***Supporting Information***

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

Alice E. Williamson1, Thomas MacDonald1, Joanna M Ubels1, Paul King1, Tianyi Zheng1, Sebastien J. Dath1, Christina Xia1, Benjamin Xie1, Thomas York1 and Matthew H. Todd1\*

**1** *School of Chemistry, The University of Sydney, NSW 2006, Australia;*

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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).

***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, the aqueous layer extracted with EtOAc (3 × 150 mL). Combined organic layers were washed with brine (~30 mL) and then concentrated under reduced pressure to yield 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-d6) 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.[[2]](#endnote-2) (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:

# 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 yield the crude title compound in quantitative yield. The pale orange powder was used in subsequent steps without purification (3.04 g); 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

# 

# Representative Example:

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 in quantitative yield. The bright yellow powder was used in subsequent steps without purification (1.97 g) and a small quantity was purified for characterisation purposes by automated flash column chromatography over silica (Biotage Isolera, 1% TEA in 40–90% EtOAc in petroleum benzene) 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.

*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+*

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

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



Representative example:

*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:

*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:

*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:

*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:

*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 yield the crude title compound in quantitative yield. The pale yellow powder was used in subsequent steps without purification (3.89 g); **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-(3,5-difluorobenzylidene)hydrazinyl)pyrazine, OSM-S-310**



Representative Example:

Prepared according to General Procedure B from: **OSM-S-302**

*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) in EtOH (200 mL); 1.5 h; to yield the crude title compound as a yellow powder (3.67 g, 48%);

*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+*

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

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



*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:

*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**



*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/triazolopyrazine_se/11329/Synthesis_of_E2chloro62cyclohexylmethylenehydrazinylpyrazine_AEW_2242.html>

AEW 85 (1.5 g, 10.4 mmol) was stirred into a solution of ethanol (33 mL) Cyclohexane carboxaldehyde (1.26 mL, 1.17 g, 10.4 mmol) was added and the reaction mixture (yellow/brown ppt in orange soln) was stirred at room temperature overnight - 9am following morning orange solution.

*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/triazolopyrazine_se/11391/post.html>

OSM-302 (1.0 g, 6.92 mmol) was stirred into a solution of AcOH (0.4 mL) and MeCN (22 mL). Propionaldehyde (0.50 mL, 0.40 g, 6.92 mmol) was added and the reaction mixture (yellow solution) was stirred at room temperature overnight. The reaction mixture was evaporated to yield a brown/orange solid. TLC indicated two new spots and no SM, Crude NMR also indicated product and an additional apparent imine side-procuct with the triplet for imine protons coupled to the propionyl protons. Quantitative yield - used directly in [Synthesis of 5-chloro-3-ethyl-[1,2,4]triazolo[4,3-a]pyrazine (AEW 218-1)](http://malaria.ourexperiment.org/triazolopyrazine_se/11396/Synthesis_of_5chloro3ethyl124triazolo43apyrazine_AEW_2181.html) without further purification.

*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+*

***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, ~12.4 mmol) and PIDA (4.00 g, 12.4 mmol); x h; purified by automated flash column chromatography over silica (Biotage Isolera, 30–100% EtOAc in petroleum benzine) to give the title compound as a xxx (xx g, xx% yield); **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 (MH+, 100%); **HRMS** (APCI+) found 297.03505 [M+H]+, C­­­­12H8ClF2N­4Orequires297.03492.

*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*

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

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



# 25 (pure, 250 mg, 0.94 mmol) was reacted according to General Procedure B. Purification (Biotage isolera, 7–85% ethyl acetate/hexanes) gave the title compound as pale yellow crystals (207 mg, 83%); mp 172–173 °C; νmax (film)/cm-1 3089, 1601, 1465; δH (200 MHz; CDCl3) 9.35 (s, 1 H), 7.89 (s, 1 H), 7.56–7.49 (m, 4 H); δC (101 MHz; DMSO-*d6*) 147.1, 146.5, 142.7, 135.5, 133.2, 129.3, 127.9, 126.2, 121.9; *m/z* (APCI) 265 (MH+, 100%); HRMS (ESI) 265.00440 ([M+H]+), calcd. for C11H7Cl2N4+ 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**

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# *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*

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

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

# 

# *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*

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

# 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 B from: crude OSM-S-X (~26.3 mmol, 1 equiv.) and PhI(OAc)2 (8.4 g, 26.3 mmol) in anhydrous CH2Cl2 (263 mL) at rt for 16 h.

# *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*

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

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

# 

# 22 (crude, 2.0 g, ~8 mmol) was reacted according to General Synthetic Procedure B. Purification (Biotage isolera, 50–100% ethyl acetate/hexanes) gave the title compound as an orange powder (1.14 g, 56%); mp 226–227 °C; νmax (film)/cm-1 3089, 2228, 1597; δH (200 MHz; DMSO-*d6*) 9.53 (s, 1 H), 8.14 (s, 1 H), 8.08–7.93 (m, 4 H); δC (75 MHz; DMSO-*d6*) 147.1, 146.1, 142.7, 132.3, 132.0, 131.6, 129.4, 121.9, 118.4, 113.1; *m/z* (APCI) 256 (MH+, 100%); HRMS (ESI) 256.03845 ([M+H]+), calcd. for C12H7N5Cl+ 256.03845.

# 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

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

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

# 

# 34 (550 mg, 2.4 mmol) was reacted according to General Synthetic Procedure B. Purification (Biotage isolera, 60–100% ethyl acetate/hexanes) gave the title compound as a pale yellow powder (406 mg, 75%); mp 165–167 °C; νmax (film)/cm-1 3036, 3003, 1593; δH (200 MHz; DMSO-*d6*) 9.54 (s, 1 H), 8.81–8.78 (m, 2 H), 8.16 (s, 1 H), 7.79–7.76 (m, 2 H); δC (101 MHz; DMSO-*d6*) 149.1, 147.2, 145.4, 142.7, 135.3, 129.5, 125.8, 121.9; *m/z* (APCI) 232 (MH+, 100%); HRMS (APCI) 232.03834 ([M+H]+), calcd. for C10H7ClN5+ 232.03845.

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

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

**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>

**HRMS** (ESI+) found 267.02431 [M+H]+, C­­­­11H6ClF2N4 requires267.02436.

*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*

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

**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, ~10.4 mmol) and PIDA (3.35 g, 10.4 mmol); 15 h; purified by automated flash column chromatography over silica (Biotage Isolera, 15–100% EtOAc in petroleum benzine) to give the title compound as a yellow powder (2.65 g, 96% yield); **m.p** xx–2xx ˚C; **IR νmax** (film) /cm-1 xx; **1H NMR** (xx MHz, CDCl3) δ: ; **13C NMR** (xx MHz, CDCl3) δ:; **HRMS** (APCI+) found 300.02583 [M+H]+, C­­­­11H6ClF3N5 requires300.02594.

*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*

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

**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, ~10.4 mmol) and PIDA (3.35 g, 10.4 mmol); 7 h; purified by automated flash column chromatography over silica (Biotage Isolera, 15–100% EtOAc in petroleum benzine) to give the title compound as an orange solid (2.02 g, 82% yield); **m.p** xx–2xx ˚C; **IR νmax** (film) /cm-1 xx; **1H NMR** (xx MHz, CDCl3) δ: ; **13C NMR** (xx MHz, CDCl3) δ:; **m/z** (APCI+) 237 [M+H]+.

*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*

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

**5-Chloro-3-ethyl-[1,2,4]triazolo[4,3-*a*]pyrazine, OSM-S-222**

**

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

Prepared according to General Procedure **C** from: **OSM-S-316** (crude, ~6.92 mmol) and PIDA (2.23 g, 6.92 mmol); 2 h; purified by automated flash column chromatography over silica (Biotage Isolera, xx-xx% EtOAc in petroleum benzine) to give the title compound as xxx (xx g, xx% yield); **m.p** xx–2xx ˚C; **IR νmax** (film) /cm-1 xx; **1H NMR** (xx MHz, CDCl3) δ: ; **13C NMR** (xx MHz, CDCl3) δ:; **m/z** (APCI+) 183 [M+H]+.

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

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

***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, ~2.35 mmol) and PIDA (757 mg, 2.35 mmol); x h; purified by automated flash column chromatography over silica (Biotage Isolera, 15–100% EtOAc in petroleum benzine) to give the title compound as a brown/orange oil (xx g, xx% yield); **IR νmax** (film) /cm-1 xx; **1H NMR** (xx MHz, CDCl3) δ: ; **13C NMR** (xx MHz, CDCl3) δ:; **HRMS** (ESI+) found 360.11986 [M+Na]+, C­­­­15H20ClN5O2Narequires360.11977.

*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*

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

**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, ~10.4 mmol) and PIDA (3.35 g, 10.4 mmol); 15 h; purified by automated flash column chromatography over silica (Biotage Isolera, 15-–100% EtOAc in petroleum benzine) to give the title compound as a yellow solid (2.09 g, 87% yield); **m.p** xx–2xx ˚C; **IR νmax** (film) /cm-1 xx; **1H NMR** (200MHz, CDCl3) δ: 9.89 (1H, s), 7.87 (1H, s), 7.56-7.47 (5H, m); **13C NMR** (xx MHz, CDCl3) δ:; **m/z** (APCI+) 231 [M+H]+.

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

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

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

******

**HRMS** (ESI+) found 303.04075 [M+Na]+, C­­­­15H20ClN5O2Narequires303.04080.

*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*

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

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

******

**HRMS** (ESI+) found 297.01487 [M+Na]+, C­­­­12H7ClN4O2Narequires297.01497.

*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*

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

***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, 1 equiv.) was weighed into an oven-dried flask under Ar and 3,4-Difluorobenzaldehyde (1.00 g, 7.00 mmol) in CH2Cl2 (6 mL) and added at 0 ˚C. Trimethylsilyl cyanide (0.70 g, 0.90 mL, 7.00 mmol, 1 equiv.) was added at 0 ˚C and the reaction mixture stirred in the ice bath for 30 min before being allowed 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 yield a straw coloured oil (1.38 g) 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.[[3]](#endnote-3) Procedure adapted from the literature.[[4]](#endnote-4)

**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** (300MHz, CDCl­3) δ: 7.30–724 (1H, m), 7.16–7.10 (2H, m), 5.14 (1H, s), 3.79 (3H, s); **13C NMR** (76MHz, 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: -xxx; **HRMS** (xx+) found xx [M+x]+, xrequiresxxx.

*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.[[5]](#endnote-5)

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 column chromatography over silica (details of method required) to provide the title compound as a pale yellow oil (108 mg, 34% yield) and starting material xx mg; **IR νmax** (film) /cm-1 xx; **1H NMR** (xxMHz, CDCl­3) δ: etc. etc.

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

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

**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** (300MHz, 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).

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

**

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

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

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

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

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

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

**

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

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

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



*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*

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

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

**

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

*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*

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

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

**

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

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

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



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

*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*

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

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



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

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

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

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

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

**Ethyl 3-hydroxy-2-phenylpropanoate, OSM-S-335**

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*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*

*O=C(OCC)C(CO)C1=CC=CC=C1* ***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.), 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 column chromatography over silica (Biotage Isolera, 50–100% EtOAc in petroleum benzine) to give the title compound as a pale brown needles (85 mg, 32% yield); **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.

*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*

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

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



; **m.p** 156-157 ˚C; **IR νmax** (film) /cm-1 1604, 1505, 1435, 1364, 1297; **m/z** (ESI+) 373 [M+Na]+; **HRMS** (ESI+) found 373.08253 [M+Na]+, C19H15ClN4ONa requires 373.08266.

*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*

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

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



**m/z** (ESI+) 373 [M+Na]+; **HRMS** (ESI+) found 373.08256 [M+Na]+, C19H15ClN4ONa requires 373.08266.

*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*

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

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



; **m.p** 1263-125 ˚C; **IR νmax** (film) /cm-1 3067, 3030, 1609, 1501, 1361, 1317; **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**



**m/z** (ESI+) 317 [M+H]+; **HRMS** (ESI+) found 339.12160 [M+Na]+, C19H16N4ONa requires 339.12163.

*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*

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

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



**m/z** (ESI+) 375 [M+Na]+; **HRMS** (ESI+) found 375.10279 [M+Na]+, C19H14F2N4ONa requires 375.10279.

*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*

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

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



**m/z** (ESI+) 383 [M+Na]+; **HRMS** (ESI+) found 383.11132 [M+Na]+, C20H16N4O3Na requires 383.11146.

*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*

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

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



**m/z** (ESI+) 389 [M+Na]+; **HRMS** (ESI+) found 389.13701 [M+Na]+, C23H18N4ONa requires 389.13728.

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

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

**(±)-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.) in toluene (1 mL); 40 ˚C (oil bath temp.) 1h; purified by automated flash column chromatography over silica (Biotage Isolera, 25 g, 10–100% EtOAc in petroleum benzine) to give the title compound as a yellow solid (43 mg, 25%); **m.p.** xx ˚C; **IR νmax** (film) /cm-1; **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: **AEW 187-1** (53 mg, 0.34 mmol, 1.1 equiv.), **OSM-S-219** (80 mg, 0.31 mmol, 1.0 equiv.), KOH (58 mg, 1.0 mml, 3.3 equiv.) and 18-crown-6 (4.0 mg, 20 μmol, 0.05 equiv.) in toluene (1.5 mL); 40 ˚C (oil bath temp.) 1h; purified by automated flash column chromatography over silica (Biotage Isolera, 10 g, 10–100% EtOAc in petroleum benzine) to give the title compound as a pale brown solid (21 mg, 18%); **m.p.** xx ˚C; **IR νmax** (film) /cm-1; **1H NMR** (400 MHz, CDCl3): δ; **13C NMR** (101 MHz, CDCl3) δ: ; **HRMS** (ESI+) found xx [M+H]+, C­­­­21H18N5O2 requiresxxx.

# *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*

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

# 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 PRO B MEED TO REPEAT*

# m/z (APCI+) 333 [M+H]+; HRMS (ESI+) found 355.11654 [M+Na]+, C­­­­19H16N4O2Narequires355.11655.

# *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*

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

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

# 

# Phenylethyl mercaptan (60 μL, 60 mg, 0.4 mmol, 1 equiv.) and 23 (103 mg, 0.4 mmol, 1 equiv.) were reacted according to General Synthetic Procedure C. Purification (manual, 50–100% ethyl acetate/hexanes) gave the title compound as pearlescent cream stars (55 mg, 38%); mp 237–238 °C; νmax (film)/cm-1 2324, 1450, 1273; δH (500 MHz; DMSO-*d6*) 8.43 (d, *J* = 5.0 Hz, 1 H), 8.16–8.10 (m, 4 H), 7.89 (d, *J* = 5.0 Hz, 1 H), 7.34–7.23 (m, 5 H), 3.61 (tapp, *J* = 8.0, 7.5 Hz, 2 H), 3.06 (t, *J* = 7.5 Hz, 2 H); δC (126 MHz; DMSO-*d6*) 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 (MH+, 100%); HRMS (ESI) 358.11199 ([M+H]+), calcd. for C20H16N5S+ 358.11209.

# *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*

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

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

# 

# *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*

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

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

# 

2-­(3-Chlorophenyl)ethylamine (0.06 μL, 67 mg, 0.43 mmol, 1.1 equiv) and **23** (101 mg, 0.39 mmol, 1.0 equiv) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 17–100% ethyl acetate/hexanes) gave the title compound as a cream powder (25 mg, 17%); mp 246–248 °C; νmax (film)/cm-1 3250, 2923, 2227, 1573; δH (400 MHz; DMSO-*d6*) 8.40 (t, *J* = 5.6 Hz, 1 H), 8.14–8.08 (m, 4 H), 7.85 (d, *J* = 4.8 Hz, 1 H), 7.41 (d, *J* = 4.8 Hz, 1 H), 7.37–7.23 (m, 4 H), 3.75 (qapp, *J* = 6.8, 6.4 Hz, 2 H), 2.99 (t, *J* = 7.6 Hz, 2 H); δC (101 MHz; DMSO-*d6*) 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 (MH+, 100%); HRMS (ESI) 375.11174 ([M+H]+), calcd. for C20H16ClN6+ 375.11195.

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

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

# 

2-­(3-Chlorophenyl)ethylamine (50 μL, 56 mg, 0.36 mmol, 1.0 equiv.) and **26** (103 mg, 0.39 mmol, 1.1 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 12–100% ethyl acetate/hexanes) gave the title compound as a cream powder (46 mg, 33% yield); mp 191–193 °C; νmax (film)/cm-1 3248, 3111, 2917, 2034, 1975, 1613, 1582; δH (400 MHz; DMSO-*d6*) 8.35 (t, *J* = 5.6 Hz, 1 H), 7.94–7.91 (m, 2 H), 7.77 (d, *J* = 4.8 Hz, 1 H), 7.71–7.67 (m, 2 H), 7.37–7.23 (m, 5 H), 3.75 (m, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H); δC (101 MHz; DMSO-*d6*) 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 (MH+, 100%); HRMS (ESI) 384.07772 ([M+H]+), calcd. for C19H16ClN5+ 384.07773.

# *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*

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

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



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. (3,4-difluorophenyl)methanol (80 μL, 100 mg, 0.7 mmol, 1.2 equiv) and **26** (154 mg, 0.6 mmol, 1.0 equiv) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 30–100% ethyl acetate/hexanes) gave the title compound as fluffy white needles (86 mg, 38%); mp 181–182 °C; νmax (film)/cm-1 3070, 1612, 1509, 1303; δH (500 MHz; DMSO-*d6*) 9.11 (s, 1 H), 7.67 (s, 1 H), 7.66–7.64 (m, 2 H), 7.36–7.33 (m, 2 H), 7.13–7.05 (m, 3 H), 5.29 (s, 2 H); δC (126 MHz; DMSO-*d6*) 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 (MH+, 100%), 345 (52%) 318 (23%); HRMS (APCI) 373.06609 ([M+H]+), calcd. for C18H12ClF2N4O+ 373.06622.

*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*

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

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

# 

2-(3,4-Difluorophenyl)ethan-1-ol (98 mg, 0.62 mmol, 1.1 equiv.) and **37** (159 mg, 0.54 mmol, 1.0 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 50–100% ethyl acetate/hexanes) did not yield pure product. The product was purified a second time by flash chromatography over silica (20% ethanol/hexanes) before recrystallisation from ethyl acetate (washed with cold methanol) to give the title compound as white needles (43 mg, 19%); mp 111–112 °C; νmax (film)/cm-1 3074, 2956, 1612, 1508, 1118, 1046; δH (200 MHz; DMSO-*d6*) 9.05 (s, 1 H), 7.79–7.73 (m, 2 H), 7.60 (s, 1 H), 7.36 (t, *J*HF = 73.6 Hz, 1 H), 7.30–6.69 (m, 5 H), 4.51 (t, *J* = 6.2, 2 H), 2.90 (t, *J* = 6.2, 6.0 Hz, 2 H); δC (75 MHz; DMSO-*d6*) 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 Hz), 108.8, 70.6, 32.8; *m/z* (APCI) 419 (MH+, 100%); HRMS (APCI) 419.11215 ([M+H]+), calcd. for C20H15F4N4O+ 419.11256.

*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*

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

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

# 

# 2-Chlorophenethyl alcohol (0.18 mL, 210 mg, 1.3 mmol, 1.0 equiv.) and 35 (300 mg, 1.3 mmol, 1.0 equiv.) were reacted together according to General Synthetic Procedure C. Purification (Biotage isolera, 15–80% ethanol/hexanes/1% TEA) gave the title compound as light brown plates (56 mg, 12%); mp 132–134 °C; νmax (film)/cm-1 2959, 2926, 1602, 1507, 1465, 1359, 1239, 824; δH (200 MHz; DMSO-*d6*) 9.11 (s, 1 H), 8.67–8.64 (m, 2 H), 7.75 (s, 1 H), 7.71–7.68 (m, 2 H), 7.41 (dd, *J* = 7.8, 7.6, 1.2, 1.0 Hz, 1 H), 7.24 (tdapp, *J* = 7.8, 7.6, 7.4, 1.8, 1.6 Hz, 1 H) 7.14 (tdapp, *J* = 7.4, 7.2, 1.2 Hz, 1 H) 6.90 (dd, *J* = 7.4, 1.6 Hz, 1 H), 4.58 (t, *J* = 6.6, 6.4 Hz, 2 H), 3.03 (t, *J* = 6.6, 6.4 Hz, 2 H); δC (75 MHz; DMSO-*d6*) 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 (MH+, 100%) 324 (25%); HRMS (APCI) 352.09599 ([M+H]+), calcd. for C18H15ClN5O+ 352.09596.

*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*

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

**(*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**

**

# HRMS (ESI+) found 412.15807 [M+H]+, C­­­­21H20F2N5O2 requires412.15796.

*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*

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

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

****

# m/z (ESI+) 362 [M+Na]+; HRMS (ESI+) found 362.08222 [M+Na]+, C­­­­17H11F2N5ONarequires362.08239.

*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*

*FC1=CC(C2=NN=C3N2C(OCC4=NC=CC=C4)=CN=C3)=CC(F)=C1*

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

****

# m/z (ESI+) 370 [M+Na]+; HRMS (ESI+) found 370.09080 [M+Na]+, C­­­­18H13N5O3Narequires370.09106.

*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*

*C12=NN=C(C3=CC(OCO4)=C4C=C3)N1C(OCC5=NC=CC=C5)=CN=C2*

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

**

# m/z (ESI+) 376 [M+Na]+; HRMS (ESI+) found 376.11666 [M+Na]+, C­­­­21H15N5ONarequires376.11688.

*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*

*C12=NN=C(C3=CC(C=CC=C4)=C4C=C3)N1C(OCC5=NC=CC=C5)=CN=C2*

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

****

**AEW 256-1**

**m.p** 175-177 ˚C; **IR νmax** (film) /cm-1 3070, 3019, 1613, 1504, 1460, 1370, 1322;

# m/z (ESI+) 392 [M+Na]+; HRMS (ESI+) found 392.09295 [M+Na]+, C­­­­18H13F2N5O2Narequires392.09295.

*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*

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

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

******

**HRMS** (ESI+) found 301.05084 [M+Na]+, C­­­­12H8F2N4O2Narequires301.05075.

*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*

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

***3. Amide Synthesis***

**3.1 Amide Coupling**

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

****

Representative Example:

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 furnish 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* 1.9Hz), 7.83 (1H, dd, *J* 8.2 and 1.1), 7.41 (1H, t, *J* 8.1), 7.22 (1H, dd, *J* 7.9 and 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.

*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)*

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

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

**

Representative Example:

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 furnish 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* 1.2 and 8.0), 7.27 (1H, dd, *J* 1.3 and 8.2), 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]+).

*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)*

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

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



Representative Example:

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 furnish 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 and 1.6), 7.21 (1H, ddd, *J* 8.2, 6.6 and 1.7), 7.15 (1H, dd, *J* 8.2 and 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]+).

*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)*

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

**6-Chloro-*N*-(5-chloro-2-methylphenyl)pyrazine-2-carboxamide**

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Representative Example:

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 furnish the title compound as 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 and 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]+).

*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)*

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

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



*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)*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

***3.2 Hydrazine displacement***

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



*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)*

*O=C(NC1=CC(Cl)=CC=C1)C2=NC(NN)=CN=C2*

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



*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)*

*O=C(NC1=C(C)C(Cl)=CC=C1)C2=NC(NN)=CN=C2*

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



*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)*

*O=C(NC1=C(F)C(Cl)=CC=C1)C2=NC(NN)=CN=C2*

***N*-(5-Chloro-2-methylphenyl)-6-hydrazinylpyrazine-2-carboxamide**



*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)*

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

**N-(3,5-Bis(trifluoromethyl)phenyl)-6-hydrazinylpyrazine-2-carboxamide**



*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)*

*O=C(NC1=CC(C(F)(F)F)=CC(C(F)(F)F)=C1)C2=CN=CC(NN)=N2*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

***3.3 Condensation Reaction***

**(E)-N-(3,5-Bis(trifluoromethyl)phenyl)-6-(2-(4-(difluoromethoxy)benzylidene)hydrazinyl)pyrazine-2-carboxamide**



*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-*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

**N-(3,5-bis(Trifluoromethyl)phenyl)-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine-5-carboxamide. OSM-S-206**



*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)*

All approaches:

Example (AEW 120-1):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (500 MHz, CD3CN): 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 (xx MHz, CD3CN) δ: 19F {1H} NMR (xx MHz, CD3CN) δ: -63.7, -83.9; IR νmax (neat) /cm-1 ; HRMS submitted.

Literature

Compound:

Procedure:

**(6-Chloropyrazin-2-yl)(4-fluoroisoindolin-2-yl)methanone**



*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*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

**(4-Fluoroisoindolin-2-yl)(6-hydrazinylpyrazin-2-yl)methanone**



*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)*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

**(E)-(6-(2-(4-(Difluoromethoxy)benzylidene)hydrazinyl)pyrazin-2-yl)(4-fluoroisoindolin-2-yl)methanone**



*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-*

All approaches:

Example (xxx -x):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

**4-(5-(4-Fluoroisoindoline-2-carbonyl)-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)benzonitrile. OSM-S-207**



*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*

All approaches:

Example (AEW 133-1):

Prepared according to general procedure x from:

Prep:

m.p. xx ˚C; 1H NMR (xx MHz, CDCl3): ;13C NMR (xx MHz, CDCl3) δ: {1H} NMR (xx MHz, CDCl3) δ: xx ; IR νmax (neat) /cm-1 ; HRMS.

Literature

Compound:

Procedure:

1. Dunetz JR, Xiang Y, Baldwin A, Ringling J (2011) General and scalable amide bond formation with epimerization-prone substrates using T3P and pyridine. *Org. Lett.*, 13:5048– 5051. (10.1021/ol201875q) [↑](#endnote-ref-1)
2. Bradac J, Furek Z, Janezic D, Molan S, Smerkolj I, Stanovnik B, Tisler M, Vercek B (1977) Telesubstitution and other transformations of imidazo[1,2-a]- and s-triazolo[4,3-a]pyrazines. *J. Org. Chem.*, 42:4197–4201. (10.1021/jo00862a005)   [↑](#endnote-ref-2)
3. CRO Briefing Document Link [↑](#endnote-ref-3)
4. Massolini G, Fracchiolla G, Calleri E, Carbonara G, Temporini C, Lavecchia A, Cosconati S, Novellino E, Loiodice F (2006) Elucidation of the enantioselective recognition mechanism of a penicillin G acylase-based chiral stationary phase towards a series of 2-aryloxy-2-arylacetic acids. *Chirality*, 18:633–643. (10.1002/chir.20300) [↑](#endnote-ref-4)
5. CRO Briefing Document Link [↑](#endnote-ref-5)