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/946

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC(OC1OCCCC1)C2=CC(F)=C(F)C=C2*

*InChI=1S/C13H16F2O3/c14-10-5-4-9(7-11(10)15)12(8-16)18-13-3-1-2-6-17-13/h4-5,7,12-13,16H,1-3,6,8H2*

**Ethyl 2-(3,4-difluorophenyl)acetate, OSM-S-XXX**

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# Representative Example: http://bit.ly/2jRWo5V

# 3,4-Difluorophenylacetic acid (5.0 g, 29.1 mmol, 1 equiv.) and *p*-TsOH (50.0 mg, 0.29 mmol, 0.01 equiv.) were dissolved in EtOH (66 mL) and the reaction was heated to reflux for 18 h. The reaction was allowed to cool to rt and the solvent was removed to give the crude title compound as a pale yellow oil (5.95 g, quant. yield) that was used without further purification in the subsequent reaction; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(CC(OCC)=O)=C1*

*InChI=1S/C10H10F2O2/c1-2-14-10(13)6-7-3-4-8(11)9(12)5-7/h3-5H,2,6H2,1H3*

**Ethyl 2-bromo-2-(3,4-difluorophenyl)acetate, OSM-S-XXX**

****

# Representative Example:

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(C(Br)C(OCC)=O)=C1*

*InChI=1S/C10H9BrF2O2/c1-2-15-10(14)9(11)6-3-4-7(12)8(13)5-6/h3-5,9H,2H2,1H3*

**Ethyl 2-(3,4-difluorophenyl)-2-(dimethylamino)acetate, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2ldVmgL

# OSM-S-XXX (500 mg, 1.79 mmol, 1 equiv.) was dissolved in DMF (5 mL). Dimethylamine solution (33% in alcohol, 0.32 mL, 1.79 mmol, 1 equiv.) and K2CO3 (743 mg, 5.37 mmol, 3 equiv.) were added and the reaction stirred at rt for 2 h. The reaction was filtered and the solvent removed. The residue was partitioned between EtOAc and water and the organic layer was separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water (2 x 5 mL), brine (2 x 5 mL), dried (Na2SO4), filtered and concentrated under reduced pressure to give the crude title compound as a yellow oil (410 mg, 94%) that was used without further purification in the subsequent reaction; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(C(N(C)C)C(OCC)=O)=C1*

*InChI=1S/C12H15F2NO2/c1-4-17-12(16)11(15(2)3)8-5-6-9(13)10(14)7-8/h5-7,11H,4H2,1-3H3*

**2-(3,4-Difluorophenyl)-2-(dimethylamino)ethan-1-ol, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2jROUQv

# OSM-S-XXX (450 mg, 1.85 mmol, 1 equiv.) was dissolved in anhydrous THF (6 mL) and cooled to 0 ˚C. Lithium aluminium hydride (1M in THF, 1.18 mL, 0.18 mmol, 0.64 equiv.) was added dropwise and the reaction mixture stirred at 0 ˚C for 10 min, then at rt for 21 h. The reaction was cooled to 0 ˚C and excess LAH was quenched with EtOAc dropwise, then a saturated aqueous solution of Rochelle’s salt was added. The mixture was then stirred at rt for 1.5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (MgSO4), filtered and concentrated under reduced pressure to give the crude title compound as a yellow oil (245 mg, 66%) that was used without further purification in the subsequent reaction; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(C(N(C)C)CO)=C1*

*InChI=1S/C10H13F2NO/c1-13(2)10(6-14)7-3-4-8(11)9(12)5-7/h3-5,10,14H,6H2,1-2H3*

**Methyl 2-hydroxy-2-phenylacetate, OSM-S-336**

**

Representative Example: http://malaria.ourexperiment.org/uri/67c

DL-Mandelic acid (5.0 g, 32.9 mmol, 1 equiv.) and *p*-TsOH (57 mg, 0.33 mmol, 0.01 equiv.) were dissolved in MeOH (66 mL) and the reaction mixture was heated to reflux for 3 h. The solvent was removed *in vacuo* to give the title compound as a yellow oil (5.46 g, quant. yield) that was used without further purification in the subsequent reaction; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl­3) δ: 7.48–7.31 (5H, m), 5.18 (1H, s), 3.76 (3H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C(OC)=O)C1=CC=CC=C1*

*InChI=1S/C9H10O3/c1-12-9(11)8(10)7-5-3-2-4-6-7/h2-6,8,10H,1H3*

**Methyl 2-methoxy-2-phenylacetate,** **OSM-S-337**

******

Representative example: <http://malaria.ourexperiment.org/uri/6cc>

**OSM-S-336** (500 mg, 3.01 mmol, 1 equiv.) was dissolved in DMF (6 mL) under Ar. Cs2CO3 (980 mg, 3.01 mmol, 1 equiv.) was added and the reaction mixture was stirred at rt for 10 min. MeI (0.2 mL, 3.31 mmol, 1.1 equiv.) was added and the reaction stirred at rt for 20 h. The reaction mixture was diluted with EtOAc (12 mL) and washed with water (5 x 8 mL). Combined aqueous layers were washed withe EtOAc (10 mL) and then combined organic layers were washed with brine (6 mL), dried (MgSO4), filtered and evaporated to give a crude orange oil (560 mg) which was purified by automated flash chromatography (Biotage Isolera, 15-100% EtOAc in hexanes) to give the title compound as a colourless oil (242 mg, 1.34 mmol, 45%); **IR** νmax (film) /cm-1 XX; **1H NMR** (400 MHz, CDCl3) δ: 7.46–7.42 (2H, m), 7.40–7.33 (3H, m), 4.78 (1H, s), 3.72 (3H, s), 3.41 (3H, s); **13C NMR** (126 MHz, CDCl3) δ: 171.1, 136.2, 128.8, 128.7, 127.2, 82.6, 57.4, 52.3; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(OC)C(OC)C1=CC=CC=C1*

*InChI=1S/C10H12O3/c1-12-9(10(11)13-2)8-6-4-3-5-7-8/h3-7,9H,1-2H3*

Preparation adapted from the literature.[[7]](#endnote-7)

**2-Methoxy-2-phenylethan-1-ol,** **OSM-S-338**

**

Representative Example: http://malaria.ourexperiment.org/uri/6e2

Lithium aluminium hydride (74 mg, 1.96 mmol, 1.5 equiv.) was dissolved in anhydrous THF (2 mL) and then stirred at 0 ˚C. **OSM-S-337** (235 mg, 1.30 mmol, 1 equiv.) was dissolved in anhydrous THF (1 mL) and added dropwise to the solution at 0 ˚C and then stirred whilst reaching rt for 1.5 h. On completion, the reaction mixture was quenched by the dropwise addition of HCl (2M aq. soln., 2 mL) and then extracted with EtOAc (2 x 12 mL), washed with brine (6 mL), dried (MgSO4), filtered and evaporated to give a pale yellow oil (X mg, X%) that was used as crude in the subsequent reaction; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC(OC)C1=CC=CC=C1*

*InChI=1S/C9H12O2/c1-11-9(7-10)8-5-3-2-4-6-8/h2-6,9-10H,7H2,1H3*

**Methyl 2-phenyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)acetate,** **OSM-S-339**



Representative Example: http://malaria.ourexperiment.org/uri/92e

**OSM-S-336** (2 g, 12.0 mmol, 1 equiv.) and DHP (1.86 mL, 1.72 g, 20.4 mmol, 1.7 equiv.) were dissolved in anhydrous CH2Cl2 (8.5 mL) under Ar and cooled to 0 ˚C. PPTS (74 mg, 0.30 mmol, 0.03 eq.) was added and the reaction mixture was stirred at 0 ˚C for 3 h and then at rt for 20 h. CH2Cl2 (80 mL) was added and the resulting solution was shaken with portions of ice-cold water (3 x 10 mL) and once with saturated NaHCO3 (10 mL). The organic phase was dried (MgSO4), filtered and the solvent removed under reduced pressure to give \_\_\_ (X g, X%). Purification? **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(OC)C(OC1OCCCC1)C2=CC=CC=C2*

*InChI=1S/C14H18O4/c1-16-14(15)13(11-7-3-2-4-8-11)18-12-9-5-6-10-17-12/h2-4,7-8,12-13H,5-6,9-10H2,1H3*

**2-Phenyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethan-1-ol,** **OSM-S-340**

**

Representative Example: <http://malaria.ourexperiment.org/uri/7bd>

To a stirred solution of lithium aluminium hydride (97 mg, 2.56 mmol, 0.64 equiv.) in anhydrous diethyl ether (2.6 mL) at 0 ˚C and under Argon was added a solution of **OSM-S-339** (1 g, 4 mmol, 1.0 equiv.) in anhydrous diethyl ether (1.64 mL) over 5 min. The reaction mixture was stirred at 0 ˚C for 1 h and then at rt for 2 h before refluxing for 20 h. The reaction mixture was cooled to rt then to 0 ˚C and saturated ammonium chloride solution (1 mL) was added dropwise followed by dropwise addition of a 10% aqueous solution of NaOH (1 mL) and water (1 mL). The mixture was stirred for 10 min at 0 ˚C, 10 min whilst reaching rt and then refluxed for 4 h before leaving to stir at rt overnight. The white/yellow solid was filtered through CeliteTM and then washed with diethyl ether (5 x 30 mL). The combined organic layers were dried (MgSO4), filtered and evaporated to give a yellow oil that was purified by automated flash chromatography (Biotage Isolera, XX-XX% EtOAc in hexanes) to give the title compound as a pale straw oil (434 mg, 1.95 mmol, 49%); **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC(OC1OCCCC1)C2=CC=CC=C2*

*InChI=1S/C13H18O3/c14-10-12(11-6-2-1-3-7-11)16-13-8-4-5-9-15-13/h1-3,6-7,12-14H,4-5,8-10H2*

**(*R*)-2-Amino-2-phenylethan-1-ol, OSM-S-341**

**

Representative Example: http://malaria.ourexperiment.org/uri/67f

A 2-necked RB was charged with lithium aluminium hydride (1.3 g, 34.3 mmol, 2.1 equiv.) and cooled in an ice bath under Ar. THF (30 mL) was added slowly via syringe and the suspension was stirred at -5 ˚C. D-(–)-α-phenylglycine (2.5 g, 16.6 mmol, 1 equiv.) was added portionwise over 10 mins and the reaction stirred at -5 ˚C for 0.5 h, then heated to reflux for 15 h. The reaction mixture was allowed to cool to rt then in an ice bath. Ether (40 mL) was added, followed by dropwise addition of an aqueous solution of NaOH (2M, 10 mL). The reaction mixture was left to stir for 15 minutes at rt then filtered and the residue washed with copious amounts of cool ether (~300 mL). The filtrate was concentrated at under reduced pressure to give a yellow oil containing fine white swirls of powder. Ether (20 mL) was added and the reaction mixture cooled to -78 ˚C. A small amount of white solid formed, the mixture was sonicated for 30 seconds and the solid crashed out. Cooled to -78 C and then filtered to yield a white solid which was dried at the high vac (1.6 g, 11.7 mmol, 70%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*N[C@@H](CO)C1=CC=CC=C1*

*InChI=1S/C8H11NO/c9-8(6-10)7-4-2-1-3-5-7/h1-5,8,10H,6,9H2/t8-/m0/s1*

**(*R*)-2-(Carboxyamino)-2-phenylacetic acid, OSM-S-342**



Representative Example:http://malaria.ourexperiment.org/uri/783

To a stirred solution of D-(–)-α-phenylglycine (1.0 g, 6.6. mmol) in 8% formic acid (8 mL) at 0 ˚C was added dropwise acetic anhydride (4.3 mL). The reaction mixture was stirred at rt for 10 min, then warmed to rt. Workup? \_\_\_ to give \_\_\_ (1.3 g, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(O)[C@H](NC(O)=O)C1=CC=CC=C1*

*InChI=1S/C9H9NO4/c11-8(12)7(10-9(13)14)6-4-2-1-3-5-6/h1-5,7,10H,(H,11,12)(H,13,14)/t7-/m1/s1*

**(*R*)-2-(Methylamino)-2-phenylethan-1-ol, OSM-S-343**



Representative Example: http://malaria.ourexperiment.org/uri/6e3

**OSM-S-341** (150 mg, 1.09 mmol, 1.00 equiv.) was suspended in MeOH (2 mL) and AcOH (0.05 mL). Aqueous formaldehyde (37% wt. 0.15 mL) was added and the mixture stirred for 5 min. Sodium cyanoborohydride (72 mg, 1.15 mmol, 1.05 equiv.) was added portionwise and the reaction was stirred at rt for 4 h until no SM was present. The reaction mixture was quenched by the addition of water (2 mL) and then the volatiles were removed *in vacuo*. The aqueous mixture was partioned between EtOAc (8 mL) and water (4 mL) and then extracted with EtOAc (3 x 8 mL), washed with brine (8 mL), dried (MgSO4), filtered and evaportated to give a milky oil (63 mg, 0.38 mmol, 35%) of the dimethylated product - surprising but good as wanted this compound too, low yield surprising. Used crude in AEW 192-1.

**IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC[C@H](NC)C1=CC=CC=C1*

*InChI=1S/C9H13NO/c1-10-9(7-11)8-5-3-2-4-6-8/h2-6,9-11H,7H2,1H3*

**(*R*)-2-(Dimethylamino)-2-phenylethan-1-ol, OSM-S-344**

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Representative Example: http://malaria.ourexperiment.org/uri/884

**OSM-S-341** (0.25 g, 1.82 mmol) was dissolved in formic acid (2.3 mL, 18.2 mmol) and aqueous formaldehyde (0.34 mL, 10.9 mmol) was added. The reaction was stirred at reflux (100 ˚C) for 24 h. The reaction mixture was allowed to cool to rt and was basified with 1M NaOH (pH 11) and extracted with diethyl ether (4 x 40 mL). The combined organic layers were dried (Na2SO4) and concentrated *in vacuo* to give a pale yellow oil (26 mg, X%). The organic layers were re-extracted with EtOAc (4 x 40 mL), dried (Na2SO4), filtered and concentrated *in vacuo* to give the remaining crude title compound as a pale yellow oil (120 mg, X%). Purification? **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC[C@H](N(C)C)C1=CC=CC=C1*

*InChI=1S/C10H15NO/c1-11(2)10(8-12)9-6-4-3-5-7-9/h3-7,10,12H,8H2,1-2H3*

**Ethyl 3-hydroxy-2-phenylpropanoate, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8bd

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(OCC)C(CO)C1=CC=CC=C1*

*InChI=1S/C11H14O3/c1-2-14-11(13)10(8-12)9-6-4-3-5-7-9/h3-7,10,12H,2,8H2,1H3*

**Ethyl 2-phenyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propanoate. OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8c8

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(OCC)C(COC1OCCCC1)C2=CC=CC=C2*

*InChI=1S/C16H22O4/c1-2-18-16(17)14(13-8-4-3-5-9-13)12-20-15-10-6-7-11-19-15/h3-5,8-9,14-15H,2,6-7,10-12H2,1H3*

**2-Phenyl-3-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/951

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC(COC1OCCCC1)C2=CC=CC=C2*

*InChI=1S/C14H20O3/c15-10-13(12-6-2-1-3-7-12)11-17-14-8-4-5-9-16-14/h1-3,6-7,13-15H,4-5,8-11H2*

**(3,4-Difluorophenyl)methanol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/687

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=CC=C(CO)C=C1F*

*InChI=1S/C7H6F2O/c8-6-2-1-5(4-10)3-7(6)9/h1-3,10H,4H2*

**(3,4-Dichlorophenyl)methanol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8c6

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CC=C(CO)C=C1Cl*

*InChI=1S/C7H6Cl2O/c8-6-2-1-5(4-10)3-7(6)9/h1-3,10H,4H2*

**(4-Chlorophenyl)methanol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8c7

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CC=C(CO)C=C1*

*InChI=1S/C7H7ClO/c8-7-3-1-6(5-9)2-4-7/h1-4,9H,5H2*

**1-(3,4-Difluorophenyl)ethan-1-ol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/9ac

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=CC=C(C(C)O)C=C1F*

*InChI=1S/C8H8F2O/c1-5(11)6-2-3-7(9)8(10)4-6/h2-5,11H,1H3*

**1-(3,4-Dichlorophenyl)ethan-1-ol, OSM-S-XXX**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8c5

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CC=C(C(C)O)C=C1Cl*

*InChI=1S/C8H8Cl2O/c1-5(11)6-2-3-7(9)8(10)4-6/h2-5,11H,1H3*

**4-(1-Hydroxyethyl)benzonitrile, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kIQTWG

# 4-Formylbenzonitrile (1.00 g, 7.63 mmol, 1.00 equiv.) was dissolved in anhydrous Et2O (14 mL) and stirred at 0 ˚C. MeMgBr solution (3M in ether, 2.57 mL, 7.70 mmol, 1.01 equiv.) was added and the reaction stirred for 5 min at 0 ˚C, then at rt until completion as indicated by TLC (25% ethyl acetate in hexanes). The reaction was cooled to 0 ˚C and HCl (1M aqueous, 10 mL) was added dropwise with stirring. The solvent was removed and the residue partitioned between EtOAc (20 mL) and a saturated aqueous solution of NH4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers washed with water (10 mL), brine (10 mL), dried (MgSO4), filtered and concentrated under reduced pressure to give the crude title compound as a yellow liquid (1.38 g, >100%) that was used without further purification in the subsequent reaction; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*CC(O)C1=CC=C(C#N)C=C1*

*InChI=1S/C9H9NO/c1-7(11)9-4-2-8(6-10)3-5-9/h2-5,7,11H,1H3*

**(Azidomethyl)benzene, OSM-S-XXX**



# Representative Example: http://bit.ly/2jSLp7A

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*[N-]=[N+]=NCC1=CC=CC=C1*

*InChI=1S/C7H7N3/c8-10-9-6-7-4-2-1-3-5-7/h1-5H,6H2*

**(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanol, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2leny3S

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC1=CN(N=N1)CC2=CC=CC=C2*

*InChI=1S/C10H11N3O/c14-8-10-7-13(12-11-10)6-9-4-2-1-3-5-9/h1-5,7,14H,6,8H2*

**Azidobenzene, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khwWW9

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*[N-]=[N+]=NC1=CC=CC=C1*

*InChI=1S/C6H5N3/c7-9-8-6-4-2-1-3-5-6/h1-5H*

**(1-Phenyl-1*H*-1,2,3-triazol-4-yl)methanol, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2khv0x3

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC1=CN(N=N1)C2=CC=CC=C2*

*InChI=1S/C9H9N3O/c13-7-8-6-12(11-10-8)9-4-2-1-3-5-9/h1-6,13H,7H2*

**2-Azido-6-chloropyrazine, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2kxCc6s

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N=[N+]=[N-])=N1*

*InChI=1S/C4H2ClN5/c5-3-1-7-2-4(8-3)9-10-6/h1-2H*

**(1-(6-Chloropyrazin-2-yl)-1*H*-1,2,3-triazol-4-yl)methanol, OSM-S-XXX**

****

# Representative Example: http://bit.ly/2l9Eg7O

# Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC1=CN(N=N1)C2=CN=CC(Cl)=N2*

*InChI=1S/C7H6ClN5O/c8-6-1-9-2-7(10-6)13-3-5(4-14)11-12-13/h1-3,14H,4H2*

**(4-Iodocuban-1-yl)methanol, OSM-S-XXX**

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# Representative Example: http://bit.ly/2jS7TdB

4-Iodocubanecarboxylic acid (200 mg, 0.73 mmol) was dissolved in dry THF (7 mL) under Ar and cooled to 0 ˚C. Borane dimethyl sulfide complex (0.23 mL, 1.16 mmol) was added and the reaction stirred for 20 min at 0 ˚C, then at rt for 4 h. The solution was quenched with water and stirred at rt overnight. After adding EtOAc, the solution was washed with water, brine, dried (MgSO4), filtered and concentrated under reduced pressure to give the crude title compound as a white solid (162 mg, 85%) that was used without further purification in the subsequent reaction; **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX;**1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OCC12C3C4C1C5C2C3C54I*

*InChI=1S/C9H9IO/c10-9-5-2-6(9)4-7(9)3(5)8(2,4)1-11/h2-7,11H,1H2*

**4-Iodocubane-1-carbaldehyde, OSM-S-XXX**

******

# Representative Example: http://bit.ly/2jS3ZSa

# A stirring solution of oxalyl chloride (63.8 μL, 0.75 mmol) in dry DCM (1 mL) was prepared under Ar at -78 ˚C. Dry DMSO (0.11 mL, 1.54 mmol) in dry DCM (1 mL) was added dropwise. After 20 min at -78 ˚C, OSM-S-XXX (162 mg, 0.62 mmol) dissolved in dry DCM (4.25 mL) under Ar was added dropwise. The mixture was maintained at -78 ˚C for 1.5 h and then dry Et3N (0.39 mL, 2.80 mmol) was added. The mixture was warmed to rt and quenched with water (4 mL). The aqueous layer was extracted with DCM (2 x 4 mL) and the combined organic layers were washed with water (4 mL), brine (4 mL), dried (MgSO4), filtered and concentrated under reduced pressure to give an off-white solid (161 mg, quant. yield); purified by automated flash chromatography on silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a white solid (130 mg, 81%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; HRMS (XX) found XX [M+X]+, XXrequiresXX.

*[H]C(C12C3C4C1C5C2C3C54I)=O*

*InChI=1S/C9H7IO/c10-9-5-2-6(9)4-7(9)3(5)8(2,4)1-11/h1-7H****2.5 Nucleophilic Aromatic Substitution***

**4-(5-Phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzonitrile,** **OSM-S-187**

****

Representative Example: http://malaria.ourexperiment.org/uri/662

Prepared according to General Procedure **D** from: **OSM-S-219** (0.20 g, 0.78 mmol, 1.0 equiv.), 2-phenethyl alcohol (0.12 mL, 0.12 g, 1.0 mmol, 1.2 equiv.), KOH (0.15 g, 2.6 mmol, 3.3 equiv.) and 18-crown-6 (20 mg, 80μmol, 0.10 equiv.); 40 ˚C, 1.5 h; purified by automated flash chromatography over silica (Biotage Isolera, 50–100% EtOAc in hexanes) to give the title compound as pale brown needles (85 mg, 32%); **m.p** 142–143 ˚C; **IR** νmax (film) /cm-1 3063, 2228, 1610, 1507, 1297; **1H NMR** (400 MHz, DMSO-d*6*) δ: 7.19–7.18 (3H, m), 6.92–6.90 (2H, m), 4.54 (2H, t, *J* 6.4), 2.89 (2H, t, *J* 6.4); **13C NMR** (101 MHz, DMSO-d*6*) δ: 147.6, 144.9, 143.9, 137.2, 134.9, 132.4, 131.5, 131.5, 128.7, 128.2, 126.4, 118.6, 112.2, 109.3, 71.1, 33.7; **m/z** (APCI+) 342 [M+H]+; **HRMS** (APCI+) found 342.13477 [M+H]+, C­­­­20H16N5Orequires342.13494.

*N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32*

*InChI=1S/C20H15N5O/c21-12-16-6-8-17(9-7-16)20-24-23-18-13-22-14-19(25(18)20)26-11-10-15-4-2-1-3-5-15/h1-9,13-14H,10-11H2*

**3-(2-Chlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-291**



Representative Example:

Prepared according to General Procedure **D** from: **OSM-S-334** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 373 [M+Na]+; **HRMS** (ESI+) found 373.08253 [M+Na]+, C19H15ClN4ONa requires 373.08266.

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

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

**3-(3-Chlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-292**



Representative Example:

Prepared according to General Procedure **D** from: **OSM-S-333** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 373 [M+Na]+; **HRMS** (ESI+) found 373.08256 [M+Na]+, C19H15ClN4ONa requires 373.08266.

*ClC1=CC=CC(C2=NN=C3N2C(OCCC4=CC=CC=C4)=CN=C3)=C1*

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

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



Representative Example:

Prepared according to General Procedure **D** from: **OSM-S-220** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 373 [M+Na]+; **HRMS** (ESI+) found 373.08250 [M+Na]+, C19H15ClN4ONa requires 373.08266.

*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*

**5-Phenethoxy-3-phenyl-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-294**



Representative Example:

Prepared according to General Procedure **D** from: **OSM-S-325** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 317 [M+H]+; **HRMS** (ESI+) found 339.12160 [M+Na]+, C19H16N4ONa requires 339.12163.

*C12=NN=C(C3=CC=CC=C3)N1C(OCCC4=CC=CC=C4)=CN=C2*

*InChI=1S/C19H16N4O/c1-3-7-15(8-4-1)11-12-24-18-14-20-13-17-21-22-19(23(17)18)16-9-5-2-6-10-16/h1-10,13-14H,11-12H2*

**3-(3,4-Difluorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-349**

**

Representative Example: http://malaria.ourexperiment.org/uri/8d7

Prepared according to General Procedure **D** from: **OSM-S-XXX** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as a brown solid (251 mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **m/z** (ESI+) 375 [M+Na]+; **HRMS** (ESI+) found 375.10276 [M+Na]+, C19H14F2N4ONa requires 375.10279.

*FC(C=C1)=C(F)C=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32*

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

**3-(3,4-Dichlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-350**

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Representative Example: http://malaria.ourexperiment.org/uri/8d8

Prepared according to General Procedure **D** from: **OSM-S-XXX** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as a pale brown solid (206 mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 407 [M+Na]+; **HRMS** (ESI+) found 407.04368 [M+Na]+, C19H14Cl2N4ONa requires 407.04369.

*ClC(C=C1)=C(Cl)C=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32*

*InChI=1S/C19H14Cl2N4O/c20-15-7-6-14(10-16(15)21)19-24-23-17-11-22-12-18(25(17)19)26-9-8-13-4-2-1-3-5-13/h1-7,10-12H,8-9H2*

**3-(2,4-Dichlorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-351**

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Representative Example: http://malaria.ourexperiment.org/uri/8d9

Prepared according to General Procedure **D** from: **OSM-S-XXX** (X g, X mmol, 1.0 equiv.), 2-phenethyl alcohol (X g, X mmol, X equiv.), KOH (X g, X mmol, X equiv.) and 18-crown-6 (X mg, Xμmol, X equiv.); X ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (118 mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 407 [M+Na]+; **HRMS** (ESI+) found 407.04369 [M+Na]+, C19H14Cl2N4ONa requires 407.04369.

*ClC1=CC=CC(C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32)=C1Cl*

*InChI=1S/C19H14Cl2N4O/c20-15-8-4-7-14(18(15)21)19-24-23-16-11-22-12-17(25(16)19)26-10-9-13-5-2-1-3-6-13/h1-8,11-12H,9-10H2*

**3-(3,5-Difluorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine,** **OSM-S-295**



Representative Example: http://malaria.ourexperiment.org/uri/853

Prepared according to General Procedure **D** from: **OSM-S-319** (533 mg, 2.00 mmol, 1.0 equiv.), 2-phenylethanol (244 mg, 2.00 mmol, 1.0 equiv.), KOH (393 mg, 7.00 mmol, 3.5 equiv.) and 18-crown-6 (37.0 mg, 140μmol, 0.07 equiv.); 40 ˚C, 0.5 h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (319 mg, 60%); **m.p.** 172–173 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (500 MHz, DMSO-d*6*) δ: 9.10 (1H, s), 1.38 (1H, s), 7.47–7.40 (7H, m), 7.26–7.05 (3H, m), 6.85–6.90 (4H, m), 4.52 (2H, t, *J* 22), 2.85 (2H, t, *J* 35); **13C NMR** (126 MHz, CDCl3) δ: 149, 148, 147, 147, 145, 138, 136, 129 ,128, 126, 125, 112, 110, 108, 103, 72, 40, 35; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **m/z** (ESI+) 375 [M+Na]+; **HRMS** (ESI+) found 375.10279 [M+Na]+, C19H14F2N4ONa requires 375.10279.

*FC1=CC(F)=CC(C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32)=C1*

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

**3-(3,5-Difluorophenyl)-5-(pyridin-2-ylmethoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-298**

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Representative Example: http://malaria.ourexperiment.org/uri/870

Prepared according to General Procedure **D** from: **OSM-S-319** (267 mg, 1.00 mmol, 1.0 equiv.), pyridine-2-ylmethanol (109 mg, 1.00 mmol, 1.0 equiv.), KOH (196 mg, 3.50 mmol, 3.5 equiv.) and 18-crown-6 (19.0 mg, 70μmol, 0.07 equiv.); rt, 20 min; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (58 mg, 17%); **m.p.** 191–192 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.06 (1H, d, *J* 4.6), 8.58 (2H, s), 7.67–7.61 (2H, m), 7.50 (1H, d, *J* 3.8), 7.25–7.23 (8H, m), 7.02–6.98 (1H, m), 6.98–6.85 (1H, m); **13C NMR** (126 MHz, DMSO-d*6*) δ: 164, 161, 154, 150, 148, 145, 144, 137, 135, 132, 124, 123, 114, 114, 110, 106, 73, 40; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 362.01 [M+Na]+, C18H13N5O3Na requires 362.29.

*FC1=CC(F)=CC(C2=NN=C3C=NC=C(OCC4=CC=CC=N4)N32)=C1*

*InChI=1S/C17H11F2N5O/c18-12-5-11(6-13(19)7-12)17-23-22-15-8-20-9-16(24(15)17)25-10-14-3-1-2-4-21-14/h1-9H,10H2*

**3-(Benzo[*d*][1,3]dioxol-5-yl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine,** **OSM-S-296**



Representative Example: http://malaria.ourexperiment.org/uri/85d

Prepared according to General Procedure **D** from: **OSM-S-327** (549 mg, 2.00 mmol, 1.0 equiv.), 2-phenylethanol (244 mg, 2.00 mmol, 1.0 equiv.), KOH (393 mg, 7.00 mmol, 3.5 equiv.) and 18-crown-6 (37.0 mg, 140μmol, 0.07 equiv.); 40 ˚C, 2.5 h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (342 mg, 62%); **m.p.** 162–163 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (400 MHz, DMSO-d*6*) δ: 8.98 (1H, s), 7.54 (1H, s), 7.27 (1H, s) 7.19–7.15 (4H, m), 7.03 (XH, d, *J* 12), 6.94–6.87 (3H, m), 6.05 (2H, s), 4.47–4.40 (2H, m), 3.03–2.97 (2H, m); **13C NMR** (101 MHz, DMSO-d6) δ: 149, 148, 149, 147, 146, 138, 137, 130, 129, 127, 127, 112, 109, 108, 102, 71.8, 40.0, 34.4; **m/z** (ESI+) 383 [M+Na]+; **HRMS** (ESI+) found 383.11132 [M+Na]+, C20H16N4O3Na requires 383.11146.

*C12=NN=C(C3=CC(OCO4)=C4C=C3)N1C(OCCC5=CC=CC=C5)=CN=C2*

*InChI=1S/C20H16N4O3/c1-2-4-14(5-3-1)8-9-25-19-12-21-11-18-22-23-20(24(18)19)15-6-7-16-17(10-15)27-13-26-16/h1-7,10-12H,8-9,13H2*

**3-(Benzo[*d*][1,3]dioxol-5-yl)-5-(pyridin-2-ylmethoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-299**

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Representative Example: http://malaria.ourexperiment.org/uri/871

Prepared according to General Procedure **D** from: **OSM-S-327** (273 mg, 1.00 mmol, 1.0 equiv.), pyridine-2-ylmethanol (109 mg, 1.00 mmol, 1.0 equiv.), KOH (X mg, 3.50 mmol, 3.5 equiv.) and 18-crown-6 (26.2 mg, 70μmol, 0.07 equiv.); 40 ˚C, 1.5 min; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (80.3 mg, 23%); **m.p.** 187–188 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.04 (1H, s), 8.58 (1H, d, *J* 3.4), 7.72–7.58 (1H, m), 7.38 (1H, s), 7.27–7.12 (6H, m), 6.87–6.80 (2H, m), 5.99 (2H, s), 4.78 (1H, s); **HRMS** (ESI+) found 370.09 [M+Na]+, C18H13N5O3Na requires 370.32.

*C12=NN=C(C3=CC=C(OCO4)C4=C3)N1C(OCC5=NC=CC=C5)=CN=C2*

*InChI=1S/C18H13N5O3/c1-2-6-20-13(3-1)10-24-17-9-19-8-16-21-22-18(23(16)17)12-4-5-14-15(7-12)26-11-25-14/h1-9H,10-11H2*

**3-(Naphthalen-2-yl)-5-phenethoxy-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-297**



Representative Example: http://malaria.ourexperiment.org/uri/85c

Prepared according to General Procedure **D** from: **OSM-S-326** (0.56 g, 2.00 mmol, 1.0 equiv.), 2-phenylethanol (244 mg, 2.00 mmol, 1.0 equiv.), KOH (393 mg, 7.00 mmol, 3.5 equiv.) and 18-crown-6 (106 mg, 400μmol, 0.20 equiv.); 40 ˚C, X h; purified by automated flash chromatography over silica (Biotage Isolera, 50-80% EtOAc in hexanes) to give the title compound as \_\_\_ (0.36 g, 50%); **m.p.** 183–184 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (400 MHz, DMSO-d*6*) δ: 9.04 (1H, s), 8.31 (1H, d, *J* 1.0), 8.11–8.00 (3H, m), 7.82 (1H, dd, *J* 8.5, 1.7), 7.67–7.61 (2H, m), 7.57 (1H, s), 7.03–6.97 (1H, m), 6.91– 6.86 (2H, m), 6.56–6.51 (2H, m), 4.46 (2H, t, *J* 6.3), 2.73 (2H, t, *J* 6.2); **13C NMR** (101 MHz, DMSO-d*6*) δ: 148.7, 147.4, 146.7, 146.3, 144.1, 137.5, 135.1, 128.8, 128.4, 126.6, 125.4, 121.4, 111.4, 108.9, 107.7, 101.7, 71.4, 34.1; **m/z** (ESI+) 389 [M+Na]+; **HRMS** (ESI+) found 389.13701 [M+Na]+, C23H18N4ONa requires 389.13728.

*C12=NN=C(C3=CC(C=CC=C4)=C4C=C3)N1C(OCCC5=CC=CC=C5)=CN=C2*

*InChI=1S/C23H18N4O/c1-2-6-17(7-3-1)12-13-28-22-16-24-15-21-25-26-23(27(21)22)20-11-10-18-8-4-5-9-19(18)14-20/h1-11,14-16H,12-13H2*

**3-(Naphthalen-2-yl)-5-(pyridin-2-ylmethoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-300**

****

Representative Example: http://malaria.ourexperiment.org/uri/874

Prepared according to General Procedure **D** from: **OSM-S-326** (280 mg, 1.00 mmol, 1.0 equiv.), pyridine-2-ylmethanol (109 mg, 1.00 mmol, 1.0 equiv.), KOH (197 mg, 3.50 mmol, 3.5 equiv.) and 18-crown-6 (27.0 mg, 102μmol, 0.07 equiv.); 40 ˚C, 1.5 min; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (96.8 mg, 29%); **m.p.** 169–170 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (200 MHz, CDCl3) δ: 9.10 (1H, s), 8.42 (1H, d, *J* 2.4), 8.21 (1H, s), 7.94–7.67 (6H, m), 7.64–7.45 (4H, m), 7.10–6.84 (2H, m), 6.29 (1H, d, *J* 3.8); **HRMS** (ESI+) found 376.11666 [M+Na]+, C21H15N5ONa requires 376.36647.

*C12=NN=C(C3=CC(C=CC=C4)=C4C=C3)N1C(OCC5=CC=CC=N5)=CN=C2*

*InChI=1S/C21H15N5O/c1-2-6-16-11-17(9-8-15(16)5-1)21-25-24-19-12-22-13-20(26(19)21)27-14-18-7-3-4-10-23-18/h1-13H,14H2*

**(±)-4-(5-(2-(3,4-Difluorophenyl)-2-methoxyethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-208**



Representative Example: <http://malaria.ourexperiment.org/uri/5a4>

Prepared according to General Procedure **D** from: **OSM-S-331** (81 mg, 0.43 mmol, 1.1 equiv.), **OSM-S-219** (0.12 g, 0.45 mmol, 1.0 equiv.), KOH (80 mg, 1.4 mml, 3.3 equiv.) and 18-crown-6 (9.0 mg, 30 μmol, 0.08 equiv.); 40 ˚C, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, 10–100% EtOAc in hexanes) to give the title compound as a yellow solid (43 mg, 25%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (400 MHz, CDCl3) δ: 9.06 (1H, bs), 7.93 (2H, d, *J* 8.1), 7.82 (2H, d, *J* 8.1), 7.36 (1H, bs), 7.19–7.09 (1H, m), 6.95–6.85 (2H, m), 4.32–4.18 (3H, m), 3.13 (3H, s); **13C NMR** (101 MHz, CDCl3) δ: 151.8 (dd, *J* 12.4, 11.6), 149.4 (dd, *J*, 12.4, 11.6), 147.9, 145.5, 143.6, 136.7, 133.2 (m, *J* 4.1, 4.4), 132.1, 131.5 (d, *J* 7.2), 122.9 (dd, *J* 6.4, 3.7), 118.1, 117.9 (d, *J* 17.6), 115.7 (d, *J* 17.6), 113.6, 109.0, 79.7, 73.8, 56.9; **19F{1H} NMR** (377 MHz, CDCl3) δ: -135.6 (d, *J* 20.7), -136.5 (d, *J* 20.7); **HRMS** (ESI+) found 408.12683 [M+H]+, C­­­­21H16F2N5O2 requires408.12666.

*FC1=C(F)C=CC(C(OC)COC2=CN=CC3=NN=C(C4=CC=C(C#N)C=C4)N32)=C1*

*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*

All approaches: http://malaria.ourexperiment.org/uri/5ba

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# 4-(5-(2-Methoxy-2-phenylethoxy)-[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)benzonitrile, OSM-S-265

# 

Representative Example: http://malaria.ourexperiment.org/uri/6f3

Prepared according to General Procedure **D** from: **OSM-S-338** (53 mg, 0.34 mmol, 1.0 equiv.), **OSM-S-219** (80 mg, 0.31 mmol, 1.0 equiv.), KOH (58 g, 1.0 mmol, 3.3 equiv.) and 18-crown-6 (4.0 mg, 20 μmol, 0.05 equiv.); 40 ˚C, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, 10–100% EtOAc in hexanes) to give the title compound as a pale brown solid (21 mg, 18%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **HRMS** (ESI+) found XX [M+H]+, C­­­­21H18N5O2 requiresXX.

# *N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC(C4=CC=CC=C4)OC)N32*

# *InChI=1S/C21H17N5O2/c1-27-18(16-5-3-2-4-6-16)14-28-20-13-23-12-19-24-25-21(26(19)20)17-9-7-15(11-22)8-10-17/h2-10,12-13,18H,14H2,1H3*

# 1-Phenyl-2-((3-phenyl-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)ethan-1-ol, OSM-S-277

# 

# *AEW 230-1 PROB NEED TO REPEAT*

# Representative Example: http://malaria.ourexperiment.org/uri/7d4

# Needs deprotection procedure written (general?)

# m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; m/z (APCI+) 333 [M+H]+; HRMS (ESI+) found 355.11654 [M+Na]+, C­­­­19H16N4O2Narequires355.11655.

# *OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(C4=CC=CC=C4)N32*

# *InChI=1S/C19H16N4O2/c24-16(14-7-3-1-4-8-14)13-25-18-12-20-11-17-21-22-19(23(17)18)15-9-5-2-6-10-15/h1-12,16,24H,13H2*

# 4-(5-(Phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-188

# 

# Representative Example: http://malaria.ourexperiment.org/uri/57d

# Prepared according to General Procedure D from: OSM-S-219 (103 mg, 0.40 mmol, 1.0 equiv.), phenylethyl mercaptan (60 μL, 60 mg, 0.4 mmol, 1.0 equiv.), KOH (74 mg, 1.3 mmol, 3.3 equiv.) and 18-crown-6 (8 mg, 0.03 mmol, 0.08 equiv.); 40 ˚C, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, 50–100% EtOAc in hexanes) to give the title compound as pearlescent creamy crystals (55 mg, 38%); m.p. 237–238 °C; IR νmax (film)/cm-1 2324, 1450, 1273; 1H NMR (500 MHz; DMSO-d*6*) δ: 8.43 (1H, d, *J* 5.0), 8.16–8.10 (4H, m), 7.89 (1H, d, *J* 5.0), 7.34–7.23 (5H, m), 3.61 (2H, tapp, *J* 8.0, 7.5), 3.06 (2H, t, *J* 7.5); 13C NMR (126 MHz; DMSO-d*6*) δ: 153.1, 146.4, 144.1, 139.9, 133.2, 130.1, 129.9, 129.0, 128.6, 128.4, 126.4, 118.3, 113.5, 112.8, 54.9, 34.4; m/z (APCI+) 358 [M+H]+; HRMS (ESI+) found 358.11199 ([M+H]+), C20H16N5S requires 358.11209.

*N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(SCCC4=CC=CC=C4)N32*

# *InChI=1S/C20H15N5S/c21-12-16-6-8-17(9-7-16)20-24-23-18-13-22-14-19(25(18)20)26-11-10-15-4-2-1-3-5-15/h1-9,13-14H,10-11H2*

# 4-(5-(2-Chlorophenethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-189

# 

# Representative Example: http://malaria.ourexperiment.org/uri/58a

# Prepared according to General Procedure D from: OSM-S-219 (107 mg, 0.42 mmol, 1.0 equiv.), 2-chlorophenethyl alcohol (60 μL, 60 mg, 0.4 mmol, 1.0 equiv.), KOH (78 mg, 1.4 mmol, 3.5 equiv.) and 18-crown-6 (8 mg, 0.03 mmol, 0.08 equiv.); 40 ˚C, 1 h; purified by flash chromatography over silica (manual, 50–100% EtOAc in hexanes) to give the title compound as pearlescent creamy crystals (78 mg, 53%); m.p. 183–185 ˚C; IR νmax (film) /cm-1 2229, 1611, 1507, 1369, 1298; 1H NMR (400 MHz, DMSO-d*6*) δ: 9.10 (1H, s), 7.87–7.81 (4H, m), 7.72 (1H, s), 7.40 (1H, dd, *J* 8.0, 1.2), 7.24 (1H, tdapp, *J* 7.7, 1.7), 7.13 (1H, tdapp, *J* 7.5, 1.3), 6.90 (1H, dd, *J* 7.7, 1.6), 4.58 (2H, t, *J* 6.4), 2.99 (2H, t, *J* 6.4); 13C NMR (101 MHz, DMSO-d*6*) δ: 147.6, 144.9, 143.8, 135.1, 134.4, 133.1, 132.4, 131.4, 131.3, 130.3, 129.2, 128.5, 127.1, 118.5, 112.2, 109.3, 68.9, 31.3; m/z (APCI+) 376 [M+H]+; HRMS (ESI+) found 376.09585 ([M+H]+), C20H15ClN5O requires 376.09596.

*N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4Cl)N32*

# *InChI=1S/C20H14ClN5O/c21-17-4-2-1-3-15(17)9-10-27-19-13-23-12-18-24-25-20(26(18)19)16-7-5-14(11-22)6-8-16/h1-8,12-13H,9-10H2*

# 4-(5-((3-Chlorophenethyl)amino)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-190

# 

Representative Example: http://malaria.ourexperiment.org/uri/58d

Prepared according to General Procedure **D** from: **OSM-S-219** (101 mg, 0.39 mmol, 1.0 equiv.), 2-(3-chlorophenyl)ethylamine (60 μL, 67 mg, 0.43 mmol, 1.1 equiv.), KOH (78 mg, 1.4 mmol, 3.6 equiv.) and 18-crown-6 (9 mg, 0.03 mmol, 0.08 equiv.); 40 ˚C, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, 17–100% EtOAc in hexanes) to give the title compound as a cream powder (25 mg, 17%); **m.p.** 246–248 °C; **IR** νmax (film)/cm-1 3250, 2923, 2227, 1573; **1H NMR** (400 MHz; DMSO-d*6*) δ: 8.40 (1H, t, *J* 5.6), 8.14–8.08 (4H, m), 7.85 (1H, d, *J* 4.8), 7.41 (1H, d, *J* 4.8), 7.37–7.23 (4H, m), 3.75 (2H, qapp, *J* 6.8, 6.4), 2.99 (2H, t, *J* 7.6); **13C NMR** (101 MHz; DMSO-d*6*) δ: 161.1, 147.9, 146.5, 142.2, 141.9, 139.9, 133.2, 132.9, 130.7, 130.6, 130.2, 128.7, 128.6 127.5, 126.1, 118.4, 112.5, 106.3; **m/z** (APCI+) 375 [M+H]+; **HRMS** (ESI+) found 375.11174 ([M+H]+), C20H16ClN6 requires 375.11195.

# *N#CC(C=C1)=CC=C1C2=NN=C3C=NC=C(NCCC4=CC(Cl)=CC=C4)N32*

# *InChI=1S/C20H15ClN6/c21-17-3-1-2-14(10-17)8-9-24-18-12-23-13-19-25-26-20(27(18)19)16-6-4-15(11-22)5-7-16/h1-7,10,12-13,24H,8-9H2*

# N-(3-Chlorophenethyl)-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-amine, OSM-S-191

# 

Representative Example: http://malaria.ourexperiment.org/uri/591

Prepared according to General Procedure **D** from: **OSM-S-220** (103 mg, 0.39 mmol, 1.1 equiv.), 2-(3-chlorophenyl)ethylamine (50 μL, 56 mg, 0.36 mmol, 1.0 equiv.), KOH (70 mg, 1.25 mmol, 3.3 equiv.) and 18-crown-6 (5 mg, 0.02 mmol, 0.05 equiv.); 40 ˚C, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, 12–100% EtOAc in hexanes) to give the title compound as a cream powder (46 mg, 33%); **m.p.** 191–193 °C; **IR** νmax (film)/cm-1 3248, 3111, 2917, 2034, 1975, 1613, 1582; **1H NMR** (400 MHz; DMSO-d*6*) δ: 8.35 (1H, t, *J* 5.6), 7.94–7.91 (2H, m), 7.77 (1H, d, *J* 4.8), 7.71–7.67 (2H, m), 7.37–7.23 (5H, m), 3.75 (2H, m), 2.99 (2H, t, *J* 7.1); **13C NMR** (101 MHz; DMSO-d*6*) δ: 147.9, 146.8, 142.2, 139.7, 135.0, 132.9, 130.3, 130.2, 129.9, 129.4, 128.6, 127.5, 126.1, 125.1, 106.1, 41.2, 33.9; **m/z** (APCI+) 384 [M+H]+; **HRMS** (ESI+) found 384.07772 ([M+H]+), C19H16ClN5 requires 384.07773.

# *ClC(C=C1)=CC=C1C2=NN=C3C=NC=C(NCCC4=CC(Cl)=CC=C4)N32*

# *InChI=1S/C19H15Cl2N5/c20-15-6-4-14(5-7-15)19-25-24-18-12-22-11-17(26(18)19)23-9-8-13-2-1-3-16(21)10-13/h1-7,10-12,23H,8-9H2*

# 3-(4-Chlorophenyl)-5-((3,4-difluorobenzyl)oxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-259



Representative Example: http://malaria.ourexperiment.org/uri/68a

Prepared according to General Procedure **D** from: **OSM-S-220** (154 mg, 0.58 mmol, 1.0 equiv.), **OSM-S-XXX** (80 μL, 100 mg, 0.69 mmol, 1.2 equiv.), KOH (110 mg, 2.00 mmol, 3.4 equiv.) and 18-crown-6 (18 mg, 0.07 mmol, 0.12 equiv.); 40 ˚C, 1.25 h; purified by automated flash chromatography over silica (Biotage Isolera, 30–100% EtOAc in hexanes) to give the title compound as fluffy white needles (86 mg, 38%); **m.p.** 181–182 °C; **IR** νmax (film)/cm-1 3070, 1612, 1509, 1303; **1H NMR** (500 MHz; DMSO-d*6*) δ: 9.11 (1H, s), 7.67 (1H, s), 7.66–7.64 (2H, m), 7.36–7.33 (2H, m), 7.13–7.05 (3H, m), 5.29 (2H, s); **13C NMR** (126 MHz; DMSO-d*6*) δ: 147.4, 145.4, 143.8, 135.4, 134.6, 132.4, 127.4, 126.7, 131.7 (2C), 125.4 (2C), 117.4, 117.3, 109.2, 70.9; **m/z** (APCI+) 373 [M+H]+; **HRMS** (APCI+) found 373.06609 [M+H]+, C18H12ClF2N4O requires 373.06622.

Part 1 of this procedure was adapted from a procedure developed by Ms Katrina Badiola.78 To a dry flask was added 3,4-difluorobenzaldehyde (0.4 mL, 520 mg, 3.7 mmol, 1.0 equiv.) and tetrahydrofuran (10 mL). The mixture was cooled in an ice bath (0 °C) under argon. Sodium borohydride (500 mg, 13.0 mmol, 3.5 equiv.) was added carefully in portions. The reaction mixture was stirred for 15 min on ice before warming to room temperature and stirring for a further 25 min. The solution was adjusted to pH 7 with hydrochloric acid (1 M) and extracted with dichloromethane (3 × 15 mL). The combined organic fractions were dried (MgSO4) and concentrated under reduced pressure and dried *in vacuo* to give the crude material ((3,4-difluorophenyl)methanol) as a pale yellow oil (620 mg, 116%). The identity of the crude material was verified by 1H NMR (CDCl3) and carried through to the next step without purification.

*ClC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC4=CC=C(F)C(F)=C4)N32*

*InChI=1S/C18H11ClF2N4O/c19-13-4-2-12(3-5-13)18-24-23-16-8-22-9-17(25(16)18)26-10-11-1-6-14(20)15(21)7-11/h1-9H,10H2*

**5-(1-(3,4-Dichlorophenyl)ethoxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-346**

****

# Representative Example: http://malaria.ourexperiment.org/uri/8cd

# Prepared according to General Procedure D from: OSM-S-324 (120 mg, 0.40 mmol, 1.0 equiv.), OSM-S-XXX (77 mg, 0.40 mmol, 1.0 equiv.), KOH (79 mg, 1.42 mmol, 3.5 equiv.) and 18-crown-6 (7.5 mg, 0.03 mmol, 0.07 equiv.); 40 ˚C, 0.5 h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as a yellow oil (123 mg, 67%); IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; 19F{1H} NMR (377 MHz, CDCl3) δ: XX; m/z (ESI+) 473 [M+Na]+; HRMS (ESI+) found 473.03533 [M+Na]+, C­­­­20H14Cl2F­2N4O2Narequires473.03541.

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

*InChI=1S/C20H14Cl2F2N4O2/c1-11(13-4-7-15(21)16(22)8-13)29-18-10-25-9-17-26-27-19(28(17)18)12-2-5-14(6-3-12)30-20(23)24/h2-11,20H,1H3*

**5-((3,4-Dichlorobenzyl)oxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-347**

******

# Representative Example: http://malaria.ourexperiment.org/uri/8ce

# Prepared according to General Procedure D from: OSM-S-324 (120 mg, 0.40 mmol, 1.0 equiv.), OSM-S-XXX (72 mg, 0.40 mmol, 1.0 equiv.), KOH (79 mg, 1.42 mmol, 3.5 equiv.) and 18-crown-6 (7.5 mg, 0.03 mmol, 0.07 equiv.); 40 ˚C, 0.5 h; purified by automated flash chromatography over silica (Biotage Isolera, XX–XX% EtOAc in hexanes) to give the title compound as a pale yellow solid (107 mg, 61%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; 19F{1H} NMR (377 MHz, CDCl3) δ: XX; m/z (ESI+) 459 [M+Na]+; HRMS (ESI+) found 459.01969 [M+Na]+, C19H12Cl2F2N4O2Narequires459.01976.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC4=CC=C(Cl)C(Cl)=C4)N32*

*InChI=1S/C19H12Cl2F2N4O2/c20-14-6-1-11(7-15(14)21)10-28-17-9-24-8-16-25-26-18(27(16)17)12-2-4-13(5-3-12)29-19(22)23/h1-9,19H,10H2*

**5-((4-Chlorobenzyl)oxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-348**

**

# Representative Example: http://malaria.ourexperiment.org/uri/8cf

# Prepared according to General Procedure D from: OSM-S-324 (120 mg, 0.40 mmol, 1.0 equiv.), OSM-S-XXX (58 mg, 0.40 mmol, 1.0 equiv.), KOH (79 mg, 1.42 mmol, 3.5 equiv.) and 18-crown-6 (7.5 mg, 0.03 mmol, 0.07 equiv.); 40 ˚C, 0.5 h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as a pale yellow solid (83 mg, 51%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; 19F{1H} NMR (377 MHz, CDCl3) δ: XX; m/z (ESI+) 425 [M+Na]+; HRMS (ESI+) found 425.05874 [M+Na]+, C19H13ClF2N4O2Narequires425.05873.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC4=CC=C(Cl)C=C4)N32*

*InChI=1S/C19H13ClF2N4O2/c20-14-5-1-12(2-6-14)11-27-17-10-23-9-16-24-25-18(26(16)17)13-3-7-15(8-4-13)28-19(21)22/h1-10,19H,11H2*

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

# 

Representative Example: http://malaria.ourexperiment.org/uri/6e7

Prepared according to General Procedure **D** from: **OSM-S-324** (159 mg, 0.54 mmol, 1.0 equiv.), 2-(3,4-difluorophenyl)ethanol (98 mg, 0.62 mmol, 1.1 equiv.), KOH (90 mg, 1.60 mmol, 2.9 equiv.) and 18-crown-6 (9 mg, 0.03 mmol, 0.05 equiv.); 40 ˚C, 1.3 h; purified by automated flash chromatography over silica (Biotage Isolera, 50–100% EtOAc in hexanes); repurified by flash chromatography over silica (20% EtOH in hexanes); recrystallised from EtOAc (washed with cold MeOH) to give the title compound as white needles (43 mg, 19%); **m.p.** 111–112 °C; **IR** νmax (film)/cm-1 3074, 2956, 1612, 1508, 1118, 1046; **1H NMR** (200 MHz; DMSO-d*6*) δ: 9.05 (1H, s), 7.79–7.73 (2H, m), 7.60 (1H, s), 7.36 (1H, t, *J*HF 73.6), 7.30–6.69 (5H, m), 4.51 (2H, t, *J* 6.2), 2.90 (2H, t, *J* 6.2, 6.0); **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*CF 256.7), 108.8, 70.6, 32.8; **m/z** (APCI+) 419 [M+H]+; **HRMS** (APCI+) found 419.11215 [M+H]+, C20H15F4N4O requires 419.11256.

*FC1=C(F)C=CC(CCOC2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32)=C1*

*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*

# 5-(2-Chlorophenethoxy)-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-258

# 

# Representative Example: http://malaria.ourexperiment.org/uri/6b6

# Prepared according to General Procedure D from: OSM-S-332 (152 mg, 0.65 mmol, 1.0 equiv.), 2-chlorophenethyl alcohol (0.09 mL, 107 mg, 0.68 mmol, 1.0 equiv.), KOH (138 mg, 2.50 mmol, 3.8 equiv.) and 18-crown-6 (13 mg, 0.05 mmol, 0.07 equiv.); 40 ˚C, 2.5 h; purified by automated flash chromatography over silica (Biotage Isolera, 1% TEA in 15–80% EtOH in hexanes) to give the title compound as light brown plates (56 mg, 12%); m.p. 132–134 °C; IR νmax (film)/cm-1 2959, 2926, 1602, 1507, 1465, 1359, 1239, 824; 1H NMR (200 MHz; DMSO-d*6*) δ: 9.11 (1H, s), 8.67–8.64 (2H, m), 7.75 (1H, s), 7.71–7.68 (2H, m), 7.41 (1H, dd, *J* 7.8, 7.6, 1.2, 1.0), 7.24 (1H, tdapp, *J* 7.8, 7.6, 7.4, 1.8, 1.6), 7.14 (1H, tdapp, *J* 7.4, 7.2, 1.2) 6.90 (1H, dd, *J* 7.4, 1.6), 4.58 (2H, t, *J* 6.6, 6.4), 3.03 (2H, t, *J* 6.6, 6.4); 13C NMR (75 MHz; DMSO-d*6*) δ: 148.9, 147.7, 144.2, 143.6, 135.5, 135.0, 134.3, 133.1, 130.7, 129.3, 128.6, 127.2, 124.9, 109.5, 69.3, 31.4; *m/z* (APCI+) 352 [M+H]+; HRMS (APCI+) found 352.09599 [M+H]+, C18H15ClN5O requires 352.09596.

*ClC1=CC=CC=C1CCOC2=CN=CC3=NN=C(C4=CC=NC=C4)N32*

*InChI=1S/C18H14ClN5O/c19-15-4-2-1-3-13(15)7-10-25-17-12-21-11-16-22-23-18(24(16)17)14-5-8-20-9-6-14/h1-6,8-9,11-12H,7,10H2*

**(*R*)-2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-yl)oxy)-*N*-methyl-1-phenylethan-1-amine, OSM-S-281**

**

# Representative Example: http://malaria.ourexperiment.org/uri/790

# Prepared according to General Procedure D from: OSM-S-324 (100 mg, 0.36 mmol, 1.0 equiv.), OSM-S-343 (54 mg, 0.36 mmol, 1.0 equiv.), KOH (70 mg, 1.26 mmol, 3.5 equiv.) and 18-crown-6 (6 mg, 25 μmol, 0.07 equiv.); rt, 1 h; purified by automated flash chromatography over silica (Biotage Isolera, X–X% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); m.p. XX–XX ˚C; IR νmax (film) /cm-1 XX; 1H NMR (X MHz, CDCl3) δ: XX; 13C NMR (X MHz, CDCl3) δ: XX; 19F{1H} NMR (377 MHz, CDCl3) δ: XX; HRMS (ESI+) found 412.15807 [M+H]+, C­­­­21H20F2N5O2 requires412.15796.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OC[C@H](NC)C4=CC=CC=C4)N32*

*InChI=1S/C21H19F2N5O2/c1-24-17(14-5-3-2-4-6-14)13-29-19-12-25-11-18-26-27-20(28(18)19)15-7-9-16(10-8-15)30-21(22)23/h2-12,17,21,24H,13H2,1H3*

**3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-*a*]pyrazin-5-ol, OSM-S-328**

******

Representative Example: http://malaria.ourexperiment.org/uri/87e

Side product from AEW 260-1

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 301.05084 [M+Na]+, C­­­­12H8F2N4O2Narequires301.05075.

*OC1=CN=CC2=NN=C(C3=CC=C(OC(F)F)C=C3)N21*

*InChI=1S/C12H8F2N4O2/c13-12(14)20-8-3-1-7(2-4-8)11-17-16-9-5-15-6-10(19)18(9)11/h1-6,12,19H*

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

**

Representative Example: http://malaria.ourexperiment.org/uri/8db

Deprotection procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **m/z** (ESI+) 435 [M+Na]+; **HRMS** (ESI+) found 435.12401 [M+Na]+, C­­­­21H18F2N4O3Narequires435.12392.

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

*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*

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

**

Representative example: http://malaria.ourexperiment.org/uri/8e8

Prepared according to General Procedure **D** from: **OSM-S-320** (350 mg, 1.17 mmol, 1.0 equiv.), 2-(3,4-difluorophenyl)ethanol(185 mg, 1.17 mmol, 1.0 equiv.), KOH (229 mg, 4.09 mmol, 3.5 equiv.) and 18-crown-6 (21.6 mg, 81.8 μmol, 0.07 equiv.); rt, 0.5 h; purified by automated flash chromatography over silica (Biotage Isolera, X–100% EtOAc in hexanes) to give the title compound as a pearlescent cream solid (218 mg, 44%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(CCOC2=CN=CC3=NN=C(C4=CN=C(C(F)(F)F)C=C4)N32)=C1*

*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*

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

****

Representative Example: http://malaria.ourexperiment.org/uri/923

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC(F)=C(F)C=C4)N32*

*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*

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

****

Representative Example: http://malaria.ourexperiment.org/uri/95d

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(C(OC)COC2=CN=CC3=NN=C(C4=CC=C(C#N)C=C4)N32)=C1*

*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*

**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**

****

Representative Example: http://bit.ly/2jFGKG4

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC(F)=C(F)C=C1)COC2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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*

**4-(5-(2-(3,4-difluorophenyl)-2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-XXX**

**

**HRMS** (ESI+) found 500.15043 [M+Na]+, C25H21F2N5O3 requires500.15047.

**4-(5-(2-(3,4-Difluorophenyl)-2-hydroxyethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-376**

****

Representative Example: http://malaria.ourexperiment.org/uri/95e

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC(F)=C(F)C=C1)COC2=CN=CC3=NN=C(C4=CC=C(C#N)C=C4)N32*

*InChI=1S/C20H13F2N5O2/c21-15-6-5-14(7-16(15)22)17(28)11-29-19-10-24-9-18-25-26-20(27(18)19)13-3-1-12(8-23)2-4-13/h1-7,9-10,17,28H,11H2*

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

****

Representative Example: http://bit.ly/2kUbU1m

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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-(3,4-difluorophenyl)-N,N-dimethylethan-1-amine, OSM-S-389**

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Representative Example: http://bit.ly/2jG3DsF

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC1=C(F)C=CC(C(N(C)C)COC2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32)=C1*

*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*

**4-(5-(2-(3,4-Difluorophenyl)-2-(dimethylamino)ethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-378**

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Representative Example: http://bit.ly/2kYsMji

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(C=C1)=C(F)C=C1C(N(C)C)COC2=CN=CC3=NN=C(C4=CC=C(C#N)C=C4)N32*

*InChI=1S/C22H18F2N6O/c1-29(2)19(16-7-8-17(23)18(24)9-16)13-31-21-12-26-11-20-27-28-22(30(20)21)15-5-3-14(10-25)4-6-15/h3-9,11-12,19H,13H2,1-2H3*

**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**

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Representative Example: http://bit.ly/2kuCZXS

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(C4=CN=C(C(F)(F)F)C=C4)N32*

*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*

**5-(Benzylthio)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-359**

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Representative Example: http://bit.ly/2jza7yD

Prepared according to General Procedure **D** from: **OSM-S-XXX** (1.00 g, 3.40 mmol, 1.0 equiv.), benzyl mercaptan (400 μL, 3.40 mmol, 1.0 equiv.), KOH (630 mg, 11.2 mmol, 3.3 equiv.) and 18-crown-6 (80 mg, 0.30 mmol, 0.08 equiv.); rt, 4 h; purified by recrystallisation from EtOAc to give the title compound as a pearlescent white powder (745 mg, 57%); **m.p.** 231–233 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 9.27 (1H, s), 7.75 (2H, d, *J* 5.6), 7.71 (1H, s), 7.37–7.16 (6H, m), 6.97–6.88 (1H, m), 6.64 (1H, t, *J* 73.1), 3.73 (2H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 407.08 [M+Na]+; **HRMS** (ESI+) found 407.07523 [M+Na]+, C19H14F2N4OSNarequires407.07482.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)SCC4=CC=CC=C4)C=C1*

*InChI=1S/C19H14F2N4OS/c20-19(21)26-15-8-6-14(7-9-15)18-24-23-16-10-22-11-17(25(16)18)27-12-13-4-2-1-3-5-13/h1-11,19H,12H2*

**5-(Benzylsulfinyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-360**

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Representative Example: http://bit.ly/2jFLAD4

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 150 mg, 0.37 mmol); overnight; purified by automated flash chromatography over silica (Biotage Isolera, 12–100% EtOAc in hexanes) to give the title compound as a pale yellow powder (30.0 mg, 20%); **m.p.** 227–228 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 9.46 (1H, s), 8.19 (1H, s), 7.78 (2H, d, *J* 8.4), 7.41(2H, d, *J* 8.0), 7.17 (4H, t, *J* 7.5), 6.70 (1H, t, *J* 72.4), 6.53 (1H, d, *J* 7.7), 3.64 (2H, dd, *J* 106.7, 13.3); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 423.06 [M+Na]+; **HRMS** (ESI+) found 423.07010 [M+Na]+, C19H14F2N4O2SNarequires423.06982.

*O=S(CC1=CC=CC=C1)C(N23)=CN=CC2=NN=C3C4=CC=C(OC(F)F)C=C4*

*InChI=1S/C19H14F2N4O2S/c20-19(21)27-15-8-6-14(7-9-15)18-24-23-16-10-22-11-17(25(16)18)28(26)12-13-4-2-1-3-5-13/h1-11,19H,12H2*

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

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Representative Example: http://bit.ly/2k1Jyk4

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 100 mg, 0.24 mmol); overnight; purified by automated flash chromatography over silica (Biotage Isolera, 12–100% EtOAc in hexanes) to give the title compound as a pale yellow powder (24.9 mg, 25%); **m.p.** 222–224 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 9.56 (1H, s), 8.41 (1H, s), 7.76 (2H, d, *J* 8.6), 7.38 (2H, d, *J* 8.4), 7.35–7.22 (4H, m), 6.88 (1H, d, *J* 7.4), 6.69 (1H, t, *J* 72.7), 4.02 (2H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI–) 415.13 [M–H]–; **HRMS** (ESI+) found 417.08306 [M+H]+, C19H15F2N4O3Srequires417.08278.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)S(CC4=CC=CC=C4)(=O)=O)C=C1*

*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-(4-phenyl-1H-1,2,3-triazol-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-362**

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Representative Example: http://bit.ly/2kVDtUW

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)N4N=NC(C5=CC=CC=C5)=C4)C=C1*

*InChI=1S/C20H13F2N7O/c21-20(22)30-15-8-6-14(7-9-15)19-26-25-17-10-23-11-18(29(17)19)28-12-16(24-27-28)13-4-2-1-3-5-13/h1-12,20H*

**3-(4-(Difluoromethoxy)phenyl)-5-(phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-363**

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Representative Example: http://bit.ly/2kYCKkW

Prepared according to General Procedure **D** from: **OSM-S-XXX** (1.00 g, 3.40 mmol, 1.0 equiv.), phenylethyl mercaptan (455 μL, 3.40 mmol, 1.0 equiv.), KOH (630 mg, 11.2 mmol, 3.3 equiv.) and 18-crown-6 (80 mg, 0.30 mmol, 0.08 equiv.); 40 ˚C, 3 h; purified by automated flash chromatography over silica (Biotage Isolera, 12–100% ethyl acetate in hexanes) to give the title compound as a yellow powder (314 mg, 23%); **m.p.** 154–155 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: XX; **13C NMR** (75 MHz, CDCl3) δ: 155.62, 152.81, 147.20, 144.47, 140.02, 130.13, 130.06, 128.74, 128.66, 126.71, 122.98, 120.38, 119.01 115.54, 112.08, 111.21, 35.39, 30.48; **m/z** (ESI+) 421.12 [M+Na]+; **HRMS** (ESI+) found 421.09059 [M+Na]+, C20H16F2N4OSNarequires421.09052.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)SCCC4=CC=CC=C4)C=C1*

*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*

**3-(4-(Difluoromethoxy)phenyl)-5-(phenethylsulfinyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-364**

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Representative Example: http://bit.ly/2kUe2pH

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 300 mg, 0.72 mmol); overnight; purified by automated flash chromatography over silica (Biotage Isolera, 18–100% EtOAc in hexanes) to give the title compound as an off-white powder (262 mg, 88%); **m.p.** 151–154 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 9.43 (1H, s), 8.52 (1H, s), 7.67 (2H, d, *J* 8.8), 7.32 (2H, d, *J* 8.7), 7.17 (4H, m), 6.82 (1H, m), 6.65 (1H, t, *J* 72.5), 2.99–2.54 (4H, m); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 437.10 [M+Na]+; **HRMS** (ESI+) found 437.08558 [M+Na]+, C20H16F2N4O2SNarequires437.08542.

*O=S(CCC1=CC=CC=C1)C(N23)=CN=CC2=NN=C3C4=CC=C(OC(F)F)C=C4*

*InChI=1S/C20H16F2N4O2S/c21-20(22)28-16-8-6-15(7-9-16)19-25-24-17-12-23-13-18(26(17)19)29(27)11-10-14-4-2-1-3-5-14/h1-9,12-13,20H,10-11H2*

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

**

Representative Example: http://bit.ly/2kU7CXK

Prepared according to General Procedure **C** from: **OSM-S-XXX** (crude, 275 mg, 0.64 mmol); overnight; purified by automated flash chromatography over silica (Biotage Isolera, 12–100% EtOAc in hexanes) to give the title compound as a pale yellow powder (179 mg, 65%); **m.p.** 142–143 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 9.50 (1H, s), 8.62 (1H, s), 7.65 (2H, d, *J* 8.7), 7.39–7.11 (6H, m), 6.89 (1H, m), 6.61 (1H, t, *J* 72.8), 3.03 (2H, ddd, *J* 8.4, 6.1, 1.8), 2.88 (2H, ddd, *J* 8.3, 6.1, 1.8); **13C NMR** (X MHz, CDCl3) δ: XX; **m/z** (ESI+) 453.13 [M+Na]+; **HRMS** (ESI+) found 431.09863 [M+H]+, C20H17F2N4O3Srequires431.09838.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)S(CCC4=CC=CC=C4)(=O)=O)C=C1*

*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*

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

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Representative Example: http://bit.ly/2kVKbdB

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)OCC4=CC=CC=C4)C=C1*

*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**

****

Representative Example: http://bit.ly/2kVCpA3

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)OCCC4=CC=CC=C4)C=C1*

*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*

**5-(3-(Cuban-1-yl)propoxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-370**

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Representative Example: http://bit.ly/2kt1pkZ

Prepared according to General Procedure **D** from: **OSM-S-XXX** (37.0 g, 0.12 mmol, 1.0 equiv.), 3-cubylpropanol (20 mg, 0.12 mmol, 1.0 equiv.), KOH (23.0 mg, 0.41 mmol, 3.3 equiv.) and 18-crown-6 (2.60 mg, 0.01 mmol, 0.08 equiv.); 40 ˚C, 2 h; purified by automated flash chromatography over silica (Biotage Isolera, 18–100% ethyl acetate in hexanes) to give the title compound as a light brown powder (24.3 mg, 47%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (75 MHz, CDCl3) δ: 152.57, 147.90, 146.33, 144.28, 136.31, 132.54, 125.08, 119.16, 118.57, 115.70, 112.24, 108.35, 71.43, 58.19, 48.68, 48.18, 44.14, 29.11, 23.56; **m/z** (ESI+) 445.16 [M+Na]+; **HRMS** (ESI+) found 445.14481 [M+Na]+, C23H20F2N4O2Narequires445.14462.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCCC45C6C7C4C8C7C6C58)N32*

*InChI=1S/C23H20F2N4O2/c24-22(25)31-11-4-2-10(3-5-11)21-28-27-12-8-26-9-13(29(12)21)30-7-1-6-23-18-15-14-16(18)20(23)17(14)19(15)23/h2-5,8-9,14-20,22H,1,6-7H2*

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

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Representative Example: http://bit.ly/2kUevZj

Prepared according to General Procedure **D** from: **OSM-S-XXX** (37.0 g, 0.12 mmol, 1.0 equiv.), 3-cubylpropanol (18.5 mg, 0.12 mmol, 1.0 equiv.), KOH (23.0 mg, 0.41 mmol, 3.3 equiv.) and 18-crown-6 (2.60 mg, 0.01 mmol, 0.08 equiv.); 40 ˚C, 2 h; purified by automated flash chromatography over silica (Biotage Isolera, 18–100% ethyl acetate in hexanes) to give the title compound as a pale yellow powder (27.8 mg, 55%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (75 MHz, CDCl3) δ: 152.54, 147.94, 146.40, 144.18, 136.32, 132.70, 124.87, 119.14, 118.60, 115.68, 112.22, 108.38, 68.24, 55.69, 48.61, 48.31, 44.28, 31.83; **m/z** (ESI+) 431.15 [M+Na]+; **HRMS** (ESI+) found 431.12913 [M+Na]+, C22H18F2N4O2Narequires431.12902.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC45C6C7C4C8C7C6C58)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*

**5-(3,4-Difluorophenethoxy)-3-(4-iodocuban-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-375**

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Representative Example: http://bit.ly/2jFPs79

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(C=C1)=C(F)C=C1CCOC2=CN=CC3=NN=C(C45C6C7C4C8C7(I)C6C58)N32*

*InChI=1S/C21H15F2IN4O/c22-9-2-1-8(5-10(9)23)3-4-29-12-7-25-6-11-26-27-19(28(11)12)20-13-16-14(20)18-15(20)17(13)21(16,18)24/h1-2,5-7,13-18H,3-4H2*

**5-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-372**

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Representative Example: http://bit.ly/2jY9XN2

Prepared according to General Procedure **D** from: **OSM-S-324** (250 g, 0.84 mmol, 1.0 equiv.), **OSM-S-XXX** (159 mg, 0.84 mmol, 1.0 equiv.), KOH (156 mg, 2.78 mmol, 3.3 equiv.) and 18-crown-6 (17.8 mg, 0.07 mmol, 0.08 equiv.); 40 ˚C, 3 h; purified by automated flash chromatography over silica (Biotage Isolera, 0–10% DCM in MeOH) to give the title compound as a pale yellow powder (331 mg, 87%); **m.p.** 109–111 ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (300 MHz, CDCl3) δ: 8.98 (1H, s), 7.56 (2H, d, *J* 8.7), 7.42 (1H, s), 7.39–7.26 (3H, m), 7.23–7.15 (2H, m), 7.11 (1H, s), 6.97 (2H, d, *J* 8.4), 6.53 (1H, t, *J* 73.4), 5.43 (2H, s), 5.26 (2H, s); **13C NMR** (75 MHz, CDCl3) δ: 152.34, 147.90, 146.39, 143.47, 140.70, 137.12, 134.12, 132.71, 129.42, 129.22, 128.26, 124.69, 123.36, 119.22, 118.31, 115.77, 112.31, 109.13, 64.05, 54.47; **m/z** (ESI+) 472.15 [M+H]+; **HRMS** (ESI+) found 472.12966 [M+Na]+, C22H17F2N7O2Narequires472.13042.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)OCC4=CN(CC5=CC=CC=C5)N=N4)C=C1*

*InChI=1S/C22H17F2N7O2/c23-22(24)33-18-8-6-16(7-9-18)21-28-27-19-10-25-11-20(31(19)21)32-14-17-13-30(29-26-17)12-15-4-2-1-3-5-15/h1-11,13,22H,12,14H2*

**3-(4-(Difluoromethoxy)phenyl)-5-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-373**

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Representative Example: http://bit.ly/2k1U3nz

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC1=CC=C(C2=NN=C3C=NC=C(N32)OCC4=CN(C5=CC=CC=C5)N=N4)C=C1*

*InChI=1S/C21H15F2N7O2/c22-21(23)32-17-8-6-14(7-9-17)20-27-26-18-10-24-11-19(30(18)20)31-13-15-12-29(28-25-15)16-4-2-1-3-5-16/h1-12,21H,13H2*

**5-((1-(6-Chloropyrazin-2-yl)-1H-1,2,3-triazol-4-yl)methoxy)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-374**

****

Representative Example: http://bit.ly/2kU9Vu0

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=CN=CC(N2N=NC(COC(N34)=CN=CC3=NN=C4C5=CC=C(C=C5)OC(F)F)=C2)=N1*

*InChI=1S/C19H12ClF2N9O2/c20-14-5-23-6-15(25-14)30-9-12(26-29-30)10-32-17-8-24-7-16-27-28-18(31(16)17)11-1-3-13(4-2-11)33-19(21)22/h1-9,19H,10H2*

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

****

Representative Example: http://bit.ly/2jYpzAf

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC(OC)=CC=C4)N32*

*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**

****

Representative Example: http://bit.ly/2kU9srC

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC=C(OC)C=C4)N32*

*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*

**3-(4-(Difluoromethoxy)phenyl)-5-(1-(3,4-difluorophenyl)ethoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-385**

****

Representative Example: http://bit.ly/2kuU2ZW

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

*InChI=1S/C20H14F4N4O2/c1-11(13-4-7-15(21)16(22)8-13)29-18-10-25-9-17-26-27-19(28(17)18)12-2-5-14(6-3-12)30-20(23)24/h2-11,20H,1H3*

**4-(1-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)oxy)ethyl)benzonitrile, OSM-S-386**

****

Representative Example: http://bit.ly/2kuNFpj

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

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

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

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Representative Example: http://bit.ly/2jFOwzz

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(C=C1)=C(F)C=C1CCOC2=CN=CC3=NN=C([H])N32*

*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-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazin-5-ol, OSM-S-388**

****

Representative Example: http://malaria.ourexperiment.org/uri/959

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC1=CN=CC2=NN=C(N3CCCCC3)N21*

*InChI=1S/C10H13N5O/c16-9-7-11-6-8-12-13-10(15(8)9)14-4-2-1-3-5-14/h6-7,16H,1-5H2*

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

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC(C=C1)=CC=C1C2=CN=C3C=NC=C(OCCC4=CC(F)=C(F)C=C4)N32*

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

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC(C=C1)=CC=C1C2=NC=C3C=NC=C(OCCC4=CC(F)=C(F)C=C4)N32*

*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*

**2-((3-Cyclohexyl-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)oxy)-1-phenylethan-1-ol, OSM-S-275**

****

Representative Example: http://malaria.ourexperiment.org/uri/7e0

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(C4CCCCC4)N32*

*InChI=1S/C19H22N4O2/c24-16(14-7-3-1-4-8-14)13-25-18-12-20-11-17-21-22-19(23(17)18)15-9-5-2-6-10-15/h1,3-4,7-8,11-12,15-16,24H,2,5-6,9-10,13H2*

**2-((3-Ethyl-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)oxy)-1-phenylethan-1-ol, OSM-S-276**

****

Representative Example: http://malaria.ourexperiment.org/uri/7e1

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*OC(C1=CC=CC=C1)COC2=CN=CC3=NN=C(CC)N32*

*InChI=1S/C15H16N4O2/c1-2-13-17-18-14-8-16-9-15(19(13)14)21-10-12(20)11-6-4-3-5-7-11/h3-9,12,20H,2,10H2,1H3*

**3-(4-(Difluoromethoxy)phenyl)-5-methoxy-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-280**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

*InChI=1S/C13H10F2N4O2/c1-20-11-7-16-6-10-17-18-12(19(10)11)8-2-4-9(5-3-8)21-13(14)15/h2-7,13H,1H3*

**2-((3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)oxy)-1-phenylethan-1-amine, OSM-S-283**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

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

*InChI=1S/C20H17F2N5O2/c21-20(22)29-15-8-6-14(7-9-15)19-26-25-17-10-24-11-18(27(17)19)28-12-16(23)13-4-2-1-3-5-13/h1-11,16,20H,12,23H2*

**3-(4-(Difluoromethoxy)phenyl)-5-(pyridin-2-ylmethoxy)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-301**

**

Representative Example: http://malaria.ourexperiment.org/uri/878

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 392.09280 [M+Na]+, C18H13F2N5O2Narequires392.092595.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCC4=CC=CC=N4)N32*

*InChI=1S/C18H13F2N5O2/c19-18(20)27-14-6-4-12(5-7-14)17-24-23-15-9-21-10-16(25(15)17)26-11-13-3-1-2-8-22-13/h1-10,18H,11H2*

**3-(4-Fluorophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-352**

****

Representative Example: http://malaria.ourexperiment.org/uri/8da

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found 357.11221 [M+Na]+, C19H15FN4ONa requires357.11221.

*FC(C=C1)=CC=C1C2=NN=C3C=NC=C(OCCC4=CC=CC=C4)N32*

*InChI=1S/C19H15FN4O/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-((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**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*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-(isoindolin-2-ylmethyl)-[1,2,4]triazolo[4,3-a]pyrazine, OSM-S-380**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(CN4CC(C=CC=C5)=C5C4)N32*

*InChI=1S/C21H17F2N5O/c22-21(23)29-18-7-5-14(6-8-18)20-26-25-19-10-24-9-17(28(19)20)13-27-11-15-3-1-2-4-16(15)12-27/h1-10,21H,11-13H2*

**(*R*)-4-(5-(2-(Difluoromethoxy)-2-(3,4-difluorophenyl)ethoxy)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile, OSM-S-377**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)O[C@H](C1=CC(F)=C(F)C=C1)COC2=CN=CC3=NN=C(C4=CC=C(C#N)C=C4)N32*

*InChI=1S/C21H13F4N5O2/c22-15-6-5-14(7-16(15)23)17(32-21(24)25)11-31-19-10-27-9-18-28-29-20(30(18)19)13-3-1-12(8-26)2-4-13/h1-7,9-10,17,21H,11H2/t17-/m0/s1*

***3. Amide Synthesis***

**3.1 Amide Coupling**

**6-Chloro-*N*-(3-chlorophenyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/674

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(1.50 g, 9.46 mmol), 3-chloroaniline, (1.21 g, 9.46 mmol), DIPEA (2.5 mL, 14.2 mmol) and T3P (8.5 mL, 14.2 mmol) to give the title compound as a light brown solid (1.90 g, 75%); **m.p.** 101–102 ˚C (lit. 107–108 ˚C); **IR** νmax (film) /cm-1 3362, 1691, 1593, 1533, 1300; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.82 (1H, s), 9.24 (1H, s), 9.07 (1H, s), 8.04 (1H, t, *J* 1.9), 7.83 (1H, dd, *J* 8.2, 1.1), 7.41 (1H, t, *J* 8.1), 7.22 (1H, dd, *J* 7.9, 1.3); **13C NMR** (101 MHz, DMSO-d*6*) δ: 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]+; **CHNX** Anal. Calcd. for C11H7Cl­­2N3O: C, 49.28; H, 2.63; N, 15.67. Found: C, 49.73; H, 2.42; N, 15.22.

*ClC1=CN=CC(C(NC2=CC(Cl)=CC=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)*

**6-Chloro-*N*-(3-chloro-2-methylphenyl)pyrazine-2-carboxamide, OSM-S-XXX**

**

Representative Example: http://malaria.ourexperiment.org/uri/4fc

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(530 mg 3.35 mmol), 3-chloro-2-methylaniline, (474 mg 3.35 mmol), DIPEA (0.876 mL, 5.03 mmol) and T3P (2.99 mL, 5.03 mmol) to give the title compound as a crystalline beige solid (580 mg, 62%); **m.p.** 155–156 ˚C; **IR** νmax (film) /cm-1 3367, 1701, 1579, 1542, 1436; **1H NMR** (400 MHz, CDCl3) δ: 9.44 (1H, s), 9.40 (1H, s), 8.84 (1H, s), 7.98 (1H, dd, *J* 8.0, 1.2), 7.27 (1H, dd, *J* 8.2, 1.3), 7.21 (1H, t, *J* 8.0), 2.44 (3H, s); **13C NMR** (101 MHz, CDCl3) δ: 159.7, 147.9, 147.7, 144.1, 142.4, 136.2, 135.2, 127.9, 127.4, 126.8, 121.3, 14.6; **m/z** (APCI+) 282 [M+H]+, (EI) 281 [M]+.

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

**6-Chloro-*N*-(3-chloro-2-fluorophenyl)pyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/5e7

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(560 mg 3.54 mmol), 3-chloro-2-fluoroaniline, (515 mg 3.54 mmol), DIPEA (0.925 mL, 5.31 mmol) and T3P (3.16 mL, 5.31 mmol) to give the title compound as an off-white solid (602 mg, 59%); **m.p.** 107–109 ˚C; **IR** νmax (film) /cm-13359, 1703, 1609, 1533, 1454; **1H NMR** (400 MHz, CDCl3) δ: 9.71 (1H, s), 9.38 (1H, s), 8.84 (1H, s), 8.41 (1H, ddd, *J* 8.2, 6.8, 1.6), 7.21 (1H, ddd, *J* 8.2, 6.6, 1.7), 7.15 (1H, dd, *J* 8.2, 1.3); **13C NMR** (101 MHz, CDCl3) δ: 159.8, 149.1 (d, *J* 247), 148.2, 147.9, 143.6, 142.3, 127.0 (d, *J* 10), 126.1, 125.0 (d, *J* 5), 121.2, 120.0; **m/z** (EI) 285 [M]+.

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

*InChI=1S/C11H6Cl2FN3O/c12-6-2-1-3-7(10(6)14)17-11(18)8-4-15-5-9(13)16-8/h1-5H,(H,17,18)*

**6-Chloro-*N*-(5-chloro-2-methylphenyl)pyrazine-2-carboxamide, OSM-S-XXX**

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Representative Example: http://malaria.ourexperiment.org/uri/5e8

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(515 mg 3.26 mmol), 3-chloro-6-methylaniline, (462 mg 3.26 mmol), DIPEA (0.852 mL, 4.89 mmol) and T3P (2.91 mL, 4.89 mmol) to give the title compound as a beige powder (545 mg, 59%); **m.p.** 161–162 ˚C; **IR** νmax (film) /cm-1 3373, 1698, 1587, 1537; **1H NMR** (400 MHz, CDCl3) δ: 9.43 (1H, s), 9.40 (1H, s), 8.83 (1H, s), 8.28 (1H, d, *J* 2.1), 7.17 (1H, d, *J* 8.2), 7.11 (1H, dd, *J* 8.1, 2.1), 2.37 (3H, s); **13C NMR** (101 MHz, CDCl3) δ: 159.5, 147.9, 147.7, 144.0, 142.4, 136.1, 132.6, 131.6, 126.6, 125.5, 121.7, 17.3; **m/z** (APCI+) 282 [M+H]+, (EI) 281 [M]+.

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

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

**N-(3,5-Bis(trifluoromethyl)phenyl)-6-chloropyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/4e3

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(250 mg, 1.58 mmol, 1.0 equiv.), 3,5-bis(trifluoroethyl)aniline (0.30 mL, 1.89 mmol, 1.2 equiv.), DIPEA (0.56 mL, 3.15 mmol, 2.0 equiv.) and T3P (1.50 mL, 2.37 mmol, 1.5 equiv.) to give the title compound as a white powder (394 mg, 67%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (400 MHz, CDCl3) δ: 9.65 (1H, s), 9.42 (1H, s), 8.87 (1H, s), 8.29 (1H, s), 7.70 (1H, s); **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: -63.02; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(NC2=CC(C(F)(F)F)=CC(C(F)(F)F)=C2)=O)=CN=C1*

*InChI=1S/C13H6ClF6N3O/c14-10-5-21-4-9(23-10)11(24)22-8-2-6(12(15,16)17)1-7(3-8)13(18,19)20/h1-5H,(H,22,24)*

**(6-Chloropyrazin-2-yl)(4-fluoroisoindolin-2-yl)methanone, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/557

Prepared according to General Procedure **E** from: 6-chloropyrazine-2-carboxylic acid(240 mg, 1.51 mmol), 4-fluoroisoindoline (200 mg, 1.51 mmol), DIPEA (0.53 mL, 3.03 mmol, 2.0 equiv.) and T3P (1.35 mL, X mmol) to give the title compound as a light purple solid (X mg, X%);**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(N2CC(C(F)=CC=C3)=C3C2)=O)=CN=C1*

*InChI=1S/C13H9ClFN3O/c14-12-5-16-4-11(17-12)13(19)18-6-8-2-1-3-10(15)9(8)7-18/h1-5H,6-7H2*

**6-Chloro-*N*-(4-chlorophenyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example:

Prepared according to General Procedure **E** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(NC2=CC=C(Cl)C=C2)=O)=CN=C1*

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

**6-Chloro-*N*-(3-chloro-4-fluorophenyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/921

Prepared according to General Procedure **E** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(NC2=CC=C(F)C(Cl)=C2)=O)=CN=C1*

*InChI=1S/C11H6Cl2FN3O/c12-7-3-6(1-2-8(7)14)16-11(18)9-4-15-5-10(13)17-9/h1-5H,(H,16,18)*

**6-Chloro-*N*-(2-(trifluoromethyl)pyridin-4-yl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/913

Prepared according to General Procedure **E** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(NC2=CC=NC(C(F)(F)F)=C2)=O)=CN=C1*

*InChI=1S/C11H6ClF3N4O/c12-9-5-16-4-7(19-9)10(20)18-6-1-2-17-8(3-6)11(13,14)15/h1-5H,(H,17,18,20)*

**(6-Chloropyrazin-2-yl)(isoindolin-2-yl)methanone, OSM-S-XXX**

****

Representative Example:

Prepared according to General Procedure **E** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*ClC1=NC(C(N2CC(C=CC=C3)=C3C2)=O)=CN=C1*

*InChI=1S/C13H10ClN3O/c14-12-6-15-5-11(16-12)13(18)17-7-9-3-1-2-4-10(9)8-17/h1-6H,7-8H2*

***3.2 Hydrazine displacement***

***N*-(3-Chlorophenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/521

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a drab yellow solid (1.46 g, 82%); **m.p.** 187 ˚C; **IR** νmax (film) /cm-1 3234, 1675, 1585, 1516, 1422; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.47 (1H, s), 8.52 (1H, s), 8.32 (1H, s), 8.19 (1H, s), 8.00 (1H, t, *J* 2.0), 7.81 (1H, dd, *J* 8.0, 1.6), 7.42 (1H, t, *J* 8.1), 7.20 (1H, dd, *J* 7.9, 1.9), 4.64 (2H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 162.58, 154.96, 140.80, 139.58, 135.71, 133.04, 130.43, 129.74, 123.76, 119.72, 118.66; **m/z** (ESI+) 264 [M+H]+.

*O=C(NC1=CC(Cl)=CC=C1)C2=NC(NN)=CN=C2*

*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)*

***N*-(3-Chloro-2-methylphenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/531

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a yellow solid (525 mg, quant. yield); **IR** νmax (film) /cm-1 2914, 1672, 1579, 1516, 1429; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.15 (1H, s), 9.83 (1H, s), 8.65 (1H, s), 8.54 (1H, s), 7.69 (1H, d, *J* 7.0), 7.34 (1H, dd, *J* 7.9, 1.4), 7.27 (1H, t, *J* 7.8), 4.37 (2H, s), 2.33 (3H, s); **m/z** (ESI+) 278 [M+H]+.

*O=C(NC1=C(C)C(Cl)=CC=C1)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)*

***N*-(3-Chloro-2-fluorophenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/590

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a yellow solid (225 mg, quant. yield); **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.38 (1H, s), 8.56 (1H, s), 8.32 (1H, s), 8.26 (1H, s), 7.88 (1H, ddd, *J* 8.3, 6.9, 1.5), 7.45 (1H, ddd, *J* 8.4, 6.8, 1.6), 7.29 (1H, td, *J* 8.3, 1.7), 4.56 (2H, s); **m/z** (ESI+) 282 [M+H]+.

*O=C(NC1=C(F)C(Cl)=CC=C1)C2=NC(NN)=CN=C2*

*InChI=1S/C11H9ClFN5O/c12-6-2-1-3-7(10(6)13)17-11(19)8-4-15-5-9(16-8)18-14/h1-5H,14H2,(H,16,18)(H,17,19)*

***N*-(5-Chloro-2-methylphenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/5ff

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a yellow solid (621 mg, quant. yield); **IR** νmax (film) /cm-1 3351, 1686, 1581, 1517, 1430; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.22 (1H, s), 8.59 (1H, s), 8.33 (1H, s), 8.26 (1H, s), 7.96 (1H, d, *J* 2.2), 7.32 (1H, d, *J* 8.4), 7.18 (1H, d, *J* 8.2, 2.2), 4.55 (2H, s), 2.32 (3H, s); **m/z** (ESI+) 278 [M+H]+.

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

*InChI=1S/C12H12ClN5O/c1-7-2-3-8(13)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)*

**N-(3,5-Bis(trifluoromethyl)phenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/502

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as an orange solid (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC(C(F)(F)F)=CC(C(F)(F)F)=C1)C2=CN=CC(NN)=N2*

*InChI=1S/C13H9F6N5O/c14-12(15,16)6-1-7(13(17,18)19)3-8(2-6)22-11(25)9-4-21-5-10(23-9)24-20/h1-5H,20H2,(H,22,25)(H,23,24)*

**(4-Fluoroisoindolin-2-yl)(6-hydrazinylpyrazin-2-yl)methanone, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/55d

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a pale yellow solid (250 mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(N1CC(C(F)=CC=C2)=C2C1)C3=CN=CC(NN)=N3*

*InChI=1S/C13H12FN5O/c14-10-3-1-2-8-6-19(7-9(8)10)13(20)11-4-16-5-12(17-11)18-15/h1-5H,6-7,15H2,(H,17,18)*

***N*-(4-Chlorophenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**

**

Representative Example:

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(C(NC2=CC=C(Cl)C=C2)=O)=CN=C1*

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

***N*-(3-Chloro-4-fluorophenyl)-6-hydrazinylpyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/92a

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(C(NC2=CC=C(F)C(Cl)=C2)=O)=CN=C1*

*InChI=1S/C11H9ClFN5O/c12-7-3-6(1-2-8(7)13)16-11(19)9-4-15-5-10(17-9)18-14/h1-5H,14H2,(H,16,19)(H,17,18)*

**6-Hydrazinyl-*N*-(2-(trifluoromethyl)pyridin-4-yl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/91a

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(C(NC2=CC=NC(C(F)(F)F)=C2)=O)=CN=C1*

*InChI=1S/C11H9F3N6O/c12-11(13,14)8-3-6(1-2-17-8)18-10(21)7-4-16-5-9(19-7)20-15/h1-5H,15H2,(H,19,20)(H,17,18,21)*

**(6-Hydrazinylpyrazin-2-yl)(isoindolin-2-yl)methanone, OSM-S-XXX**

****

Representative Example:

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%)**; m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*NNC1=NC(C(N2CC(C=CC=C3)=C3C2)=O)=CN=C1*

*InChI=1S/C13H13N5O/c14-17-12-6-15-5-11(16-12)13(19)18-7-9-3-1-2-4-10(9)8-18/h1-6H,7-8,14H2,(H,16,17)*

***3.3 Condensation Reaction***

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

****

Representative Example: http://malaria.ourexperiment.org/uri/609

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a pale yellow powder (217 mg, 46%); **m.p.** 220–230 ˚C; **IR** νmax (film) /cm-1 3250, 1671, 1578, 1432, 1243, 1157; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.48 (1H, s), 10.43 (1H, s), 8.89 (1H, s), 8.59 (1H, s), 8.16 (1H, s), 8.02 (1H, t, *J* 2.0), 7.84 (2H, dapp, *J* 8.8), 7.71 (1H, ddd, *J* 8.1, 1.7, 0.6), 7.42 (1H, t, *J* 8.1), 7.31 (1H, t, *J* 73.9), 7.24 (2H, dapp, *J* 8.6), 7.21 (1H, ddd, *J* 8.0, 2.0, 0.8); **13C NMR** (100 MHz, DMSO-d*6*) δ: 162.60, 151.55 (t, *J* 3.2), 151.19, 142.33, 141.14, 139.63, 134.03, 133.41, 133.13, 131.60, 130.54, 128.26 (2 C), 123.84, 119.46, 118.82 (2 C), 118.43, 116.17 (t, *J* 257.8); **m/z** (APCI+) 418 [M+H]+; **HRMS** (APCI+) found 418.08770 [M+H]+, C19H15ClF2N5O2 requires 418.08769; **CHNX** Anal. Calcd. for C19H14ClF2N5O2: C, 54.62; H, 3.38; N, 16.76. Found: C, 54.56; H, 3.11; N, 16.65.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=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+*

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

****

Representative Example: http://malaria.ourexperiment.org/uri/605

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as bright yellow flakes (265 mg, 56%); **m.p.** 209 ˚C; **IR** νmax (film) /cm-1 2174, 1674, 1577, 1508, 1421, 1226, 1112; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.48 (1H, s), 10.06 (1H, s), 8.87 (1H, s), 8.62 (1H, s), 8.17 (1H, s), 7.84 (2H, dapp, *J* 8.8), 7.79 (1H, dd, *J* 7.9, 1.6), 7.34 (1H, dd, *J* 8.1, 1.7), 7.32 (1H, t, *J* 73.9), 7.29 (1H, t, *J* 7.9), 7.24 (2H, dapp, *J* 8.7), 2.37 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 161.91, 151.62 (t, *J* 3.1), 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); **m/z** (APCI+) 432 [M+H]+; **HRMS** (APCI+) found 432.10329 [M+H]+, C20H17ClF2N5O2 requires 432.10334.

*O=C(NC1=CC=CC(Cl)=C1C)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=N2*

*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+*

**(E)-N-(3-Chloro-2-fluorophenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/60a

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as lemon yellow flakes (256 mg, 56%); **m.p.** 215–217 ˚C; **IR** νmax (film) /cm-1 1680, 1511, 1454, 1423, 1226, 1114; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.54 (1H, s), 10.09 (1H, sre), 8.89 (1H, s), 8.63 (1H, s), 8.16 (1H, s), 8.13 (1H, ddd, *J* 8.3, 6.8, 1.4), 7.84 (2H, d, *J* 8.7), 7.41 (1H, ddd, *J* 8.3, 6.8, 1.4), 7.31 (1H, t, *J* 73.9), 7.29 (1H, td, *J* 8.1, 1.3), 7.23 (2H, d, *J* 8.6); **13C NMR** (100 MHz, DMSO-d*6*) δ: 161.76, 151.59, 150.97, 150.46, 148.01, 141.39, 140.77, 134.85, 133.14, 131.59, 130.19, 128.27 (2 C), 127.05 (d, *J* 10.6), 125.95, 125.31 (d, *J* 4.8), 121.73, 119.83 (d, *J* 15.9), 118.80 (2 C), 118.68, 116.17 (t, *J* 258.0); **m/z** (APCI+) 436 [M+H]+; **HRMS** (APCI+) found 436.07825 [M+H]+, C19H14ClF3N5O2 requires 436.07826.

*O=C(NC1=CC=CC(Cl)=C1F)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=N2*

*InChI=1S/C19H13ClF3N5O2/c20-13-2-1-3-14(17(13)21)27-18(29)15-9-24-10-16(26-15)28-25-8-11-4-6-12(7-5-11)30-19(22)23/h1-10,19H,(H,26,28)(H,27,29)/b25-8+*

**(E)-N-(5-Chloro-2-methylphenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/60c

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as bright yellow flakes (271 mg, 58%); **m.p.** 212 ˚C; **IR** νmax (film) /cm-1 3342, 3247, 1689, 1583, 1523, 1430; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.47 (1H, s), 9.94 (1H, s), 8.85 (1H, s), 8.64 (1H, s), 8.18 (1H, s), 8.14 (1H, d, *J* 2.3), 7.84 (2H, dapp, *J* 8.9), 7.33 (1H, dd, *J* 8.1, 0.7), 7.31 (1H, t, *J* 73.8), 7.25 (2H, dapp, *J* 8.8), 7.18 (1H, dd, *J* 8.1, 2.3), 2.38 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 161.42, 151.60, 150.79, 141.44, 141.09, 136.92, 134.80, 132.99, 131.84, 131.61, 130.46, 130.19, 128.26 (2 C), 127.75, 124.36, 120.90, 118.83 (2 C), 116.17 (t, *J* 258.0), 16.76; **m/z** (APCI+) 432 [M+H]+; **HRMS** (APCI+) found 432.10331 [M+H]+, C20H17ClF2N5O2 requires 432.10334.

*O=C(NC1=C(C)C=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=N2*

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

**(E)-N-(3-Chloro-2-methylphenyl)-6-(2-(4-methoxybenzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/629

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a dark yellow solid (224 mg, 63%); **m.p.** 192.9–193.4 ˚C; **IR** νmax (film) /cm-1 3353, 3238, 1685, 1579, 1513, 1427, 1250; **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.29 (1H, s), 10.04 (1H, s), 8.82 (1H, s), 8.58 (1H, s), 8.13 (1H, s), 7.81 (1H, d, *J* 8.5), 7.72 (2H, d, *J* 7.2), 7.34 (1H, d, *J* 8.5), 7.28 (1H, t, *J* 8.6), 7.01 (2H, d, *J* 7.3), 3,81 (3H, s), 2.38 (3H, s); **13C NMR** (126 MHz, DMSO-d*6*) δ: 161.88, 160.32, 151.06, 142.48, 141.52, 137.23, 131.34, 133.73, 132.70, 128.74, 128.13 (2 C), 127.21, 128.94, 122.33, 114.27 (2 C), 55.26, 14.59; **m/z** (APCI+) 396 [M+H]+; **HRMS** found 396.12217 [M+H]+, C20H19ClN5O2 requires 396.12218.

*O=C(NC1=CC=CC(Cl)=C1C)C2=CN=CC(N/N=C/C3=CC=C(OC)C=C3)=N2*

*InChI=1S/C20H18ClN5O2/c1-13-16(21)4-3-5-17(13)25-20(27)18-11-22-12-19(24-18)26-23-10-14-6-8-15(28-2)9-7-14/h3-12H,1-2H3,(H,24,26)(H,25,27)/b23-10+*

**(E)-N-(3-Chloro-2-fluorophenyl)-6-(2-(4-methoxybenzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/62a

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as fine yellow crystals (198 mg, 55%); **m.p.** 195–196 ˚C; **IR** νmax (film) /cm-1 3352, 1691, 1608, 1515, 1456, 1251; **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.38 (1H, s), 10.09 (1H, s), 8.85 (1H, s), 8.60 (1H, s), 8.14 (1H, tapp, *J* 6.8), 8.12 (1H, s), 7.72 (2H, dapp, *J* 7.5), 7.42 (1H, tapp, *J* 7.8), 7.29 (1H, tapp, *J* 8.0), 7.00 (2H, dapp, *J* 7.4), 3.81 (3H, s); **13C NMR** (126 MHz, DMSO-d*6*) δ: 161.84, 160.33, 151.07, 149.23 (d, *J* 246.6), 142.56, 140.77, 134.73, 132.71, 128.16 (2 C), 127.17, 127.08 (d, *J* 10.3), 125.95, 125.33 (d, *J* 4.6), 121.74, 119.89, 119.76, 114.26, 55.25; **m/z** (APCI+) 400 [M+H]+; **HRMS** found 400.09711 [M+H]+, C19H16ClFN5O2 requires 400.09711.

*O=C(NC1=CC=CC(Cl)=C1F)C2=CN=CC(N/N=C/C3=CC=C(OC)C=C3)=N2*

*InChI=1S/C19H15ClFN5O2/c1-28-13-7-5-12(6-8-13)9-23-26-17-11-22-10-16(24-17)19(27)25-15-4-2-3-14(20)18(15)21/h2-11H,1H3,(H,24,26)(H,25,27)/b23-9+*

**(E)-N-(5-Chloro-2-methylphenyl)-6-(2-(4-methoxybenzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/62b

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a turmeric-yellow solid (180 mg, 50%); **m.p.** 226–227 ˚C; **IR** νmax (film) /cm-1 1691, 1605, 1515, 1431, 1252; **1H NMR** (500 MHz, DMSO-d*6*) δ: 11.31 (1H, s), 9.95 (1H, s), 8.81 (1H, s), 8.60 (1H, s), 8.15 (1H, s), 8.13 (1H, s), 7.72 (2H, s, *J* 8.8), 7.33 (1H, d, *J* 8.0), 7.18 (1H, d, *J* 8.25), 7.01 (2H, d, *J* 8.8), 3.81 (3H, s), 2.38 (3H, s); **13C NMR** (126 MHz, DMSO-d*6*) δ: 161.48, 160.35, 150.88, 142.61, 141.06, 136.94, 132.54, 131.86, 130.47, 128.14 (2 C), 127.68, 127.18, 124.32, 120.81, 114.28 (2 C), 55.27, 16.76; **m/z** (ESI+) 396 [M+H]+, 418 [M+Na]+, (APCI+) 396 [M+H]+; **HRMS** found 396.12224 [M+H]+, C20H19ClN5O2 requires 391.12218.

*O=C(NC1=C(C)C=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=CC=C(OC)C=C3)=N2*

*InChI=1S/C20H18ClN5O2/c1-13-3-6-15(21)9-17(13)25-20(27)18-11-22-12-19(24-18)26-23-10-14-4-7-16(28-2)8-5-14/h3-12H,1-2H3,(H,24,26)(H,25,27)/b23-10+*

**(*E*)-N-(3-Chlorophenyl)-6-(2-(pyridin-2-ylmethylene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

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Representative Example: http://malaria.ourexperiment.org/uri/6c2

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a yellow solid (117 mg, 44%); **m.p.** 252–254 ˚C; **IR** νmax (film) /cm-1 3355, 2925, 1693, 1579, 1527, 1429; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.74 (1H, s), 10.49 (1H, s), 8.96 (1H, s), 8.64 (1H, s), 8.58 (1H, ddd, *J* 4.8, 1.6, 1.2), 8.21 (1H, s), 8.13 (1H, dt, *J* 7.8, 1.0), 8.04 (1H, t, *J* 2.1), 7.86 (1H, td, *J* 7.8, 1.7), 7.72 (1H, ddd, *J* 8.2, 2.1, 0.8), 7.42 (1H, t, *J* 8.1), 7.37 (1H, ddd, *J* 7.5, 4.8, 1.0), 7.21 (1H, ddd, *J* 8.0, 2.1, 0.7); **13C NMR** (100 MHz, DMSO-d*6*) δ: 162.64, 153.52, 150.98, 149.39, 142.64, 142.48, 139.71, 136.74, 134.16, 134.05, 133.16, 130.60, 123.90, 123.74, 119.62, 119.48, 118.48; **m/z** (APCI+) 353 [M+H]+; **HRMS** (APCI+) found 353.09121 [M+H]+, C17H14ClN6O requires 353.09121.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=NC=CC=C3)=N2*

*InChI=1S/C17H13ClN6O/c18-12-4-3-6-13(8-12)22-17(25)15-10-19-11-16(23-15)24-21-9-14-5-1-2-7-20-14/h1-11H,(H,22,25)(H,23,24)/b21-9+*

**(E)-N-(3-Chlorophenyl)-6-(2-(pyridin-3-ylmethylene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

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Representative Example: http://malaria.ourexperiment.org/uri/6c3

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a yellow solid (152 mg, 57%); **m.p.** 241–242 ˚C; **IR** νmax (film) /cm-1 3028, 1677, 1581, 1414; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.67 (1H, s), 10.46 (1H, s), 8.95 (1H, s), 8.91 (1H, d, *J* 2.3), 8.62 (1H, s), 8.57 (1H, dd, *J* 4.8, 1.8), 8.22 (1H, dt, *J* 8.0, 2.0), 8.19 (1H, s), 8.03 (1H, t, *J* 2.1), 7.71 (1H, dd, *J* 8.2, 2.1), 7.46 (1H, dd, *J* 8.1, 4.9), 7.42 (1H, t, *J* 8.2), 7.21 (1H, dd, *J* 8.0, 2.2); **13C NMR** (100 MHz, DMSO-d*6*) δ: 163.09, 151.56, 150.40, 148.68, 142.85, 140.13, 139.67, 134.68, 134.24, 133.61, 133.56, 131.05, 130.99, 124.38, 124.34, 119.93, 118.92; **m/z** (APCI+) 353 [M+H]+; **HRMS** (APCI+) found 353.09131 [M+H]+, C17H14ClN6O requires 353.09121.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=CN=CC=C3)=N2*

*InChI=1S/C17H13ClN6O/c18-13-4-1-5-14(7-13)22-17(25)15-10-20-11-16(23-15)24-21-9-12-3-2-6-19-8-12/h1-11H,(H,22,25)(H,23,24)/b21-9+*

**(E)-N-(3-Chlorophenyl)-6-(2-(4-(trifluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

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Representative Example: http://malaria.ourexperiment.org/uri/6da

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a pale yellow solid (312 mg, 94%); **m.p.** 250.2–250.5 ˚C; **IR** νmax (film) /cm-1 3322, 3257, 1671, 1577, 1432, 1310, 1144; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.60 (1H, s), 10.46 (1H, s), 8.91 (1H, s), 8.60 (1H, s), 8.18 (1H, s), 8.03 (1H, t, *J* 2.0), 7.92 (2H, dapp, *J* 8.8), 7.71 (1H, dd, *J* 8.2, 2.1), 7.42 (2H, dapp, *J* 8.7), 7.42 (1H, t, *J* 8.1), 7.21 (1H, dd, *J* 8.0, 2.1); **13C NMR** (125 MHz, DMSO-d*6*) δ: 162.59, 151.14, 148.69, 142.37, 140.57, 139.63, 134.08, 133.94, 133.63, 133.13, 130.55, 128.37, 123.85, 121.30, 119.46, 118.44; **m/z** (ESI+) 436 [M+H]+; **HRMS** (APCI+) found 436.07823 [M+H]+, C19H14ClF3N5O2 requires 436.07826.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC(N/N=C/C3=CC=C(OC(F)(F)F)C=C3)=N2*

*InChI=1S/C19H13ClF3N5O2/c20-13-2-1-3-14(8-13)26-18(29)16-10-24-11-17(27-16)28-25-9-12-4-6-15(7-5-12)30-19(21,22)23/h1-11H,(H,26,29)(H,27,28)/b25-9+*

**(E)-N-(3,5-Bis(trifluoromethyl)phenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/506

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as an orange-brown solid (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC(C(F)(F)F)=CC(C(F)(F)F)=C1)C2=CN=CC(N/N=C/C3=CC=C(OC(F)F)C=C3)=N2*

*InChI=1S/C21H13F8N5O2/c22-19(23)36-15-3-1-11(2-4-15)8-31-34-17-10-30-9-16(33-17)18(35)32-14-6-12(20(24,25)26)5-13(7-14)21(27,28)29/h1-10,19H,(H,32,35)(H,33,34)/b31-8-*

**(E)-(6-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)pyrazin-2-yl)(4-fluoroisoindolin-2-yl)methanone, OSM-S-XXX**



Representative Example: http://malaria.ourexperiment.org/uri/55e

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as a bright yellow solid (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(N1CC(C(F)=CC=C2)=C2C1)C3=CN=CC(N/N=C/C4=CC=C(OC(F)F)C=C4)=N3*

*InChI=1S/C21H16F3N5O2/c22-17-3-1-2-14-11-29(12-16(14)17)20(30)18-9-25-10-19(27-18)28-26-8-13-4-6-15(7-5-13)31-21(23)24/h1-10,21H,11-12H2,(H,27,28)/b26-8-*

**(*E*)-*N*-(4-Chlorophenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

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Representative Example:

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(C(NC3=CC=C(Cl)C=C3)=O)=CN=C2*

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

**(*E*)-*N*-(3-Chloro-4-fluorophenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/932

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(C(NC3=CC=C(F)C(Cl)=C3)=O)=CN=C2*

*InChI=1S/C19H13ClF3N5O2/c20-14-7-12(3-6-15(14)21)26-18(29)16-9-24-10-17(27-16)28-25-8-11-1-4-13(5-2-11)30-19(22)23/h1-10,19H,(H,26,29)(H,27,28)/b25-8+*

**(*E*)-6-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example: http://malaria.ourexperiment.org/uri/91f

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(C(NC3=CC=NC(C(F)(F)F)=C3)=O)=CN=C2*

*InChI=1S/C19H13F5N6O2/c20-18(21)32-13-3-1-11(2-4-13)8-27-30-16-10-25-9-14(29-16)17(31)28-12-5-6-26-15(7-12)19(22,23)24/h1-10,18H,(H,29,30)(H,26,28,31)/b27-8+*

**(*E*)-(6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazin-2-yl)(isoindolin-2-yl)methanone, OSM-S-XXX**

****

Representative Example:

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1/C=N/NC2=NC(C(N3CC(C=CC=C4)=C4C3)=O)=CN=C2*

*InChI=1S/C21H17F2N5O2/c22-21(23)30-17-7-5-14(6-8-17)9-25-27-19-11-24-10-18(26-19)20(29)28-12-15-3-1-2-4-16(15)13-28/h1-11,21H,12-13H2,(H,26,27)/b25-9+*

**6-(2-((*E*)-((1*r*,2*R*,3*r*,8*S*)-4-Iodocuban-1-yl)methylene)hydrazinyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)pyrazine-2-carboxamide, OSM-S-XXX**

****

Representative Example:

Prepared according to General Procedure **X** from: \_\_\_ to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC=NC(C(F)(F)F)=C1)C2=CN=CC(N/N=C/[C@@]34[C@H]5C6C3C7[C@@H]4[C@@H]5C76I)=N2*

*InChI=1S/C20H14F3IN6O/c21-20(22,23)9-3-7(1-2-26-9)28-17(31)8-4-25-5-10(29-8)30-27-6-18-11-14-12(18)16-13(18)15(11)19(14,16)24/h1-6,11-16H,(H,29,30)(H,26,28,31)/b27-6+/t11-,12+,13?,14-,15?,16?,18+,19?*

**3.4 Oxidative Cyclisation of Amides**

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

****

Representative Example: http://malaria.ourexperiment.org/uri/61e

Prepared according to General Procedure **F** from: **OSM-S-XXX** (150 mg, 0.36 mmol) to give the title compound as a pearlescent white powder (60 mg, 39%); **m.p.** 257–258 ˚C; **IR** νmax (film) /cm-1 3053, 1671, 1591, 1536, 1465; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.88 (1H, s), 9.66 (1H, s), 8.30 (1H, s), 7.63 (2H, dapp, *J* 8.7), 7.40 (1H, t, *J* 1.9), 7.29 (1H, t, *J* 8.1), 7.17 (1H, d, *J* 7.9), 7.15 (1H, d, *J* 7.9), 7.15 (2H, d, *J* 8.6), 7.11 (1H, t, *J* 73.6); **13C NMR** (100 MHz, DMSO-d*6*) δ: 157.35, 152.11 (t, *J* 3.2), 146.78, 146.10, 145.71, 138.61, 132.82, 130.31, 130.25, 130.19, 124.33, 124.28, 123.98, 119.20, 118.17, 118.13, 115.86 (t, *J* 258); **m/z** (ESI+) 438 [M+Na]+; **HRMS** (APCI+) found 416.07177 [M+H]+, C19H13ClF2N5O2 requires 416.07204; **CHNX** Anal. Calcd. for C19H12ClF2N5O2: C, 54.89; H, 2.91; N, 16.84. Found: C, 55.02; H, 2.53; N, 16.61.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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**



Representative Example: http://malaria.ourexperiment.org/uri/624

Prepared according to General Procedure **F** from: **OSM-S-XXX** (200 mg, 0.46 mmol) to give the title compound as a fine pearly white powder (140 mg, 71%); **m.p.** 211–212 ˚C; **IR** νmax (film) /cm-1 1667, 1531, 1462, 1376; **1H NMR** (500 MHz, DMSO-d*6*) δ: 10.63 (1H, s), 9.66 (1H, s), 8.38 (1H, s), 7.70 (2H, dapp, *J* 8.7), 7.32 (1H, dd, *J* 8.0, 1.0), 7.32 (1H, t, *J* 73.6), 7.30 (2H, dapp, *J* 8.6), 7.14 (1H, t, *J* 8.0), 6.97 (1H, dd, *J* 8.3, 1.2), 2.22 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 158.01, 152.09 (t, *J* 3.5), 146.83, 146.11, 145.85, 136.09, 133.78, 130.50, 130.47, 130.25 (2 C), 126.91, 126.73, 124.36, 124.31, 123.92, 118.48 (2 C), 115.93 (t, *J* 256.9), 14.93; **m/z** (ESI–) 428.53 [M–H]–; **HRMS** (APCI+) found 430.08721 [M+H]+, C20H15ClF2N5O2 requires 430.08769; **CHNX** Anal. Calcd. for C20H14ClF2N5O2: C, 55.89; H, 3.28; N, 16.28. Found: C, 56.36; H, 3.01; N, 16.19.

*O=C(NC1=CC=CC(Cl)=C1C)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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)*

***N*-(3-Chloro-2-fluorophenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-204**



Representative Example: http://malaria.ourexperiment.org/uri/622

Prepared according to General Procedure **F** from: **OSM-S-XXX** (200 mg, 0.46 mmol) to give the title compound as a fine pearly white solid (129 mg, 63%); **m.p.** 218–219 ˚C; **IR** νmax (film) /cm-1 1688, 1612, 1543, 1459; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.81 (1H, s), 9.65 (1H, s), 8.28 (1H, s), 7.65 (2H, dapp, *J* 8.7), 7.52 (1H, dddapp, *J* 8.2, 7.2, 1.2), 7.35 (1H, dddapp, *J* 8.1, 6.9, 1.3), 7.19 (2H, dapp, *J* 8.6), 7.17 (1H, t, *J* 73.5), 7.12 (1H, tdapp, *J* 8.3, 1.3); **13C NMR** (100 MHz, DMSO-d*6*) δ: 158.01, 152.10 (t, *J* 3.2), 149.09 (d, *J* 249.8), 146.67, 146.05, 145.74, 130.39, 130.33 (2 C), 126.51, 126.01 (d, *J* 11.5), 124.78 (d, *J* 4.6), 124.34, 123.92, 122.26, 119.77 (d, *J* 15.8), 118.26 (2 C), 115.85 (t, *J* 258.4); **m/z** (ESI+) 434 [M+H]+, 466 [M+MeOH+H]+; **HRMS** (APCI+) found 434.06259 [M+H]+, C19H12ClF3N5O2 requires 434.06261; **CHNX** Anal. Calcd. for C19H11ClF3N5O2: C, 52.61; H, 2.56; N, 16.15. Found: C, 52.67; H, 2.18; N, 16.02.

*O=C(NC1=CC=CC(Cl)=C1F)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

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

***N*-(5-Chloro-2-methylphenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-254**



Representative Example: http://malaria.ourexperiment.org/uri/623

Prepared according to General Procedure **F** from: **OSM-S-XXX** (200 mg, 0.46 mmol) to give the title compound as a white solid (144 mg, 73%); **m.p.** 247–248 ˚C; **IR** νmax (film) /cm-1 1686, 1582, 1530, 1462; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.42 (1H, s), 9.66 (1H, s), 8.35 (1H, s), 7.70 (2H, dapp, *J* 8.7), 7.29 (2H, dapp, *J* 8.6), 7.28 (1H, t, *J* 78.5), 7.24 (1H, d, *J* 8.2), 7.17 (1H, dd, *J* 8.2, 2.2), 7.06 (1H, d, *J* 2.1), 2.19 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 157.96, 152.35, 146.76, 146.03, 145.79, 135.78, 131.85, 130.42 (2 C), 130.34, 130.32, 129.82, 125.66, 124.35, 124.10, 123.68, 118.13 (2 C), 118.93 (t, *J* 258.0), 17.12; **m/z** (ESI+) 430 [M+H]+, 462 [M+MeOH+H]+; **HRMS** (APCI+) found 430.08711 [M+H]+, C20H15ClF2N5O2 requires 430.08769; **CHNX** Anal. Calcd. for C20H14ClF2N5O2: C, 55.89; H, 3.28; N, 16.28. Found: C, 56.01; H, 2.97; N, 16.23.

*O=C(NC1=CC(Cl)=CC=C1C)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

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

***N*-(3-Chloro-2-methylphenyl)-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-255**



Representative Example: http://malaria.ourexperiment.org/uri/64b

Prepared according to General Procedure **F** from: **OSM-S-XXX** (150 mg, 0.38 mmol) to give the title compound as a tan powder (86 mg, 58%); **m.p.** 220–221 ˚C; **IR** νmax (film) /cm-1 3230, 2832, 1686, 1612, 1461, 1254; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.62 (1H, s), 9.63 (1H, s), 8.34 (1H, s), 7.57 (2H, dapp, *J* 8.7), 7.32 (1H, d, *J* 7.6), 7.16 (1H, t, *J* 8.0), 7.02 (2H, dapp, *J* 8.7), 7.01 (1H, d, *J* 7.6), 3.77 (3H, s), 2.22 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 160.61, 158.07, 147.60, 146.10, 145.76, 132.20, 133.80, 130.44, 130.30, 129.84 (2 C), 126.88, 126.76, 124.59, 123.95, 119.54, 114.08 (2 C), 55.36, 15.04; **m/z** (ESI+) 394 [M+H]+; **HRMS** (APCI+) found 394.10644 [M+H]+, C20H17ClN5O2 requires 394.10653.

*O=C(C1=CN=CC2=NN=C(C3=CC=C(OC)C=C3)N21)NC4=CC=CC(Cl)=C4C*

*InChI=1S/C20H16ClN5O2/c1-12-15(21)4-3-5-16(12)23-20(27)17-10-22-11-18-24-25-19(26(17)18)13-6-8-14(28-2)9-7-13/h3-11H,1-2H3,(H,23,27)*

***N*-(3-Chloro-2-fluorophenyl)-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-256**



Representative Example: http://malaria.ourexperiment.org/uri/64c

Prepared according to General Procedure **F** from: **OSM-S-XXX** (150 mg, 0.38 mmol) to give the title compound as a beige solid (78 mg, 58%); **m.p.** 229–230 ˚C; **IR** νmax (film) /cm-1 3175, 3046, 1672, 1525, 1455, 1287; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.75 (1H, s), 9.61 (1H, s), 8.23 (1H, s), 7.60 (1H, ddd, *J* 8.4, 7.0, 1.5), 7.50 (2H, dapp, *J* 8.7), 7.35 (1H, ddd, *J* 8.3, 6.8, 1.5), 7.14 (1H, td, *J* 8.2, 1.4), 6.89 (2H, dapp, *J* 8.7), 3.66 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 160.49, 158.12, 148.91 (d, *J* 249), 147.43, 146.01, 145.66, 130.22, 129.91 (2 C), 126.25, 124.80 (d, *J* 5.8), 124.62, 122.07, 119.68 (d, *J* 15.4), 119.17, 113.88 (2 C), 55.17; **m/z** (ESI+) 398 [M+H]+, 430 [M+MeOH+H]+, 452 [M+MeOH+Na]+; **HRMS** (APCI+) found 398.08134 [M+H]+, C19H14ClFN5O2 requires 398.08146; **CHNX** Anal. Calcd. for C19H13ClFN5O2: C, 57.37; H, 3.29; N, 17.61. Found: C, 57.36; H, 3.10; N, 17.19.

*O=C(NC1=CC=CC(Cl)=C1F)C2=CN=CC3=NN=C(C4=CC=C(OC)C=C4)N32*

*InChI=1S/C19H13ClFN5O2/c1-28-12-7-5-11(6-8-12)18-25-24-16-10-22-9-15(26(16)18)19(27)23-14-4-2-3-13(20)17(14)21/h2-10H,1H3,(H,23,27)*

***N-*(5-Chloro-2-methylphenyl)-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-257**



Representative Example: http://malaria.ourexperiment.org/uri/64d

Prepared according to General Procedure **F** from: **OSM-S-XXX** (150 mg, 0.38 mmol) to give the title compound as a white solid (81 mg, 55%); **m.p.** 273–274 ˚C; **IR** νmax (film) /cm-1 3155, 2918, 1674, 1534, 1462, 1303, 1256; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.39 (1H, s), 9.63 (1H, s), 8.29 (1H, s), 7.56 (2H, dapp, *J* 8.7), 7.23 (1H, dd, *J* 8.3, 0.5), 7.26 (1H, dd, *J* 8.2, 2.2), 7.03 (2H, dapp, *J* 8.8), 6.98 (1H, d, *J* 2.2), 3.79 (3H, s), 2.19 (3H, s); **13C NMR** (100 MHz, DMSO-d*6*) δ: 161.18, 158.43, 147.95, 146.38, 146.12, 136.31, 132.28, 130.76, 130.50 (2 C), 130.44, 130.17, 126.04, 125.06, 124.26, 119.80, 114.48 (2 C), 55.72, 17.62; **m/z** (ESI+) 394 [M+H]+, 416 [M+Na]+; **HRMS** (APCI+) found 394.10637 [M+H]+, C20H17ClN5O2 requires 394.10653; **CHNX** Anal. Calcd. for C20H16ClN5O2: C, 61.00; H, 4.10; N, 17.78. Found: C, 61.00; H, 3.90; N, 17.43.

*O=C(NC1=CC(Cl)=CC=C1C)C2=CN=CC3=NN=C(C4=CC=C(OC)C=C4)N32*

*InChI=1S/C20H16ClN5O2/c1-12-3-6-14(21)9-16(12)23-20(27)17-10-22-11-18-24-25-19(26(17)18)13-4-7-15(28-2)8-5-13/h3-11H,1-2H3,(H,23,27)*

***N*-(3-Chlorophenyl)-3-(pyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-262**

****

Representative Example: http://malaria.ourexperiment.org/uri/6d1

Prepared according to General Procedure **F** from: **OSM-S-XXX** (100 mg, 0.28 mmol) to give the title compound as a beige powder (56 mg, 57%); **m.p.** 222–224 ˚C; **IR** νmax (film) /cm-1 3055, 2918, 1686, 1591, 1536, 1425, 1310; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.21 (1H, s), 9.73 (1H, s), 8.42 (1H, s), 8.29 (1H, ddd, *J* 4.9, 1.8, 1.0), 8.15 (1H, dt, *J* 7.8, 1.1), 8.02 (1H, td, *J* 7.7, 1.7), 7.58 (1H, t, *J* 2.3), 7.41 (1H, ddd, *J* 7.6, 4.8, 1.2), 7.38–7.36 (2H, m), 7.19 (1H, dtapp, *J* 6.8, 2.1); **13C NMR** (100 MHz, DMSO-d*6*) δ: 158.56, 148.30, 146.91, 146.53, 146.44, 146.05, 139.58, 137.83, 133.01, 130.97, 130.56, 124.89, 124.61, 124.05, 123.39, 119.16, 118.14; **m/z** (ESI+) 351 [M+H]+, 373 [M+Na]+; **HRMS** (APCI+) found 351.07547 [M+H]+, C17H12ClN6O requires 351.07556.

*O=C(C1=CN=CC2=NN=C(C3=NC=CC=C3)N21)NC4=CC=CC(Cl)=C4*

*InChI=1S/C17H11ClN6O/c18-11-4-3-5-12(8-11)21-17(25)14-9-19-10-15-22-23-16(24(14)15)13-6-1-2-7-20-13/h1-10H,(H,21,25)*

***N*-(3-Chlorophenyl)-3-(pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-263**

****

Representative Example: http://malaria.ourexperiment.org/uri/6d2

Prepared according to General Procedure **F** from: **OSM-S-XXX** (100 mg, 0.28 mmol) to give the title compound as a tan powder (50 mg, 50%); **m.p.** 196–197 ˚C; **IR** νmax (film) /cm-1 3058, 1681, 1594, 1542, 1480, 1425, 1313; **1H NMR** (400 MHz, DMSO-d*6*) δ: 11.07 (1H, s), 9.71 (1H, s), 8.79 (1H, dd, *J* 2.3, 1.1), 8.55 (1H, dd, *J* 4.9, 1.6), 8.38 (1H, s), 8.01 (1H, dt, *J* 7.9, 2.0), 7.42 (1H, dd, *J* 5.2, 1.0), 7.41 (1H, t, *J* 2.2), 7.40 (1H, dd, *J* 5.0, 1.1), 7.31 (1H, t, *J* 8.1), 7.21 (1H, ddd, *J* 8.2, 1.8, 1.0), 7.18 (1H, ddd, *J* 7.9, 2.0, 1.0); **13C NMR** (100 MHz, DMSO-d*6*) δ: 157.85, 151.10, 149.02, 146.81, 146.45, 145.75, 139.09, 136.30, 133.33, 131.08, 130.87, 124.94, 124.53, 124.45, 123.71, 119.85, 118.78; **m/z** (ESI+) 351 [M+H]+; **HRMS** (APCI+) found 351.07526 [M+H]+, C17H12ClN6O requires 351.0755.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC3=NN=C(C4=CN=CC=C4)N32*

*InChI=1S/C17H11ClN6O/c18-12-4-1-5-13(7-12)21-17(25)14-9-20-10-15-22-23-16(24(14)15)11-3-2-6-19-8-11/h1-10H,(H,21,25)*

***N*-(3-Chlorophenyl)-3-(4-(trifluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide**, **OSM-S-271**



Representative example: http://malaria.ourexperiment.org/uri/705

Prepared according to General Procedure **F** from: **OSM-S-XXX** (170 mg, 0.39 mmol) to give the title compound as a fine white powder (144 mg, 85%); **m.p.** 249–250 ˚C; **IR** νmax (film) /cm-1 3222, 3197, 3052, 1673, 1432, 1466, 1313, 1167; **1H NMR** (400 MHz, DMSO-d*6*) δ: 10.94 (1H, s), 9.68 (1H, s), 8.33 (1H, s), 7.72 (2H, dapp, *J* 8.7), 7.44 (1H, t, *J* 2.1), 7.36 (2H, dapp, *J* 8.0), 7.27 (1H, t, *J* 8.1), 7.17 (1H, dd, *J* 2.9, 2.1), 7.15 (1H, ddd, *J* 3.4, 2.1, 1.1); **13C NMR** (100 MHz, DMSO-d*6*) δ: 157.38, 149.35, 146.51, 146.20, 145.82, 138.64, 132.93, 130.57 (2 C), 130.45, 130.23, 126.55, 124.32, 124.30, 120.86 (2 C), 119.89 (q, *J* 252.9), 119.03, 118.00; **HRMS** (APCI+) found 434.06242 [M+H]+, C19H12ClF3N5O2 requires 434.06261; **CHNX** Anal. Calcd. for C19H11ClF3N5O2: C, 52.61; H, 2.56; N, 16.15. Found: C, 52.02; H, 2.32; N, 15.69.

*O=C(NC1=CC=CC(Cl)=C1)C2=CN=CC3=NN=C(C4=CC=C(OC(F)(F)F)C=C4)N32*

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

**N-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide. OSM-S-206**



Representative Example: http://malaria.ourexperiment.org/uri/552

**OSM-S-XXX** (65 mg, 0.13 mmol, 1.0 equiv.) was combined with chloramine-T (42 mg, 1.5 mmol, 1.2 equiv.) in 2-methyltetrahydrofuran (1 mL) and the reaction heated to 60 ˚C for 1.5 h. The reaction was allowed to cool to rt, diluted with 2-methyltetrahydrofuran (8 mL), washed with 10 wt% aqueous sodium sulfite solution (4 mL) and aqueous NaOH solution (1 M, 2 x 4 mL). The solvent was removed under reduced pressure to give the crude title compound as a brown oil/solid (X mg, X%); purified by automated flash chromatography on silica (Biotage Isolera, 30–100% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (500 MHz, CD3CN) δ: 9.74 (1H, s), 9.25 (1H, s), 8.02 (1H, s), 7.69 (1H, s), 7.55 (1H, s), 7.45 (2H, d, *J* 8.6), 6.89 (2H, d, *J* 8.6), 6.44 (1H, t, *J* 73.6); **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: -63.7, -83.9; **HRMS** (ESI+) found 518.08578 [M+H]+, C21H12F8N5O2 requires 518.08587.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NC4=CC(C(F)(F)F)=CC(C(F)(F)F)=C4)=O)N32*

*InChI=1S/C21H11F8N5O2/c22-19(23)36-14-3-1-10(2-4-14)17-33-32-16-9-30-8-15(34(16)17)18(35)31-13-6-11(20(24,25)26)5-12(7-13)21(27,28)29/h1-9,19H,(H,31,35)*

**4-(5-(4-Fluoroisoindoline-2-carbonyl)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile. OSM-S-207**



Representative Example: http://malaria.ourexperiment.org/uri/561

**OSM-S-XXX** (X mg, 0.46 mmol, 1.0 equiv.) was combined with chloramine-T (155 mg, 5.52 mmol, 1.2 equiv.) in 2-methyltetrahydrofuran (3.7 mL) and the reaction heated to 60 ˚C for 2.5 h. The reaction was allowed to cool to rt, diluted with 2-methyltetrahydrofuran (10 mL), washed with 10 wt% aqueous sodium sulfite solution (5 mL) and aqueous NaOH solution (1 M, 2 x 5 mL). The solvent was removed under reduced pressure to give the crude title compound as a brown oil (X mg, X%); purified by automated flash chromatography on silica (Biotage Isolera, XX–XX% EtOAc in hexanes) to give the title compound as \_\_\_ (X mg, X%); **m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (ESI+) found XX [M+X]+, XXrequiresXX.

*O=C(N1CC(C(F)=CC=C2)=C2C1)C3=CN=CC4=NN=C(C5=CC=C(C#N)C=C5)N43*

*InChI=1S/C21H13FN6O/c22-17-3-1-2-15-11-27(12-16(15)17)21(29)18-9-24-10-19-25-26-20(28(18)19)14-6-4-13(8-23)5-7-14/h1-7,9-10H,11-12H2*

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

****

Representative Example: http://bit.ly/2kUg2OG

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC=C(Cl)C=C1)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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**

****

Representative Example: http://bit.ly/2jFHsmu

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC=C(F)C(Cl)=C1)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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)*

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

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Representative Example: http://malaria.ourexperiment.org/uri/920

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(NC1=CC=NC(C(F)(F)F)=C1)C2=CN=CC3=NN=C(C4=CC=C(OC(F)F)C=C4)N32*

*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-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)(isoindolin-2-yl)methanone, OSM-S-177**

****

Representative Example: http://bit.ly/2jXXARm

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(N1CC(C=CC=C2)=C2C1)C3=CN=CC4=NN=C(C5=CC=C(OC(F)F)C=C5)N43*

*InChI=1S/C21H15F2N5O2/c22-21(23)30-16-7-5-13(6-8-16)19-26-25-18-10-24-9-17(28(18)19)20(29)27-11-14-3-1-2-4-15(14)12-27/h1-10,21H,11-12H2*

**3-(4-Iodocuban-1-yl)-N-(2-(trifluoromethyl)pyridin-4-yl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-382**

****

Representative Example: http://bit.ly/2jFDGcM

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*IC12C3C4C5(C3C1C5C24)C6=NN=C7C=NC=C(C(NC8=CC(C(F)(F)F)=NC=C8)=O)N76*

*InChI=1S/C20H12F3IN6O/c21-20(22,23)8-3-6(1-2-26-8)27-16(31)7-4-25-5-9-28-29-17(30(7)9)18-10-13-11(18)15-12(18)14(10)19(13,15)24/h1-5,10-15H,(H,26,27,31)*

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

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NCC4=CC(Cl)=CC=C4)=O)N32*

*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*-(4-Chlorobenzyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-178**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NCC4=CC=C(Cl)C=C4)=O)N32*

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

**3-(4-(Difluoromethoxy)phenyl)-N-((tetrahydro-2H-pyran-4-yl)methyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-179**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NCC4CCOCC4)=O)N32*

*InChI=1S/C19H19F2N5O3/c20-19(21)29-14-3-1-13(2-4-14)17-25-24-16-11-22-10-15(26(16)17)18(27)23-9-12-5-7-28-8-6-12/h1-4,10-12,19H,5-9H2,(H,23,27)*

**3-(4-(Difluoromethoxy)phenyl)-N-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-180**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NCN4CCN(C5=NC=CC=C5)CC4)=O)N32*

*InChI=1S/C23H22F2N8O2/c24-23(25)35-17-6-4-16(5-7-17)21-30-29-20-14-26-13-18(33(20)21)22(34)28-15-31-9-11-32(12-10-31)19-3-1-2-8-27-19/h1-8,13-14,23H,9-12,15H2,(H,28,34)*

**3-(4-(Difluoromethoxy)phenyl)-N-(2-morpholinoethyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-181**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(NCCN4CCOCC4)=O)N32*

*InChI=1S/C19H20F2N6O3/c20-19(21)30-14-3-1-13(2-4-14)17-25-24-16-12-22-11-15(27(16)17)18(28)23-5-6-26-7-9-29-10-8-26/h1-4,11-12,19H,5-10H2,(H,23,28)*

**(3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)(pyrrolidin-1-yl)methanone, OSM-S-182**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(N4CCCC4)=O)N32*

*InChI=1S/C17H15F2N5O2/c18-17(19)26-12-5-3-11(4-6-12)15-22-21-14-10-20-9-13(24(14)15)16(25)23-7-1-2-8-23/h3-6,9-10,17H,1-2,7-8H2*

**(3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)(2-phenylpyrrolidin-1-yl)methanone, OSM-S-183**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*O=C(N1C(C2=CC=CC=C2)CCC1)C3=CN=CC4=NN=C(C5=CC=C(OC(F)F)C=C5)N43*

*InChI=1S/C23H19F2N5O2/c24-23(25)32-17-10-8-16(9-11-17)21-28-27-20-14-26-13-19(30(20)21)22(31)29-12-4-7-18(29)15-5-2-1-3-6-15/h1-3,5-6,8-11,13-14,18,23H,4,7,12H2*

**(3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone, OSM-S-184**

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Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(N4CCN(S(=O)(C)=O)CC4)=O)N32*

*InChI=1S/C18H18F2N6O4S/c1-31(28,29)25-8-6-24(7-9-25)17(27)14-10-21-11-15-22-23-16(26(14)15)12-2-4-13(5-3-12)30-18(19)20/h2-5,10-11,18H,6-9H2,1H3*

**(3-(4-(Difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazin-5-yl)(morpholino)methanone, OSM-S-185**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(N4CCOCC4)=O)N32*

*InChI=1S/C17H15F2N5O3/c18-17(19)27-12-3-1-11(2-4-12)15-22-21-14-10-20-9-13(24(14)15)16(25)23-5-7-26-8-6-23/h1-4,9-10,17H,5-8H2*

**(*R*)-3-(4-(Difluoromethoxy)phenyl)-N-(1-phenylethyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide, OSM-S-186**

****

Representative Example:

Procedure

**m.p.** XX–XX ˚C; **IR** νmax (film) /cm-1 XX; **1H NMR** (X MHz, CDCl3) δ: XX; **13C NMR** (X MHz, CDCl3) δ: XX; **19F{1H} NMR** (377 MHz, CDCl3) δ: XX; **HRMS** (XX) found XX [M+X]+, XXrequiresXX.

*FC(F)OC(C=C1)=CC=C1C2=NN=C3C=NC=C(C(N[C@@H](C4=CC=CC=C4)C)=O)N32*

*InChI=1S/C21H17F2N5O2/c1-13(14-5-3-2-4-6-14)25-20(29)17-11-24-12-18-26-27-19(28(17)18)15-7-9-16(10-8-15)30-21(22)23/h2-13,21H,1H3,(H,25,29)*

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