***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.

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. Sadana AK, Mirza Y, Aneja KR, Prakash O (2003) Hypervalent iodine mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-a] pyridines and 1-aryl/hetryl 5-methyl-1,2,4-triazolo[4,3- a]quinolines as antibacterial agents. *Eur. J. Med. Chem.*, 38:533–536, 2003. (10.1016/ S0223-5234(03)00061-8) [↑](#endnote-ref-2)