Synthesis of 3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (16)

1. 1-Chloro-4-hydrazinophthalazine

1,4-Dichlorophthalazine (480 g, 2.41 mol), ethanol (5.1 L) and ammonium hydroxide (sp. gr. 0.88, 210 mL) were combined in a 10 L 3-necked flask equipped with a stirrer, coil condenser, temperature probe and dropping funnel. The mixture was heated to 60 °C and hydrazine hydrate (420 mL, 8.62 mol) was added *via* a dropping funnel. After *ca.* 100 mL was added there was an exotherm (internal temperature 74 °C) and the mixture became very thick. The reaction was allowed to cool to 68 °C and the remaining hydrazine was added over 10 minutes. The reaction mixture was then heated to reflux for 10 minutes and allowed to cool down to room temperature. The yellow precipitate formed was filtered and washed with water (500 mL) and ethanol (500 mL). The solid was dried over KOH at 40 °C to give the product in 74% purity by HPLC. This material (373 g) was recrystallised from hot acetonitrile (3.25 L) to provide the product (363 g, 80%) as a yellow solid. ^{1}H NMR (250 MHz, d_6-DMSO) δ 7.84 - 8.04 (3H, m, Ar-H), 8.20 (1H, m, Ar-H); MS (ES^+) m/e 194 [MH^+].

2. 6-Chloro-3-(5-methylisoxazol-3-yl)-1,2,4-triazolo[3,4-a]phthalazine

5-Methylisoxazole-3-carboxylic acid (5.24 g, 41.3 mmol), bis-2-oxo-3-oxazolidinyl phosphinic chloride (10.5 g, 41.2 mmol) and triethylamine (11.5 mL, 82.5 mmol) were added successively to a stirred suspension of 1-chloro-4-hydrazinophthalazine (8.00 g, 41.2 mmol) in dichloromethane (1 L) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 2 h and at room temperature overnight. The solvent was evaporated *in vacuo* and the residue triturated with water. The solid was filtered off, washed with hexane and dried *in vacuo* to give the hydrazide (11 g), MS (ES^+) m/e 304 [MH^+]. This was heated at reflux in xylene (500 mL) with triethylamine hydrochloride (2.2 g, 20% w/w) for 3 h. The mixture was cooled to room temperature and the solvent evaporated *in vacuo*. The residue was dissolved in dichloromethane, washed with water (2x), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting solid was recrystallised (dichloromethane/hexane) to

give the title phthalazine (6.80 g, 58%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.59 (3H, s, Me), 6.90 (1H, s, isoxazole-H), 7.95 (1H, m, Ar-H), 8.07 (1H, m, Ar-H), 8.34 (1H, d, J=7.9Hz, Ar-H), 8.78 (1H, d, J=7.8Hz, Ar-H); MS (ES^+) m/e 286 [MH^+].

3. Synthesis of 4-hydroxymethyl-1-methyl-1,2,3-triazole

a) Methyl 1,2,3-triazole-4-carboxylate

(Reference: Klein, R. S.; Heras de Las, P. G.; Tam, S. Y.-K.; Wempen, I.; Fox, J. J. *J. Het. Chem.* **1976**, *13*, 589)

Six sealed tubes, each containing a mixture of methyl propiolate (4.45 mL, 50.0 mmol) and trimethylsilylazide (16.5 mL, 124 mmol), were heated in parallel at 105 °C for 90 h. The reaction mixtures were cooled, combined and methanol (36 mL) was added dropwise with cooling. The solid formed was allowed to stand for 0.5 h then ether was added. The solid was filtered off, washed with ether, then with hexane, and recrystallised from methanol/ether to give the product (29.7 g, 78%) as a colourless solid. ^{1}H NMR (360MHz, d_6-DMSO) δ 3.85 (3H, s, OMe), 8.56 (1H, s, triazole-H), 15.75 (1H, br s, NH); MS (ES^+) *m/e* 128 [MH^+].

b) Methyl 1-methyl-1,2,3-triazole-4-carboxylate

(Reference: Bennet, I. S.; Brooks, G.; Broom, N. J. P.; Calvert, S. H.; Coleman, K.; Francois, I., *J. Antibiotics*, **1991**, *44*, 969)

To methyl 1,2,3-triazole-4-carboxylate (29.7 g, 234 mmol) in *N,N*-dimethylformamide (480 mL) at 0 °C under nitrogen, was added potassium carbonate (19.4 g, 140 mmol) and methyl iodide (15.3 mL, 246 mmol). The mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature and stirred for 16 h. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (4x) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica, eluting with 60% then 80% ethyl acetate/hexane and finally ethyl acetate to yield the product as a colourless solid (8.86 g, 27%). ^{1}H NMR (360MHz, $CDCl_3$) δ 3.95 (3H, s, NMe), 4.17 (3H, s, OMe), 8.07 (1H, s, triazole-H); MS (ES^+) 142 [MH^+].

c) 4-Hydroxymethyl-1-methyl-1,2,3-triazole

To methyl 1-methyl-1,2,3-triazole-4-carboxylate (8.86 g, 62.8 mmol) in THF at 0 °C under nitrogen was added lithium aluminum hydride (62.8 mL of a 1.0 M solution in THF, 62.8 mmol) dropwise. The mixture was stirred at 0 °C for 0.5 h, then warmed to room temperature and stirred for 1 h. The reaction was cooled once again to 0 °C and saturated sodium sulphate solution (63 mL) was carefully added dropwise. The mixture was then warmed to room temperature, stirred for 1 h and then filtered through Hyflo Super Cel®, washing several times with THF. The solvent was evaporated *in vacuo* and the residue azeotroped with ethanol. The residue was purified by chromatography on silica eluting with dichloromethane followed by 10% methanol/dichloromethane to give the product (6.90g, 97%) as a colourless oil. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.88 (1H, br s, OH), 4.77 (2H, d, OCH_2), 4.09 (3H, s, NMe), 7.53 (1H, s, triazole-H); MS (ES^+) *m/e* 114 [MH^+].

4. 3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (16)

To 4-hydroxymethyl-1-methyl-1,2,3-triazole (0.637 g, 5.63 mmol) in dimethylformamide (150 mL) at -10 °C under nitrogen was added lithium bis(trimethylsilyl)amide (6.15 mL of a 1M solution in THF, 6.15 mmol). The mixture was stirred for 0.5 h and 6-chloro-3-(5-methylisoxazol-3-yl)-1,2,4-triazolo[3,4,a]phthalazine (1.60 g, 5.60 mmol) was added in one portion. The mixture was then allowed to warm to room temperature and stirred for 16 h. Water (100 mL) was added and the resulting precipitate was filtered off, washed with water, then hexane, and air-dried. The solid was purified by chromatography on silica using gradient elution from 1% to 3% methanol/dichloromethane to yield the product (1.13 g, 61%) as a colourless solid, mp. 260-262 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.60 (3H, s, Me), 4.09 (3H, s, Me), 5.78 (2H, s, CH_2), 6.90 (1H, d, J=0.8 Hz, isoxazole-H), 7.80 (1H, m, Ar-H), 7.94 (1H, m, Ar-H), 8.25 (1H, d, J=8.0 Hz, Ar-H), 8.65 (1H, d, J=8.0 Hz, Ar-H), 8.73 (1H, s, triazole-H); MS (ES^+) m/e 363 [MH^+]. Anal. Calcd. for $C_{17}H_{14}N_8O_2$: C, 56.35; H, 3.89; N, 30.92. Found C, 56.27, H, 3.69, N, 30.69.

6-[(6-Methylpyridin-2-yl)methyloxy]-3-phenyl-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine Hydrochloride (4): mp 255°C; ^{1}H NMR (360MHz, d_6-DMSO) δ 1.42 (4H, m, 2 of CH_2), 1.91 (4H, m, 2 of CH_2), 2.71 (3H, s, Me), 3.51 (1H, s, CH), 3.78 (1H, s, CH), 5.80 (2H, s, CH_2), 7.59 (4H, m, Ar-H), 7.80 (1H, d, J=7.8Hz, Ar-H), 8.22 (1H, m, Ar-H), 8.30 (2H, d, J=7.9Hz, Ar-H); MS (ES^+) m/e 398 [MH^+]. Anal. Found C, 61.67; H, 5.36; N, 14.74. $C_{24}H_{23}N_5O$.HCl requires C, 61.28; H, 5.36; N, 14.89%.

3-(3-Methyl-1,2,4-oxadiazol-5-yl)-6-[(6-methylpyridin-2-yl)methyloxy]-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine (5): mp 191-193°C; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.38-1.56 (4H, m, 2 of CH_2), 1.86-2.03 (4H, m, 2 of CH_2), 2.60 (6H, s, 2 of Me), 3.62 (1H, s, CH), 4.02 (1H, s, CH), 5.62 (2H, s, CH_2), 7.14 (1H, d, J=7.7Hz, Ar-H), 7.49 (1H, d, J=7.7Hz, Ar-H), 7.65 (1H, t, J=7.7Hz, Ar-H); MS (ES^+) m/e 404 [MH^+]. Anal. Found C, 61.90; H, 5.10; N, 23.50. $C_{21}H_{21}N_7O_2$.0.1(ethyl acetate).0.2H_2O requires C, 61.81; H, 5.38; N, 23.58%.

6-[(6-Methylpyridin-2-yl)methyloxy]-3-(3-thienyl)-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine (10): ^{1}H NMR (250MHz, $CDCl_3$) δ 1.39-1.57 (4H, m, 2 of CH_2), 1.86-2.00 (4H, m, 2 of CH2), 2.63 (3H, s, Me), 3.57 (1H, s, CH), 3.96 (1H, s, CH), 5.58 (2H, s, CH_2), 7.14 (1H, J=7.6Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.30 (1H, d, J=7.7Hz, Ar-H), 7.56 (1H, m, Ar-H), 7.63 (1H, dd, J=7.7 and 7.6Hz, Ar-H), 8.40 (1H, s, Ar-H); MS (ES^+) m/e 404 [MH^+]. Anal. Found C, 65.25; H, 5.31; N, 17.33. $C_{22}H_{21}N_5OS$ requires C, 65.51, H, 5.21, N, 17.37%.

3-(3-Furyl)-6-[(6-methylpyridin-2-yl)methyloxy]-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine (11): mp 205-206°C; ^{1}H NMR (250MHz, $CDCl_3$) δ 1.38-1.56 (4H, m, 2 of CH_2), 1.84-2.02 (4H, m, 2 of CH_2), 2.63 (3H, s, Me), 3.58 (1H, s, CH), 3.96 (1H, s, CH), 5.58 (2H, s, CH_2), 7.14 (1H, d, J=7.6Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.31 (1H, d, J=7.7Hz, Ar-H), 7.56 (1H, m, Ar-H), 7.64 (1H, dd, J=7.7 and 7.6Hz, Ar-H), 8.50 (1H, s, Ar-H); MS (ES^+) m/e 388 [MH^+]. Anal. Found C, 67.23; H, 5.41; N, 17.51. $C_{22}H_{21}N_5O_2$.0.25H_2O requires C, 67.41; H, 5.53; N, 17.87%.

3-(5-Methylisoxazol-3-yl)-6-[(6-methylpyridin-2-yl)methyloxy]-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine (12): mp 223-225°C; ^{1}H NMR (250MHz, $CDCl_3$) δ 1.38-1.54 (4H, m, 2 of CH_2), 1.84-1.98 (4H, m, 2 of CH_2), 2.58 (3H, s, Me), 2.60 (3H, s, Me), 3.58 (1H, s, CH), 3.98 (1H, s, CH), 5.59 (2H, s, CH_2), 6.85 (1H, s, Ar-H), 7.14 (1H, d, J=7.7Hz, Ar-H), 7.44 (1H, d, J=7.6Hz, Ar-H), 7.64 (1H, dd, J=7.7 and 7.6Hz, Ar-H); MS (ES^+) m/e 403 [MH^+]. Anal. Found C, 64.91; H, 5.38; N, 20.28. $C_{22}H_{22}N_6O_2.0.3H_2O$ requires C, 64.79; H, 5.58; N, 20.60%.

3-(5-Methylisoxazol-3-yl)-6-[(6-methylpyridin-2-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (13): ^{1}H NMR (360MHz, $CDCl_3$) δ 2.59 (3H, d, J=0.8Hz, Me), 2.61 (3H, s, Me), 5.73 (2H, s, CH_2), 6.86 (1H, d, J=0.8Hz, Ar-H), 7.16 (1H, d, J=7.6Hz, Ar-H), 7.53 (1H, d, J=7.5Hz, Ar-H), 7.66 (1H, t, J=7.7Hz, Ar-H), 7.83 (1H, m, Ar-H), 7.97 (1H, t, J=8.2Hz, Ar-H), 8.33 (1H, d, J=7.7Hz, Ar-H), 8.70 (1H, d, J=7.7Hz, Ar-H); MS (ES^+) m/e 373 [MH^+]. Anal. Found. C, 60.72; H, 4.15; N, 21.20. $C_{20}H_{16}N_6O_2.1.15H_2O$ requires C, 61.11; H, 4.69; N, 21.38%.

3-(5-Methylisoxazol-3-yl)-6-[(2-pyridyl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (14): mp 234-236°C; ^{1}H NMR (360MHz, $CDCl_3$) δ 2.59 (3H, d, J=0.8Hz, Me), 5.77 (2H, s, CH_2), 6.82 (1H, d, J=0.8Hz, Ar-H), 7.30 (1H, m, Ar-H), 7.74-7.85 (3H, m, Ar-H), 7.95 (1H, m, Ar-H), 8.33 (1H, d, J=7.8Hz, Ar-H), 8.64-8.72 (2H, m, Ar-H); MS (ES^+) m/e 359 [MH^+]. Anal. Found. C, 62.93; H, 3.56; N, 22.94. $C_{19}H_{14}N_6O_2.0.05$ (CH_2Cl_2) requires C, 63.10; H, 3.92; N, 23.17%.

3-(5-Methylisoxazol-3-yl)-6-[(2-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (15): mp 223-225°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.59 (3H, s, Me), 4.21 (3H, s, Me), 5.73 (2H, s, CH_2), 6.89 (1H, s, Ar-H), 7.79 (1H, m, Ar-H), 7.94 (1H, m, Ar-H), 8.10 (1H, s, Ar-H), 8.22 (1H, d, J=8.0Hz, Ar-H), 8.67 (1H, d, J=8.0Hz, Ar-H); MS (ES^+) m/e 363 [MH^+]; HRMS (m/e) for $C_{17}H_{15}N_8O_2$ [MH^+] 363.1318, found 363.1279.

3-(5-Methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-5-yl)methyloxy]-1,2,4-triazolo[3,4-a]phthalazine (17): mp 288-290°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 2.56 (3H, s, Me), 4.19 (3H, s, Me), 5.76 (2H, s, CH_2), 6.82 (1H, s, Ar-H), 7.80 (1H, m, Ar-H), 7.96 (1H, m, Ar-H), 8.04 (1H, s, Ar-H), 8.12 (1H, d, J=8.8Hz, Ar-H), 8.67 (1H, d, J=8.0Hz, Ar-H); MS (ES^+) m/e 363 [MH^+]; HRMS (m/e) for $C_{17}H_{15}N_8O_2$ [MH^+] 363.1318, found 363.1303. Anal. Found. C, 55.78; H, 3.93; N, 30.17. $C_{17}H_{14}N_8O_2.0.25H_2O$ requires C, 55.66; H, 3.98; N, 30.55%.