Supporting Information

Rational Design, Synthesis and Testing of Novel Tricyclic Topoisomerase Inhibitors for the Treatment of Bacterial Infections Part 1

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Synthetic Procedures

General Information

All reactions were carried out using commercial materials and reagents without further purification unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC). Visualization of the spots on TLC plates was achieved by UV light and by staining the TLC plates in potassium permanganate and charring with a heat gun, unless otherwise stated.

NMR spectral data was recorded on a LC Bruker AV400 using a 5 mm QNP probe or Bruker AVIII 400 Nanobay using a 5 mm BBFQ with z-gradients. Chemical shifts are expressed in parts per million values (ppm) and are designated as s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); quint (quintet) or m (multiplet). Where appropriate, COSY and NOE experiments were carried out to aid assignment.

Chromatography was performed on a an ISCO using silica (normal phase or C18 (reverse phase; or by flash-column chromatography using silica gel (Fluorochem silica gel 60A 40-63 μm).

LCMS methods

Method A: Instrument: **Waters Acquity UPLC H-Class system;** Column: Column: Gemini NX C18. 5 μm, 50 x 2 mm; eluent A: water, eluent B: acetonitrile, eluent C: 2 vol % ammonia (35%) in water, eluent D: 2 vol % formic acid in water; gradient: 0-4.0 min 5-95% B with A, 4.0-4.45 min 95% B, 4.45-4.5 min 95-5% B with A, 4.5-5.0 min 5% B; flow 1.0 ml/min; injection volume: 10 μL

Method B: Instrument: **Waters Acquity UPLC H-Class system;** Column: Waters XBridge C18, 5 μm, 50×2.1 mm; eluent A: water, eluent B: acetonitrile, eluent C: 2 vol % ammonia

(35%) in water, eluent D: 2 vol % formic acid in water; gradient: 0-4.0 min 5-95% B with A, 4.0-4.45 min 95% B, 4.45-4.5 min 95-5% B with A, 4.5-5.0 min 5% B; flow 0.8 ml/min; injection volume: 10 µL

Method C: Instrument: **Waters Acquity UPLC H-Class system;** Column: Acquity BEH C18 1.7 µm 2.1 x 50 mm; eluent A: water, eluent B: acetonitrile, eluent C: 2 vol % ammonia (35%) in water, eluent D: 2 vol % formic acid in water; gradient: 0-0.3 min 5% B, 0.3-2.0 min 5-95% B with A, 2.0-2.6 min 95-5% B with A, 2.6-3 min 5% B; flow 0.6 ml/min; injection volume: 2 µL

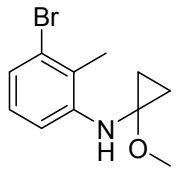
Method D: Instrument: **Waters Acquity UPLC H-Class system;** Column: Column: YMC Triart-C18 50 x 2 mm; eluent A: water, eluent B: acetonitrile, eluent C: 1 vol % formic acid in 50/50 water/acetonitrile; gradient: 0-4.0 min 0-95% B with A, 5% C, 4.0-4.5 min 95% B, 5% C throughout, 4.4-4.5 min 95-5% B with A; flow 0.8 ml/min; injection volume: 5 µL

Method E: Instrument: **Waters Acquity UPLC H-Class system;** Column: Column: YMC Triart-C18 50 x 2 mm; eluent A: water, eluent B: acetonitrile, eluent C: 1 vol % formic acid in 50/50 water/acetonitrile; gradient: 0-2.0 min 95% A, 5% C, 2.0-12 min 0-95% B with A, 5% C throughout, 12-14 min 95% B with 5% C; flow 0.8 ml/min; injection volume: 5 µL

S1: Synthesis of REDX04139

REDX04139 - 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

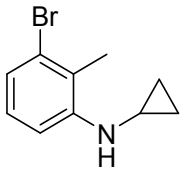
(a) Compound (2) 3-bromo-N-(1-methoxycyclopropyl)-2-methyl-aniline



To a stirring solution of 3-bromo-2-methyl-aniline (14.6 mL, 118.25 mmol) in MeOH (200 mL) was added acetic acid (27.1 mL, 472.99 mmol). To the solution was added (1-ethoxycyclopropoxy)-trimethyl-silane (28.5 mL, 141.9 mmol) dropwise at room temperature and the resulting reaction mixture was heated to reflux overnight. The mixture was concentrated *in vacuo* to obtain the title product as colourless oil in quantitative yield, which was used without further purification.

LC-MS (Method A) 256.3/258.3 $[M+H]^+$; RT 2.85 min

(b) Compound (3) 3-bromo-N-cyclopropyl-2-methyl-aniline

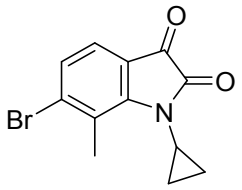


To a solution of 3-bromo-N-(1-methoxycyclopropyl)-2-methyl-aniline (31.0 g, 121.03 mmol) in THF (50 mL) was added borane THF complex (242.1 mL, 242.06 mmol) dropwise at 0°C over 20 min. The resulting mixture was allowed to warm to room temperature, stirred for 3 h and then refluxed for 18 h. The reaction mixture was cooled to room temperature and carefully quenched with MeOH until bubbling stopped. Organic solvents were removed under reduced pressure. The residue was then poured into H_2O (200 mL) and extracted with Et_2O (3 x 50 mL).

The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 3-bromo-N-cyclopropyl-2-methyl-aniline in quantitative yield. The product was used in the next step without further purification.

LC-MS (Method A) 226.3/228.3 $[M+H]^+$; RT 3.07 min

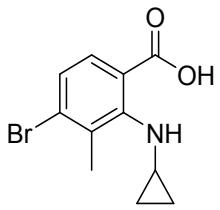
(c) Compound (4) 6-bromo-1-cyclopropyl-7-methyl-indoline-2,3-dione



A solution of 3-bromo-N-cyclopropyl-2-methyl-aniline (26.3 g, 116.32 mmol) and oxalyl chloride (22.5 mL, 261.71 mmol) in Et_2O (150 mL) was heated to reflux for 18 h. After all starting material was consumed (followed by LCMS); the reaction mixture was concentrated under reduced pressure to remove excess oxalyl chloride. The residue was dissolved in DCM (250 mL) and the resultant solution was added dropwise to a stirring solution of aluminium trichloride (62.0 g, 465.26 mmol) in DCM (250 mL) at 0^{o}C. The resulting reaction mixture was left to stir at the room temperature for 18 h before concentrating under reduced pressure. The residue was diluted with EtOAc, and carefully quenched with aqueous $NaHCO_3$. Multiple extractions and washes of organic layers were combined, washed with brine and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* to give the crude product, which was purified by flash chromatography eluting with DCM to give 6-bromo-1-cyclopropyl-7-methyl-indoline-2,3-dione (6.9 g, 21 %) as a bright orange solid.

LC-MS (Method A) 280.3/282.3 $[M+H]^+$; RT 2.34 min

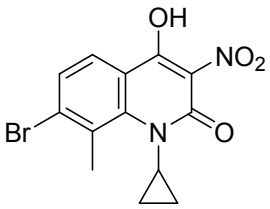
(d) Compound (5) 4-bromo-2-(cyclopropylamino)-3-methyl-benzoic acid



To a solution of 6-bromo-1-cyclopropyl-7-methyl-indoline-2,3-dione (790 mg, 2.82 mmol) in 2M aq. NaOH (15 mL, 798.81 mmol) at 0 °C, was added H_2O_2 (1.2 mL, 39.07 mmol) dropwise and the resulting reaction mixture was left to stir at room temperature for 2 h. After completion of the reaction, (monitored by LCMS), the reaction mixture was acidified to pH = 4~5 with 2M aq HCl and then extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 4-bromo-2-(cyclopropylamino)-3-methyl-benzoic acid (760 mg, 99 %) as a pale yellow-beige colour solid.

(LC-MS (Method A) 270.3/272.3 $[M+H]^+$; RT 2.29 min

(e) Compound (7) 7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-3-nitroquinolin-2(1H)-one



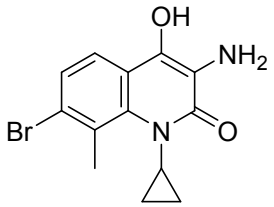
To a solution of 4-bromo-2-(cyclopropylamino)-3-methyl-benzoic acid (18 g, 66.64 mmol) (compound 4) in dry THF (360 mL) at room temperature under N_2 atmosphere was added triphosgene (11.8 g, 39.85 mmol) in one portion. This was allowed to stir at room temperature for 3 h, after which time the solvent was carefully removed *in vacuo* (rotary evaporator bath was prohibited from reaching >40 °C, vacuum was set at 1 mbar, and reached between 1-10 mbar) to afford a thick red oil which was diluted with dry THF (450 mL) under a

N_2 atmosphere. To the resulting solution Et_3N (74.3 mL, 533.1 mmol) was added dropwise, followed by the addition of ethyl nitroacetate (11.1 mL, 99.96 mmol) in one portion. The reaction mixture was heated to 60 °C overnight, after which time the solvent was *removed in vacuo*. The residue was then partitioned between EtOAc (100 mL) and brine (100 mL). 2M aqueous HCl was then added to adjust the pH to around 3.

The organic phase was separated, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give an orange oil. Purification by flash column chromatography eluting initially with 50-100% EtOAc in Petroleum ether (40-60) switching to 5-10% MeOH in DCM gave 7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-3-nitro-quinolin-2-one (6 g, 27 %) as a yellow solid.

LC-MS (Method B) 339.3/341.2 $[M+H]^+$; RT 1.60 min.

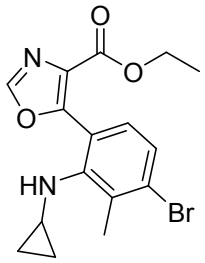
(f) Compound (8) 3-Amino-7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-quinolin-2-one



Sodium hydrosulfite (3.5 g, 20.1 mmol) was added to a stirred solution of 7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-3-nitro-quinolin-2-one (2.6 g, 8.04 mmol) in EtOH (20 mL) and H_2O (4 mL) and heated to reflux for 1 h. The reaction mixture was filtered through filter paper and the solvent removed *in vacuo.* Purification by flash column chromatography eluting with 0-10% MeOH in DCM gave 3-amino-7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-quinolin-2-one as a yellow crystalline solid. Yield assumed quantitative.

LC-MS (Method A) 308.9/310.8 $[M+H]^+$; RT 1.38 min.

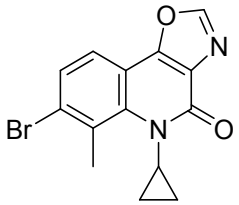
(e) Compound (9a) step 1: Ethyl 5-[4-bromo-2-(cyclopropylamino)-3-methyl-phenyl]oxazole-4-carboxylate (Scheme 1, ROUTE B)



To a solution of 4-bromo-2-(cyclopropylamino)-3-methyl-benzoic acid (530 mg, 1.96 mmol) in dry THF (15 mL) at room temperature under N_2 was added triphosgene (348 mg, 1.17 mmol) in one portion. After stirring at room temperature for 3 h the solvent was carefully removed *in vacuo*. To the resulting residue under N_2 was added dry THF (10 mL), followed by Et_3N (2.18 mL, 15.7 mmol) dropwise. To the resulting mixture was added ethyl isocyanoacetate (0.32 mL, 2.94 mmol) in one portion and the reaction heated to 60^oC overnight. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was then partitioned between EtOAc (20 mL) and brine (20 mL). 2M aqueous HCl was then added to adjust the aqueous pH to around 3. The EtOAc layer was then separated, washed 4 times with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with 50% Petroleum ether (40-60)/EtOAc to afford ethyl 5-[4-bromo-2-(cyclopropylamino)-3-methyl-phenyl]oxazole-4-carboxylate (370 mg, 52 %) as an off-white solid.

LC-MS (Method A) 365.3/367.3 $[M+H]^+$; RT 2.72 min

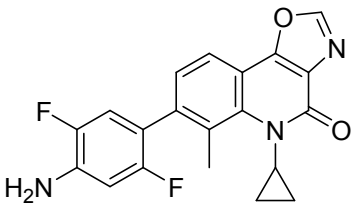
(f) Compound (9a) step 2: 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (Scheme 1, ROUTE B)



To a solution of ethyl 5-[4-bromo-2-(cyclopropylamino)-3-methyl-phenyl]oxazole-4-carboxylate (370 mg, 1.01 mmol) in dry DMF (5 mL) was added NaH (60% dispersed in mineral oil) (61 mg, 1.52 mmol) in one portion. This was then heated to 100 ^{o}C for 1 h, after which time the reaction mixture was cooled to room temperature. EtOAc and H_2O were added and the layers separated. The aqueous layer was washed once with EtOAc and the combined organic extracts were washed a further 4 times with H_2O to remove DMF. The combined organic extracts were dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography using 50% Petroleum ether (40-60)/EtOAc as the eluent system to afford 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (112 mg, 35 %) as an off white solid.

LC-MS (Method A) 319.3/321.3 $[M+H]^+$; RT 2.13 min

(g) REDX04139 - 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



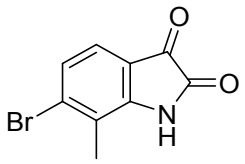
A mixture of 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (213 mg, 0.67 mmol), 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (204 mg, 0.80 mmol), Cs_2CO_3 (326 mg, 1 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (65 mg, 0.08 mmol) in toluene (3 mL), IPA (1 mL) and H_2O (1 mL) was heated to 70^oC for 1.5 h. The reaction mixture was filtered through Celite and concentrated to dryness. The mixture was then redissolved in MeOH and purified by flash chromatography using a gradient eluent system of 100% Petroleum ether (40-60) to 100% EtOAc. The fractions containing the desired product were combined and concentrated *in vacuo* and triturated with ice cold Et_2O to give 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as a yellow solid (41 mg, 17 %).

^1H NMR (400MHz, $CDCl_3$): δ ppm 8.07 (s, 1H), 7.76 (d, J = 7.8 Hz 1H), 7.21 (d, J = 7.2 Hz, 1H), 6.97-6.93 (m, 1H), 6.63- 6.59 (m, 1H), 4.00 (s, 2H), 3.66-3.60 (m, 1H), 2.53 (s, 3H), 1.27-1.19 (m, 2H), 0.67-0.65 (m, 2H); LC-MS (Method A) 368.4 $[M+H]^+$; RT 2.10 min

REDX05028 - 7-(4-Amino-2,5-difluoro-phenyl)-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

7-(4-Amino-2,5-difluoro-phenyl)-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

(a) Compound (12) 6-bromo-7-methyl-indoline-2,3-dione (commercially available)



A mixture of 3-bromo-2-methylaniline (10 mL, 60.52 mmol), chloral hydrate (14.9 g, 89.9 mmol) and anhydrous Na_2SO_4 (94.6 g, 665.7 mmol) in hydrochloric acid (6.4 mL, 211.2 mmol) and H_2O (700 mL) was stirred vigorously at room temperature overnight. To the resulting mixture, hydroxylamine hydrochloride (5.9 g, 84.3 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was ice cooled, and the resulting precipitate was collected by vacuum filtration and washed copiously with H_2O and dried under suction. The precipitate was re-dissolved in EtOAc (~500 mL) and washed with H_2O (300 mL) and brine (300 mL) then dried over $MgSO_4$. The resulting filtrate was removed *in vacuo* to give 6-bromo-7-methyl-indoline-2,3-dione as a dark brown solid (16.5 g, 100%), which was used directly in the next step without further purification.

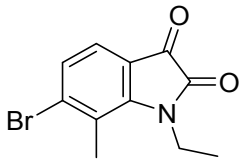
LC-MS (Method A) 255/257.0 $[M+H]^+$; RT 1.77 min.

To (2E)-N-(3-bromo-2-methyl-phenyl)-2-hydroxyimino-acetamide (16.55g, 64.38mmol) was added Sulfuric Acid (16.19mL, 303.76mmol) which was stirred at 50 ^oC until the solid had dissolved then the reaction mixture was stirred at 80 ^oC for 2.5 hours. The reaction mixture was subjected to hot filtration under vacuum and the precipitate collected, washed with water, a saturated aqueous solution of K_2CO_3, and water then dried in a dessicator under

vacuum at 50 °C to give 6-bromo-7-methyl-indoline-2,3-dione (13.3g, 55.41 mmol, 86 % yield) as a brown crystalline solid.

LC-MS (Method A) 238.5/240.5 $[M+H]^+$; RT 1.84 min.

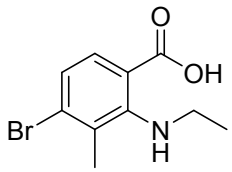
(b) Compound (13) 6-Bromo-1-ethyl-7-methyl-indoline-2,3-dione



Iodoethane (7.61 mL, 94.65 mmol) was added dropwise to a solution of 6-bromo-7-methyl-indoline-2,3-dione (11.4 g, 47.32 mmol) and anhydrous K_2CO_3 (7.9 g, 56.79 mmol) in dry DMF (20 mL) and the reaction mixture was heated to 100 °C. After 1 h the reaction mixture was then diluted with EtOAc (100 mL) and H_2O (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc (2 x 70 mL) and the combined organic phases were washed with brine (200 mL) and dried over $MgSO_4$. The resulting filtrate was removed *in vacuo* to give 6-bromo-1-ethyl-7-methyl-indoline-2,3-dione (11.2 g, 88 %) as a brown crystalline solid which was used directly in the next step without further purification.

LC-MS (Method A) 268.3/270.3 $[M+H]^+$; RT 2.32 min.

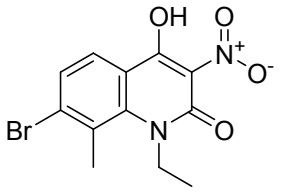
(c) Compound 13a (step 1) 4-Bromo-2-(ethylamino)-3-methyl-benzoic acid



Dropwise to a solution of 6-bromo-1-ethyl-7-methyl-indoline-2,3-dione (10.0 g, 37.3 mmol) in 2M aq. NaOH (100 mL) was added H_2O_2 (53.3 mL, 522.2 mmol) and the resulting reaction mixture was left to stir at room temperature for 2 h. The reaction mixture was diluted with DCM (150 mL) and the phases were separated. The aqueous phase was acidified to pH 3 with 2M aqueous HCl and the resulting precipitate was filtered, collected and dried overnight in a heated desiccator at 4 0^{o}C to give 4-bromo-2-(ethylamino)-3-methyl-benzoic acid (5.2 g, 54 % yield) as a pale yellow crystalline solid.

LC-MS (Method A) 258.3/260.3 $[M+H]^+$; RT 1.25 min.

(d) Compound 13a (step 2) 7-Bromo-1-ethyl-4-hydroxy-8-methyl-3-nitro-quinolin-2-one

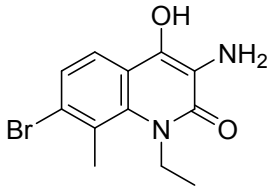


To a solution of 4-bromo-2-(ethylamino)-3-methyl-benzoic acid (1.7 g, 6.7 mmol) in dry THF (20 mL) at room temperature under N_2 atmosphere was added triphosgene (1.2 g, 4.0 mmol) in one portion. This was allowed to stir at room temperature for 3 h, after which time the solvent was carefully removed *in vacuo* (rotary evaporator bath was prohibited from reaching > 40 ^{o}C) to give a thick red oil which was diluted with dry THF (10 mL) under a N_2 atmosphere. To the resulting solution Et_3N (7.5 mL, 53.9 mmol) was added dropwise, followed by the

addition of ethyl nitroacetate (1.12 mL, 10.1 mmol) in one portion. The reaction mixture was heated to 60 ^{o}C overnight, after which time the solvent was removed *in vacuo* (maintaining bath temperature < 40 ^{o}C). The residue was then partitioned between EtOAc (20 mL) and brine (20 mL). 2M aqueous HCl was then added to adjust the pH to around 3. The organic phase was separated, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give 7-bromo-1-ethyl-4-hydroxy-8-methyl-3-nitro-quinolin-2-one as an orange solid in quantitative yield, which was used in the next step without further purification.

LC-MS (Method A) 327.3/329.3 $[M+H]^+$; RT 2.08 min.

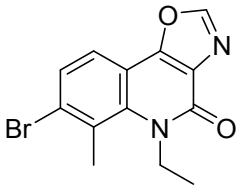
(e) Compound 13a (step 3) 3-Amino-7-bromo-1-ethyl-4-hydroxy-8-methyl-quinolin-2-one



Sodium hydrosulfite (3.5 g, 20.1mmol) was added to a stirred solution of 7-bromo-1-ethyl-4-hydroxy-8-methyl-3-nitro-quinolin-2-one (2.6 g, 8.0 mmol) in EtOH (20 mL) and H_2O (4 mL) and heated to reflux for 1 h. The reaction mixture was filtered through filter paper and the solvent removed *in vacuo*. Purification by flash column chromatography eluting with 0 – 10 % MeOH in DCM gave 3-amino-7-bromo-1-ethyl-4-hydroxy-8-methyl-quinolin-2-one (652 mg, 27 %) as a yellow crystalline solid.

LC-MS (Method A) 297.3/299.3 $[M+H]^+$; RT 1.77 min.

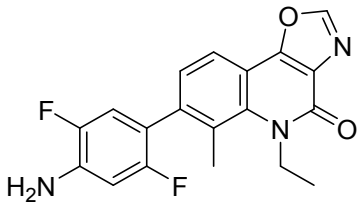
(f) Compound 13a (step 4) 7-Bromo-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



To 3-amino-7-bromo-1-ethyl-4-hydroxy-8-methyl-quinolin-2-one (101 mg, 0.3 mmol) was added to triethyl orthoformate (5 mL, 0.3 mmol). The reaction mixture was heated to 105 ^{o}C for 2 h, then excess triethyl orthoformate was removed *in vacuo*. Column chromatography eluting with 30 - 70 % EtOAc in Petroleum ether (40-60) gave 7-bromo-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one in quantitative yield, which was used in the next step without further purification.

LC-MS (Method A) 307.3/309.3 $[M+H]^{+}$; RT 2.15 min.

(g) REDX05028 7-(4-Amino-2,5-difluoro-phenyl)-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



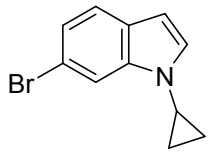
A mixture of 7-bromo-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (82 mg, 0.3 mmol), 2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (81 mg, 0.3 mmol), Cs_2CO_3 (130 mg, 0.4 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (43 mg, 0.05 mmol) in toluene (3 mL), IPA (1 mL) and H_2O (1 mL) was heated to 70 ^{o}C for 1 h. The reaction mixture was then filtered through Celite and the solvent removed *in vacuo*. Purification by flash column chromatography eluting with 30 - 70%

EtOAc in Petroleum ether (40-60) gave 7-(4-amino-2,5-difluoro-phenyl)-5-ethyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (13 mg, 13 %) as a light purple crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.09 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.95 (1H, dd, *J* = 11.0 Hz, 7.0 Hz, 1H), 6.61 (dd, *J* = 11.0 Hz, 7.0 Hz, 1H), 4.55 (m, 2H), 3.99 (m, 2H), 2.45 (d, *J* = 1.5 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); LC-MS (Method A) 356.4 $[M+H]^+$; RT 2.11 min.

REDX05166 - 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyloxazolo[4,5-c]quinolin-4(5H)-one

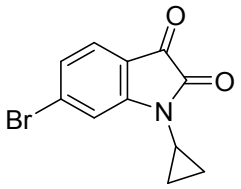
(a) Compound (29) 6-bromo-1-cyclopropyl-1H-indole



To a suspension of cyclopropylboronic acid (876.35mg, 10.2mmol) 6-bromo-1H-indole (1.g, 5.1mmol) and sodium carbonate (1081.3mg, 10.2mmol) in DCE (30 mL) was added a suspension of copper(II) acetate (926.49mg, 5.1mmol) and 2,2'-bipyridyl (796.67mg, 5.1mmol) in hot DCE (30 mL). The mixture was then heated to 70 ^{o}C for 5 hr under air.
The reaction mixture was then cooled to room temperature and aqueous ammonium chloride solution (sat.) (100 mL) was added together with DCM (100 mL) and the layers were separated. The aqueous layer was then extracted with DCM (2 x 50 mL) and the solvent was removed from the combined organics under reduced pressure.

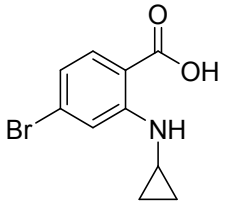
The crude product was purified by flash silica chromatography using 0-10% ethyl acetate in pet. Ether to give 6-bromo-1-cyclopropyl-indole (876mg, 73 yield) as a pale yellow oil.
LC-MS (Method A) 267/269, $[M+2OH]^+$; RT 3.27 min.

(b) Compoud (30) 6-bromo-1-cyclopropylindoline-2,3-dione



To a solution of 6-bromo-1-cyclopropyl-indole (0.87g, 3.68 mmol) in DMSO (5.5mL) was added N-Bromosuccinimide (1967 mg, 11.0 5mmol) portion-wise over 30 min. The reaction mixture was then heated to 60 ^{o}C overnight. After which time, the reaction mixture was cooled to room temperature and then poured into water. A yellow precipitate formed. The mixture was stirred at room temperature for 30 minutes. After which time the precipitate was filtered off and washed several times with water. This was then dried using a high vacuum at 40^{o}C. The product was then directly used in the next reaction.

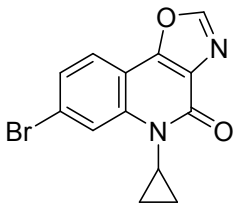
(c) Compound (31) 4-bromo-2-(cyclopropylamino)benzoic acid



A solution of 6-bromo-1-cyclopropyl-indoline-2,3-dione (0.5g, 1.88mmol) in 2 M aqueous sodium hydroxide (8 mL, 16.3 mmol) was cooled to 0 °C and hydrogen peroxide (2.35mL, 7.52mmol) was added dropwise. This was left to stir at room temperature for 2 hours. The reaction mixture was then washed with DCM (30 mL) and the phases were separated. The aqueous phase was acidified to pH 3 with 2M HCl, which resulted in precipitate formation. DCM (30 mL) was then added. The aqueous layer was then extracted with DCM (3 x 20 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give the 4-bromo-2-(cyclopropylamino)benzoic acid as an orange solid (0.48g, 99%).

LC-MS (Method A) 254.4/256.4, $[M-H]^-$; RT 2.61 min.

(d) Compound (32) 7-bromo-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one

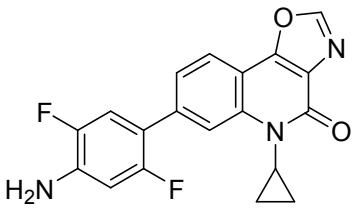


To a solution of 4-bromo-2-(cyclopropylamino)benzoic acid (0.48g, 1.87mmol) in dry THF (15 mL) was added triphosgene (332.6mg, 1.12mmol) in one portion. This was stirred at room temperature for 3 hours. After which time the solvent was carefully removed *in vacuo*

Which gave thick red oil which was diluted with dry DMF (15mL) and kept under N_2. To this was added ethyl Isocyanoacetate (0.31mL, 2.81mmol) dropwise. This was followed by the addition of sodium hydride, (60% dispersed in mineral oil) (360 mg, 15mmol) portion wise. The reaction mixture was then heated to 100^{o}C for 2 hours. After which time the reaction mixture was cooled to room temperature and DCM was added followed by careful addition of water. The DCM layer was separated and washed a further 4 times with water. The DCM layer was then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then used directly in the next step without further purification

LC-MS (Method A) 305.3/307.3, $[M+H]^+$; RT 2.05 min.

(e) REDX05166 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyloxazolo[4,5-c]quinolin-4(5H)-one



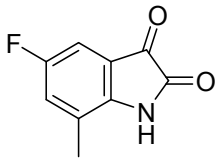
To a mixture of 7-bromo-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one (70.mg, 0.23 mmol), 4-Amino-2,5-difluorobenzeneboronic acid pinacol ester (0.12g, 0.46 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (18.74mg, 0.02 mmol), caesium Carbonate (0.11g, 0.34 mmol) was added 1,4-Dioxane (1mL) and Water (0.10 mL). This mixture was then heated to 70°C for 2 hours. After which time the reaction mixture was cooled to room temperature and directly purified by flash chromatography using an eluent system of MeOH in DCM (0:100 to 20:80). The resulting product was then re-purified by PREP chromatography to give 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyloxazolo[4,5-c]quinolin-4(5H)-one as a white solid (2 mg, 2.5%)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.21-8.17 (m, 1H), 8.05-7.95 (m, 1H), 7.49 (d, 1H), 7.19-7.15 (m, 1H), 6.67-6.55 (m, 1H), , 4.00 (s, 2H), 3.13-3.05 (m, 1H), 1.50-1.40 (m, 2H), 1.04-0.97 (m, 2H);

LC-MS (Method A) 354.4, $[M+H]^+$; RT 2.06 min.

REDX05237 - 7-(4-amino-2,5-difluoro-phenyl)-5-ethyl-8-fluoro-6-methyl-oxazolo[4,5-c]quinolin-4-one

(a) Compound (34) 5-Fluoro-7-methyl-indoline-2,3-dione



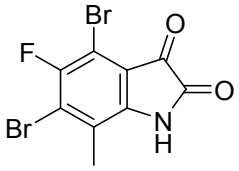
A mixture of 4-fluoro-2-methyl-aniline (8.88 mL, 79.9 mmol), chloral hydrate (19.6 g, 118.7 mmol), anhydrous Na_2SO_4 (124.9 g, 879 mmol) in hydrochloric acid (8.47 mL, 278.9 mmol) and H_2O (450 mL) was stirred vigorously at room temperature overnight. To the resulting mixture, hydroxylamine hydrochloride (7.7 g, 111.3 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was cooled to 0 °C and the resulting precipitate was collected by vacuum filtration and washed copiously with H_2O and dried under suction. The resulting filtrate was removed *in vacuo* to give 5-fluoro-7-methyl-indoline-2,3-dione as a dark brown solid which was used directly in the next step without further purification. 16.82 g, 100%

LC-MS (Method A) 197.4 $[M+H]^+$; RT 1.44 min.

To (2E)-N-(4-fluoro-2-methyl-phenyl)-2-hydroxyimino-acetamide (16.82g, 85.7mmol) was added sulfuric acid (21.56mL, 404.4mmol) which was stirred at 50 ^oC until the solid had dissolved then the reaction mixture was stirred at 80 ^oC for 45 minutes. The reaction mixture was cooled in an ice bath and water (40 ml) was added to the mixture. The deposited precipitate was filtered off and washed with water before being dried in vacuo to obtain 5-fluoro-7-methyl-indoline-2,3-dione (9.94 g, 55 mmol, 65 % yield).

LC-MS (Method A) 180.3 $[M+H]^+$; RT 1.49 min.

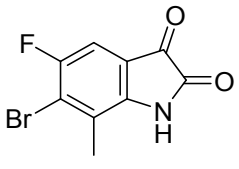
(b) Compound (35) 4,6-Dibromo-5-fluoro-7-methyl-indoline-2,3-dione



To an ice cold stirred solution of 5-fluoro-7-methyl-indoline-2,3-dione (9.9 g, 55 mmol) in H_2SO_4 (0.5 mL, 9 mmol) was added *N*-bromosuccinimide (19.7 g, 110 mmol) in portions over the course of 1 h. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h, then re-cooled to 0 – 5 °C and a further portion of *N*-bromosuccinimide (4.9 g, 27.6 mmol) was added. The reaction mixture was then allowed to warm to room temperature and stirred for a further 3 h, The reaction mixture was poured onto crushed ice with vigorous stirring forming a precipitate, which was filtered and washed with cold H_2O (20 ml). The filtrate was diluted with H_2O (100 mL) and extracted with DCM (200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* before being combined with the original precipitate to give 4,6-dibromo-5-fluoro-7-methyl-indoline-2,3-dione (17.3 g, 93 %) which was used directly in the next step.

LC-MS 357.0 $[M+Na]^+$; RT 2.27 min. (multiple bromine isotope patterns observed – main ion reported)

(c) Compound (36) 6-Bromo-5-fluoro-7-methyl-indoline-2,3-dione

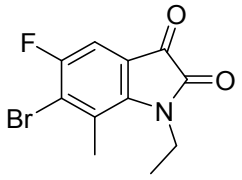


A round bottomed flask was charged with 4,6-dibromo-5-fluoro-7-methyl-indoline-2,3-dione (17.3 g, 51.31 mmol), copper (6.5 g, 102.63 mmol) and propionic acid (51.87 mL, 693.21 mmol). The resulting mixture was placed under a N_2 atmosphere and heated to 130 °C for 90

min. On cooling toluene (50 ml) was added and the mixture was filtered. The collected solids were washed with toluene (5 x 50 ml) and EtOAc (5 x 50 ml). The combined organics were washed with 2M aqueous HCl until the aqueous layer was yellow in colour. The organic layer was further washed with H_2O (50 mL), brine (50 mL) and dried over Na_2SO_4, filtered and evaporated *in vacuo* to give 6-bromo-5-fluoro-7-methyl-indoline-2,3-dione (11.0 g, 83 %).

LC-MS 286.3/288.3 $[M+H]^+$; RT 2.35 min.

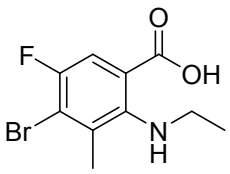
(d) Compound (37) 6-Bromo-5-fluoro-7-methyl-indoline-2,3-dione



Iodoethane (1.25 mL, 15.5 mmol) was added drop-wise to a solution of 6-bromo-5-fluoro-7-methyl-indoline-2,3-dione (2.0 g, 7.75 mmol) and anhydrous K_2CO_3 (1.3 g, 9.3 mmol) in dry DMF (1 mL) and then heated to 100 ^oC for 1 h. On cooling the reaction mixture was diluted with EtOAc (100 mL) and H_2O (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc (2 x 70 mL) and the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$ and solvent removed *in vacuo* to give 6-bromo-1-ethyl-5-fluoro-7-methyl-indoline-2,3-dione (2.2 g, 99 %) which was used directly in the next step without further purification.

LC-MS (Method A) 268.3/270.3 $[M+H]^+$; RT 2.32 min.

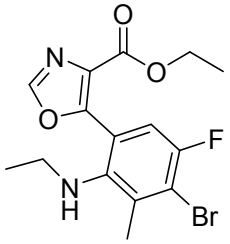
(e) Compound (38) 4-Bromo-2-(ethylamino)-5-fluoro-3-methyl-benzoic acid



Drop-wise to a solution of 6-bromo-1-ethyl-5-fluoro-7-methyl-indoline-2,3-dione (2.2 g, 7.7 mmol) in 2M aq. NaOH (21 mL) was added H_2O_2 (3.14 mL, 30.8 mmol). After 2 h stirring at room temperature the reaction mixture was diluted with DCM (150 mL) and the phases were separated. The aqueous phase was acidified to pH 3 with 2M aqueous HCl and the resulting precipitate was filtered, collected and dried overnight in a heated desiccator at 40 ^{o}C to give 4-bromo-2-(ethylamino)-5-fluoro-3-methyl-benzoic acid (1.9 g, 87 %) as a pale yellow crystalline solid.

LC-MS (Method A) 276.3/278.3 $[M+H]^+$; RT 1.18 min.

(f) Compound (39) Ethyl 5-[4-bromo-2-(ethylamino)-5-fluoro-3-methyl-phenyl]oxazole-4-carboxylate

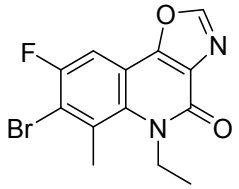


To a solution of 4-bromo-2-(ethylamino)-5-fluoro-3-methyl-benzoic acid (1.9 g, 6.7 mmol) in dry THF (50 mL) at room temperature under N_2 was added triphosgene (1.2 g, 4. mmol) in one portion. After stirring at room temperature for 3 h the solvent was carefully removed *in vacuo*. To the resulting residue under N_2 was added dry THF (40 mL), followed by Et_3N (7.47 mL, 53.6 mmol) dropwise. To the resulting mixture was added ethyl isocyanoacetate (1.1 mL,

10.05 mmol) in one portion and the reaction heated to 60 °C overnight. On cooling to room temperature, the solvent was removed under reduced pressure. The residue was then partitioned between EtOAc (20 mL) and brine (20 mL). 2M aqueous HCl was then added to adjust the aqueous pH to around 3. The EtOAc layer was then separated, washed 4 times with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford ethyl 5-[4-bromo-2-(ethylamino)-5-fluoro-3-methyl-phenyl]oxazole-4-carboxylate (2.1 g, 84 %) as a yellow solid.

LC-MS (Method A) 371.3/373.3 $[M+H]^+$; RT 2.79 min.

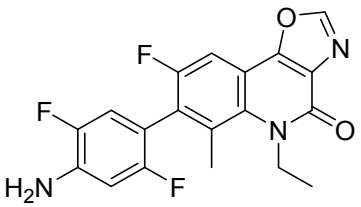
(g) Compound (40) 7-bromo-5-ethyl-8-fluoro-6-methyl-oxazolo[4,5-c]quinolin-4-one



To a solution of ethyl 5-[4-bromo-2-(ethylamino)-5-fluoro-3-methyl-phenyl]oxazole-4-carboxylate (2.1 g, 5.7 mmol) in dry DMF (5 mL) was added NaH (60% dispersed in mineral oil; 61 mg, 1.5 mmol) in one portion. The reaction mixture was then heated to 100 °C for 1 h. On cooling to room temperature EtOAc (100 mL) and H_2O (30 mL) were added and the layers separated. The aqueous layer was washed with EtOAc (50 mL) and the combined organic extracts were washed with H_2O (4 x 30 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography using 50 % EtOAc/Petroleum ether (40-60) as the eluent to give 7-bromo-5-ethyl-8-fluoro-6-methyl-oxazolo[4,5-c]quinolin-4-one (380 mg, 21 %).

LC-MS (Method A) 325.3/327.3 $[M+H]^+$; RT 2.31 min.

(h) REDX05237 7-(4-amino-2,5-difluoro-phenyl)-5-ethyl-8-fluoro-6-methyl-oxazolo[4,5-c]quinolin-4-one

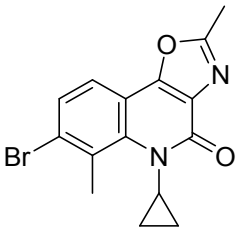


Prepared using 4-amino-2,5-difuorobenzeneboronic acid pinacol ester and 7-bromo-5-ethyl-8-fluoro-6-methyl-oxazolo[4,5-c]quinolin-4-one and a similar procedure to that described in REDX05557.

^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 6.93 (ddd, J = 1.07, 6.4, 10.95 Hz, 1H), 6.62 (dd, J = 7.2, 10.4 Hz, 1H), 4.62-4.52 (m, 1H), 4.48–4.38 (m, 1H), 4.00 (br s, 2H), 2.43 (s, 3H), 1.32 (t, J = 6.99 Hz, 3H); LC-MS (Method A) 374.3 $[M+H]^+$; RT 2.19 min.

REDX05282 - 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-2,6-dimethyl-oxazolo[4,5-c]quinolin-4-one

(a) Compound (9b) 7-Bromo-5-cyclopropyl-2,6-dimethyl-oxazolo[4,5-c]quinolin-4-one

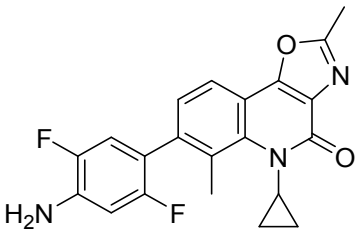


Trimethyl orthoacetate (20 mL, 159.13 mmol) was added to 3-amino-7-tromo-1-cyclopropy1-4-hydroxy-8-methyl-quinolin-2-one (920 mg, 2.98 mmol) and 0.1 mL of 1M HCl in diethyl ether was added. The reaction mixture was then refluxed for approximately four hours. The

solvent was removed under vacuum and then re-dissolved in DCM and evaporated onto silica and then purified by flash chromatography, eluting with 0-100% ethyl acetate in heptane to give 7-bromo-5-cyclopropyl-Z6-dmethyl-oxazolo[4,5-c]quinolin-4-one (400 mg, 1.20 mmol, 40.3 % yield) as a pale yellow solid.

LC-MS (Method A) 333.0/335.0 $[M+H]^+$, RT 3.84 min.

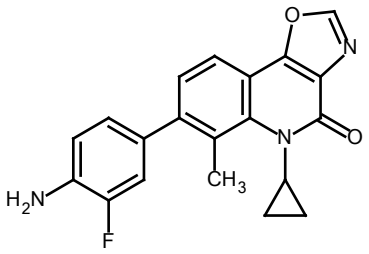
(b) REDX05282 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-2,6-dimethyl-oxazolo[4,5-c]quinolin-4-one



Prepared using 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline and 7-bromo-5-cyclopropyl-2,6-dimethyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139. (23 mg, 19 %) as a white solid.

^{1}H NMR (400MHz, CD_3OD): δ ppm 7.78-7.81 (d, J = 8.0 Hz, 1H), 7.28-7.30 (d, J = 8.0, 1H), 6.95-6.99 (dd, J = 11.3 Hz, 6.9 Hz, 1H), 6.66-6.71 (dd, J = 11.3 Hz, 7.4 Hz, 1H), 3.63-3.66 (m, 1H), 2.70 (s, 3H), 2.57 (s, 3H), 1.27 (d, 2H), 0.61 (s, 2H); LC-MS (Method C) 382.2 $[M+H]^+$, RT 1.60 min.

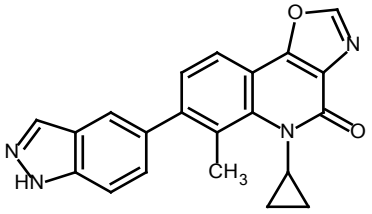
REDX05412 – 7-(4-amino-3-fluorophenyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



Prepared using 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139.

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.06 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.06 (dd, *J* = 11.8, 1.9 Hz, 1H), 6.99 (ddd, *J* = 8.1, 1.9, 0.7 Hz, 1H), 6.87 (dd, *J* = 9.0, 8.2 Hz, 1H), 3.87 (s, 2H), 3.67-3.60 (m, 1H), 2.56 (s, 3H), 1.33-1.28 (m, 2H), 0.70-0.66 (m, 2H); LC-MS (Method B) 350.5 $[M+ H]^+$; RT 2.08 min.

REDX05504 – 5-cyclopropyl-7-(1H-indazol-5-yl)-6-methyl-oxazolo[4,5-c]quinolin-4-one

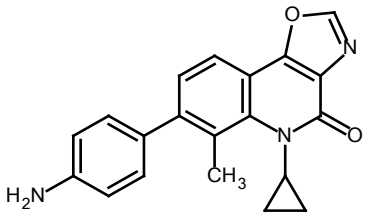


Prepared using 6-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139

^{1}H NMR (400MHz, $CDCl_3$): *δ* ppm 10.62 (s, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 3.71-3.61 (m, 1H), 2.56 (s, 3H), 1.36-1.31 (m, 2H), 0.76-0.71 (m, 2H);

LC-MS (Method B) 357.4 $[M+ H^+]$; RT 1.84 min

REDX05510 – 7-(4-aminophenyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

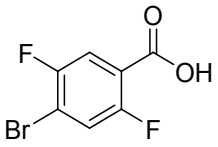


Prepared using 4-aminophenyl boronic acid pinacol ester and and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.05 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 2H), 3.66-3.62 (m, 1H), 2.56 (s, 3H), 1.32-1.27 (m, 2H), 0.71-0.66 (m, 2H); LC-MS (Method B) 332.2 $[M+H]^+$, RT 4.64 min

REDX05557 - 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one

(a) Compound (15) 4-Bromo-2,5-difluorobenzoic acid

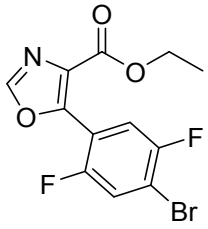


To a -78 ^{o}C solution of 1,4-dibromo-2,5-difluorobenzene (2.7 g, 9.99 mmol) in dry Et_2O (30 mL) under an inert atmosphere was added 2.5 M *n*-butyllithium solution in hexanes (4 mL, 9.99 mmol) drop-wise and the mixture left stirring for 2 h. Crushed CO_2 pellets were added slowly and the mixture was allowed to warm to ambient temperature and left stirring for 1 h. After quenching with 1M aqueous HCl (10 mL) the mixture was basified with 1M aqueous NaOH (70 mL) and then washed with Et_2O (2 x 50 mL). The aqueous layer was acidified with 1 M aqueous HCl (80 mL) and extracted with Et_2O (3 x 100 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and solvent was removed *in vacuo* to give 4-

bromo-2,5-difluoro benzoic acid (2.3 g, 97 %) as an off-white solid, which was used without further purification.

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 9.50 (br s, 1H), 7.78 (dd, *J* = 8.2, 6.1 Hz, 1H), 7.46 (dd, *J* = 9.3, 5.4 Hz, 1H); LC-MS (Method C) 234.9/236.9 $[M-H]^-$; RT 3.43 min.

(b) Compound (16) Ethyl 5-(4-bromo-2,5-difluoro-phenyl)oxazole-4-carboxylate

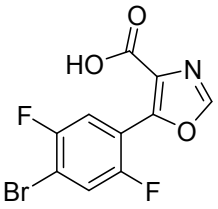


To an ice-cooled solution of 4-bromo-2,5-difluorobenzoic acid (6.3 g, 26.5 mmol) in DCM (80 mL) was added oxalyl chloride (3.46 mL, 39.7 mmol), followed by several drops of DMF. The mixture was then removed from the ice bath and stirred for 2 h. The solvent was removed under reduced pressure to give 4-bromo-2,5-difluorobenzoyl chloride.

To an ice-cooled solution of ethyl isocyanoacetate (3.18 mL, 29.1 mmol) in THF (40 mL) was added Et_3N (11.0 mL, 79.4 mmol) followed by the slow addition of 4-bromo-2,5-difluorobenzoyl chloride in THF (40 mL). The reaction mixture was then allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then diluted with DCM and washed with saturated aqueous $NaHCO_3$ followed by brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give ethyl 5-(4-bromo-2,5-difluoro-phenyl)oxazole-4-carboxylate as a solid (7.8 g, 89 %).

LC-MS (Method C) 331.9/333.9 $[M+H]^+$; RT 1.77 min.

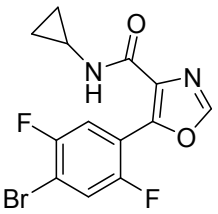
(c) Compound (17) 5-(4-Bromo-2,5-difluoro-phenyl)oxazole-4-carboxylic acid



A solution of ethyl 5-(4-bromo-2,5-difluoro-phenyl)oxazole-4-carboxylate (7.8 g, 23.4 mmol) in 1,4-dioxane (50 mL) was treated with 2M aq. LiOH (50 mL) and stirred at room temperature overnight. The 1,4-dioxane was then removed under reduced pressure and the remaining aqueous was acidified with 1M aqueous HCl, and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and then concentrated *in vacuo* to give 5-(4-bromo-2,5-difluoro-phenyl)oxazole-4-carboxylic acid as an off white solid (6.1 g, 85%), which was used without further purification.

LC-MS (Method C) 303.9/305.8 $[M+H]^+$; RT 1.46 min.

(d) Compound (18) 5-(4-Bromo-2,5-difluoro-phenyl)-N-cyclopropyl-oxazole-4-carboxamide

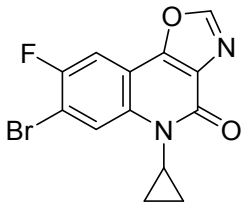


A suspension of 5-(4-bromo-2,5-difluoro-phenyl)oxazole-4-carboxylic acid (5.5 g, 18.09 mmol) in anhydrous DCM (80 mL) was cooled in an ice bath followed by the slow addition of oxalyl chloride (2.3 mL, 27.14 mmol). Several drops of DMF were added to catalyse the reaction. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, before concentrating *in vacuo* to give a brown liquid, which was dissolved in DCM (80 mL) and treated

with cyclopropylamine (2.75 mL, 39.69 mmol). After stirring at room temperature for 2 h the reaction mixture was diluted with DCM and washed with saturated aqueous $NaHCO_3$. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 5-(4-bromo-2,5-difluoro-phenyl)-*N*-cyclopropyl-oxazole-4-carboxamide (5.1 g, 83%) as a light brown solid, which was used without further purification.

LC-MS (Method C) 342.8/344.7 $[M+H]^+$; RT 1.65 min.

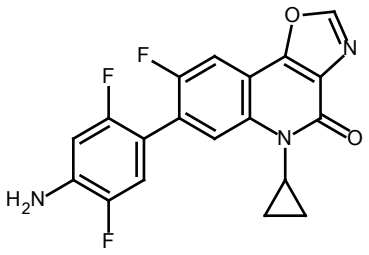
(e) Compound (19) 7-Bromo-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one



A mixture of 5-(4-bromo-2,5-difluoro-phenyl)-*N*-cyclopropyl-oxazole-4-carboxamide (1.5 g, 4.37 mmol), K_2CO_3 (1.8 g, 13.12 mmol) and 18-crown-6 (1.2 g, 4.37 mmol) in DMSO (20 mL) were heated in the microwave (Biotage Initiator) at 140 ^oC for 90 min. The reaction mixture was then diluted with EtOAc, which was washed with H_2O several times followed by brine and then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a brown solid. The crude product was purified by flash chromatography eluting with 0 – 100 % EtOAc in heptane to give 7-bromo-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one (370 mg, 26 %) as an off-white solid.

^1H NMR (400MHz, $CDCl_3$): δ ppm 8.22 (d, J = 5.7 Hz, 1H), 8.14 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 3.04 (tt, J = 6.8, 4 Hz, 1H), 1.47 (m, 2H), 0.97 (m, 2H); LC-MS (Method C) 322.9/324.8 $[M+H]^+$; RT 1.55 min.

(f) REDX05557 – 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one

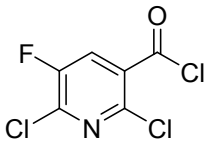


A mixture of 4-amino-2,5-difuorobenzeneboronic acid pinacol ester (31 mg, 0.12 mmol) and 7-bromo-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one (40 mg, 0.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane complex (10 mg, 0.01 mmol) and Cs_2CO_3 (121 mg, 0.37 mmol) in dimethoxyethane (1 mL) and H_2O (0.25 mL) was heated in the microwave (Biotage Initiator) at 120 °C for 20 minute. The mixture was dry loaded onto silica and purified by flash chromatography eluting with 0 - 20% MeOH in DCM to give a solid, which was further purified by preparative HPLC to yield 7-(4-amino-2,5-difluoro-phenyl)-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one (11 mg, 23%) as a beige solid.

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.87 (s,1H) , 7.94 (dd, *J* = 6.2, 7.8 Hz, 2H), 7.26 (dd, *J* = 11.5, 6.8 Hz, 1H), 7.09 (s, 2H), 6.69 (dd, *J* = 11.9, 7.4 Hz, 1H), 3.17–2.89 (m, 1H), 1.34 (t, *J* = 6.8 Hz, 2H), 0.86 (d, *J* = 3.7 Hz, 2H); LC-MS (Method C) 372.1 $[M+H]^+$; RT 1.90 min.

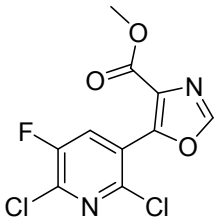
REDX05634 - 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyl-8-fluorooxazolo[4,5-c]1,8-naphthyridin-4-one

(a) Compound 23 (step 1) 2,6-Dichloro-5-fluoro-pyridine-3-carbonyl chloride



A mixture of 2,6-dichloro-5-fluoronicotinic acid (3.5 g, 16.43 mmol) and thionyl chloride (5.99 mL, 82.15 mmol) in toluene (50mL) was refluxed under the nitrogen atmosphere for 3 hours. The mixture was cooled down and the solvent was removed under reduced pressure. The residue was co-evaporated with toluene (2 x 50 mL) to give 2,6-dichloro-5-fluoro-pyridine-3-carbonyl chloride (3.8 g, 16.43 mmol, quantitative yield) as a yellow oil which was used in the next step without further purification assuming quantitative yield of the product.

(b) Compound 23 (step 2) Methyl 5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxylate

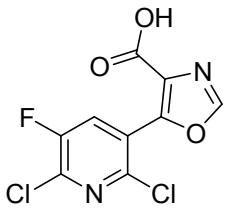


To a solution of methyl 2-isocyanoacetate (1.73 mL, 18.06 mmol) in THF (30mL) cooled in an ice bath was added triethylamine (6.83 mL, 49.25 mmol) dropwise. A solution of 2,6-dichloro-5-fluoro-pyridine-3-carbonyl chloride (3.8 g, 16.42 mmol) in THF (20 mL) was added dropwise over 5 minutes giving slight effervescence. The reaction was then allowed to warm to room temperature and stirred over weekend. The reaction was diluted with EtOAc (~100 ml) and washed with ~2M $NaHCO_3$ aq. (~40 mL) and brine (~20 mL) then the organic was dried

($MgSO_4$), filtered and evaporated under reduced pressure to leave a dark brown solid. Purification by column chromatography through silica (100 g Biotage column) using 0 – 10 % MeOH in DCM. (3.86 g, 81%)

LC-MS (Method A) 259.3 $[M\text{-}OMe+H]^+$; RT 2.19 min.

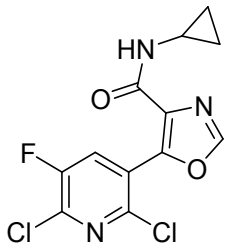
(c) Compound 23 (step 3) 5-(2,6-Dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxylic acid



To a stirred solution of methyl 5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxylate (1.2 g, 3.95 mmol) in THF (20 mL) was added lithium hydroxide (11.85 mL, 23.71 mmol) in water (5 mL) and the reaction mixture was stirred at rt for 2 h. LCMS of the crude reaction mixture showed that the desired product had been formed and that no starting material remained. DCM (20 mL) and water (20 mL) were added to the reaction mixture and then acidified to pH ~3 with HCl (2M) and extracted with DCM (2 x 30 mL). The combined organics were washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to leave the crude reaction product 5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxylic acid (1.0 g, 3.7 mmol, 94 %) which was taken on to the next reaction without further purification.

LC-MS (Method A) 277.2 $[M^+]$; RT 1.75 min. Main isotope reported.

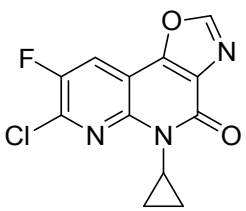
(d) Compound 24 (step 1) *N*-Cyclopropyl-5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxamide



To a solution of 5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxylic acid (8.2 g, 29.6 mmol) in DCM (150 mL) was added cyclopropylamine (2.46 mL, 35.52 mmol) *N*,*N*-diisopropylethylamine (10.3 mL, 59.2 mmol) and HATU (12.4 g, 32.56 mmol) and the reaction mixture was allowed to stir at rt overnight. The reaction mixture was then diluted with water (150 mL) and the layers were separated. The aqueous layer was then extracted with DCM (2 x 50 mL), the organics were combined, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to leave the crude reaction product. The crude reaction product was purified by flash silica chromatography using 0 - 50% ethyl acetate in petroleum ether as eluent. The solvent was removed from fractions containing the desired product to give *N*-cyclopropyl-5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxamide (6.9 g, 21.89 mmol, 74 %) as an off-white solid.

LC-MS (Method A) 316.4 $[M+H]^+$; RT 2.13 min. Main isotope reported.

(e) Compound 24 (step 2) 7-Chloro-5-cyclopropyl-8-fluoro-oxazolo[4,5-c][1,8]naphthyridin-4-one

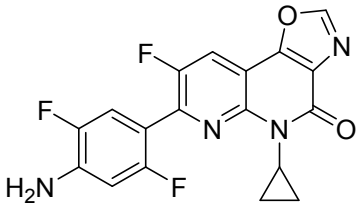


To a solution of *N*-cyclopropyl-5-(2,6-dichloro-5-fluoro-3-pyridyl)oxazole-4-carboxamide (6.9 g, 21.89 mmol) in DMF (100 mL) was added sodium hydride, (60% dispersed in mineral oil;

1.9 g, 47.06 mmol) was added in small portions at 0 °C and the resulting mixture was left to stirred overnight at rt under a nitrogen atmosphere. The reaction was carefully quenched by addition of water (100 mL), diluted with EtOAc (150 mL) and extracted the aqueous layer with EtOAc (3 x 100 mL). Combined organic layers were concentrated to dryness, re-dissolved in DCM (150 mL) and water (150 mL). Aqueous layer extracted with DCM (2 x 50 mL), combined organic layers were then washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness to give the crude 7-chloro-5-cyclopropyl-8-fluoro-oxazolo[4,5-c][1,8]naphthyridin-4-one (5.5 g, 90 %) as cream white colour solid.

LC-MS (Method A) 280.4 $[M+H]^+$; RT 1.97 min.

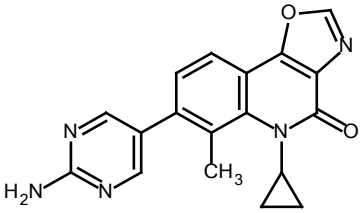
(f) REDX05634 – 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyl-8-fluorooxazolo[4,5-c][1,8]naphthyridin-4(5H)-one



Prepared using 4-amino-2,5-difuorobenzeneboronic acid pinacol ester and 7-chloro-5-cyclopropyl-8-fluoro-oxazolo[4,5-c][1,8]naphthyridin-4-one as described in REDX05557

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.90 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 7.39 (dd, J = 11.8, 6.4 Hz, 1H), 6.66 (dd, J = 12.2, 7.3 Hz, 1H), 6.01 (s, 2H), 3.05–2.99 (m, 1H), 1.29-1.17 (m, 2H), 1.01–0.78 (m, 2H); LC-MS (Method B) 373.4 $[M+H]^+$; RT 2.10 min.

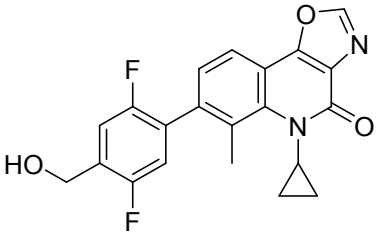
REDX05774 – 7-(2- aminopyrimidin-5-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



Prepared using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyrimidinamine and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139.

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.44 (s, 2H), 8.11 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 5.66 (br,s 2H), 3.66 (br s, 1H), 2.61 (s, 3H), 1.32 (m, 2H), 0.69 (m, 2H); LC-MS (Method C) 334.1 $[M+H]^+$; RT 1.14 min

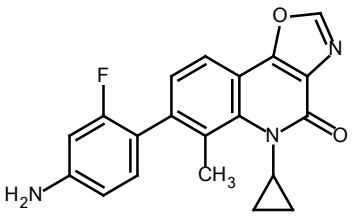
REDX05853 – 5-cyclopropyl-7-(2,5-difluoro-4-(hydroxymethyl)phenyl)-6-methyloxazolo[4,5-c]quinolin-4(5H)-one



Prepared using [2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol and 7-bromo-5-cyclopropyl-8-fluoro-oxazolo[4,5-c]quinolin-4-one as described for REDX04139

^{1}H NMR (400MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.96 (d, *J* = 6.0 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.31 (dd, *J* = 9.8, 6.0 Hz, 1H), 7.13 (m, 1H), 4.79 (s, 2H), 2.99 (m, 1H), 1.37 (m, 2H), 0.93 (m, 2H); LC-MS (Method C) 387.1 $[M+H]^+$; RT 1.47 min

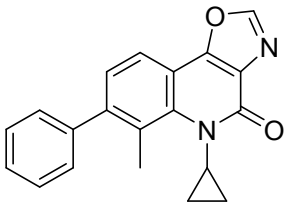
REDX05866 – 7-(4-amino-2-fluoro-phenyl)-5-cyclopropyl-6-methyl-oxazolo[4.5-c]quinolin-4-one E



Prepared using 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139 (9 mg, 4%)

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.07 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.09 (m, 1H), 6.56 (m, 1H), 6.50 (m, 1H), 3.92 (s, 2H), 3.63 (m, 1H), 2.52 (m, 3H), 1.30 – 1.23 (m, 2H), 0.67 (s, 2H); LC-MS (Method D) 350.5 $[M+H]^+$; RT 1.97 min.

REDX05867 - 5-cyclopropyl-6-methyl-7-phenyl-oxazolo[4,5-c]quinolin-4-one

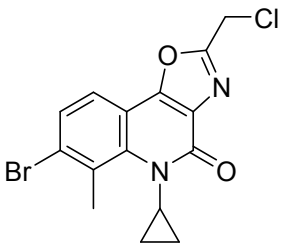


Prepared using 4.4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX4139

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.07 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.53-7.36 (m, 5H), 7.28 (d, *J* = 8.0 Hz, 1H), 3.70-3.59 (m, 1H), 2.54 (s, 3H), 1.35-1.21 (m, 2H), 0.75-0.66 (m, 2H); LC-MS (Method D) 317.5 $[M+H]^+$; RT 7.04 min.

REDX05931 - 7-(4-amino-2,5-difluorophenyl)-5-cyclopropyl-6-methyl-4-oxo-4*H*,5*H*-[1,3]oxazolo[4,5-c]quinolin-2-yl]methyl acetate

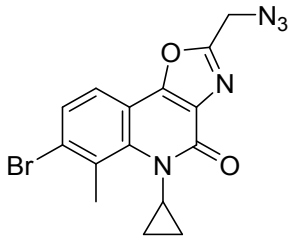
(a) Compound (41) 7-Bromo-2-(chloromethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



To a stirred suspension of 3-amino-7-bromo-1-cyclopropyl-4-hydroxy-8-methyl-quinolin-2-one (5.5 g, 17.66 mmol) in DCM (60 mL) under N_2 at 0 °C was added 2-chloro-1,1,1-trimethoxyethane (3.33 mL, 24.73 mmol) followed by boron trifluoride diethyl etherate (2.4 mL, 19.43 mmol) drop-wise. After 35 min, the reaction mixture was allowed to warm to room temperature, followed by the sequential addition of H_2O (30 mL) and DCM (60 mL). After separation of the layers the aqueous was extracted with DCM (2 x 60 mL). The organic phases were combined and solvent removed *in vacuo* to give a residue which was purified by flash chromatography using a slow gradient of 0 - 50% EtOAc in DCM as eluent to give 7-bromo-2-(chloromethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (2.8 g, 44 %) as a pale pink solid.

LC-MS (Method D) 367.2 $[M+H]^+$; RT 3.15 min. Main isotope reported.

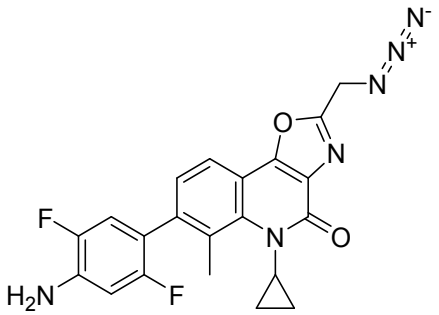
(b) Compound (42) 2-(Azidomethyl)-7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



To a stirred solution of 7-bromo-2-(chloromethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (600 mg, 1.63 mmol) in DMSO (15 mL) was added sodium azide (106 mg, 1.63mmol). The reaction mixture was allowed to stir at room temperature overnight. H_2O (15 mL) was added to the crude reaction mixture followed by EtOAc (50 mL) and the layers were separated. The organic layer was washed with H_2O (3 x 20 mL). The solvent was then removed *in vacuo* and the crude residue was purified by flash chromatography using 0 - 60% EtOAc in Petroleum ether (40-60) as eluent to give 2-(azidomethyl)-7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (531 mg, 86 %) as a pale brown solid.

LC-MS (Method D) 374.3/376.3 $[M+H]^+$; RT 2.79 min.

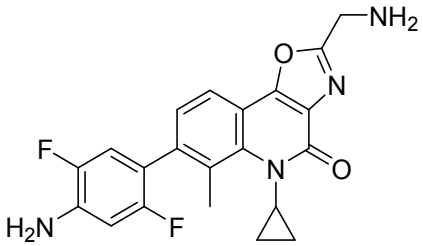
(c) Compound (43) 7-(4-Amino-2,5-difluoro-phenyl)-2-(azidomethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-on



Prepared using 4-amino-2,5-difuorobenzeneboronic acid pinacol ester and 2-(azidomethyl)-7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one and a similar procedure to that described in REDX05557

LC-MS (Method D) 423.4 $[M+H]^+$; RT 2.94 min.

(d) REDX05931 - 7-(4-amino-2,5-difluoro-phenyl)-2-(aminomethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

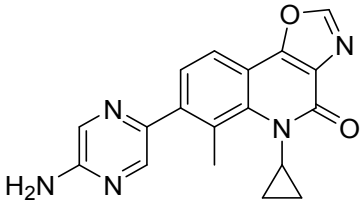


To a stirred solution of 7-(4-amino-2,5-difluoro-phenyl)-2-(azidomethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (294 mg, 0.70 mmol) in a mixture of THF (20 mL) and H_2O (2 mL) was added PPh_3 (274 mg, 1.04 mmol) and the reaction mixture was heated at 75 °C for 2 h. On cooling the solvent was removed and the residual water was removed by azeotroping with toluene (2 x 5 mL). The resulting residue was then purified by flash chromatography using 0 - 10% MeOH / NH3 (2 M) in DCM as eluent. The product containing

fractions were combined and concentrated to yield 7-(4-amino-2,5-difluoro-phenyl)-2-(aminomethyl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (236 mg, 86 %) as a pale yellow solid.

^{1}H NMR (400MHz, $CDCl_3$): *δ* ppm 7.71 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 11.0, 6.6 Hz, 1H), 6.61 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.15 (s, 2H), 4.00 (s, 2H), 3.67–3.58 (m, 1H), 2.52 (d, *J* = 1.5 Hz, 3H), 1.75 (s, 2H), 1.33–1.21 (m, 2H), 0.65 (s, 2H); LC-MS (Method B) 397.4 $[M+H]^+$; RT 5.42 min.

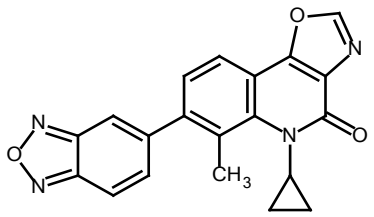
REDX06062- 7-(5-aminopyrazin-2-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



Prepared using 5-cyclopropyl-6-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one and 5-bromo-2-pyrazinamin as described for REDX04139

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.22 (d, *J* = 1.5 Hz, 1H), 8.14 (d, *J* = 1.5 Hz, 1H), 8.08 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 4.71 (s, 2H), 3.65 (m, 1H), 2.64 (s, 3H), 1.34 – 1.21 (m, 2H), 0.70 (m, 2H); LC-MS (Method D) 334.4 $[M+H]^+$; RT 4.73 min.

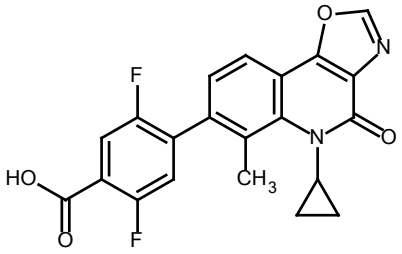
REDX06110 – 7-(2,1,3-benzoxadiazol-5-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



Prepared using 5-cyclopropyl-6-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139.

^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.11 (s, 1H), 7.95 (dd, *J* = 9.2, 1.1 Hz, 1H), 7.85 (d, *J* = 5.5 Hz, 1H), 7.84 (d, *J* = 1.1 Hz, 1H), 7.48 (dd, *J* = 9.2, 1.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 3.67-3.62 (m, 1H), 2.59 (s, 4H), 1.35-1.30 (m, 2H), 0.72-0.68 (m, 2H); LC-MS (Method E) 359.4 [M^+ H^+], RT 7.22 min

REDX06189 – 4-{5-cyclopropyl-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-7-yl}-2,5-difluorobenzoic acid

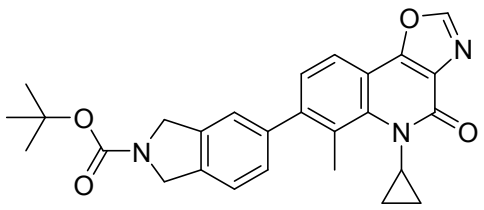


Prepared using 5-cyclopropyl-6-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.84 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.63-7.56 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.62-3.54 (m, 2H), 2.45 (s, 3H), 1.20-1.14 (m, 2H), 0.51-0.45 (m, 2H); LC-MS (Method E) 397.4 $[M+ H]^+$; RT 6.52 min

REDX06305 - 5-cyclopropyl-7-isoindolin-5-yl-6-methyl-oxazolo[4,5-c]quinolin-4-one

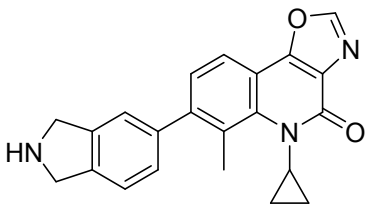
(a) tert-Butyl 5-{5-cyclopropyl-6-methyl-4-oxo-4H,5H-[1,3]oxazolo[4,5-c]quinolin-7-yl}-2,3-dihydro-1H-isoindole-2-carboxylate



Prepared using method as described in REDX04139 with 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one.

LC-MS (Method D) 458.4 $[M+H]^+$; RT 3.45 min

(b) 5-cyclopropyl-7-isoindolin-5-yl-6-methyl-oxazolo[4,5-c]quinolin-4-one

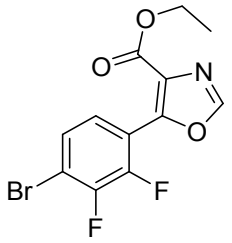


Prepared using method described in REDX07517 with *tert*-butyl 5-{5-cyclopropyl-6-methyl-4-oxo-4*H*,5*H*-[1,3]oxazolo[4,5-c]quinolin-7-yl}-2,3-dihydro-1H-isoindole-2-carboxylate.

^{1}H NMR (400MHz, CD_3OD): δ ppm 8.51 (s, 1H), 7.88 (d, J = 7.9Hz, 1H), 7.46 (d, J = 7.6Hz, 1H), 7.41 (s, 1H), 7.36 (m, 2H), 4.40 (s, 4H), 3.66 (m, 1H), 2.57 (s, 3H), 1.31 (m, 2H), 0.65 (m, 2H), LC-MS (Method D) 358.4 $[M+H]^+$; RT 1.64 min

REDX06345 – (2*S*)-6-(4-amino-2,5-difluorophenyl)-2-methyl-4,11-dioxa-1,13-diazatetracyclo[7.6.1.0^{5},^{16}.0^{10},^{14}]hexadeca-5(16),6,8,10(14),12-pentaen-15-one

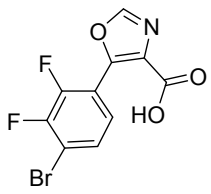
(a) Compound 26 (step 1) Ethyl 5-(4-bromo-2,3-difluoro-phenyl)oxazole-4-carboxylate



To ethyl isocyanoacetate (4.99 mL, 45.7 mmol) in THF (50 ml) at 0 ^oC was added triethylamine (17.27 mL, 124.6 mmol) dropwise, followed by the addition of 4-bromo-2,3-difluoro-benzoyl chloride (10.6 g, 41.5 mmol) in THF (50 ml) over 5 min. The reaction was allowed to warm to rt and stirred o/n. The mixture evaporated to near dryness and was diluted with DCM (100 ml). The organics were then washed with sat. $NaHCO_3$ (x3) followed by brine. The DCM layer was dried through a hydrophobic frit and evaporated to dryness to give a dark red liquid. This was then purified by column chromatograhpy using an eluent system of 0 - 40% pet ether/ethyl acetate to yield ethyl 5-(4-bromo-2,3-difluoro-phenyl)oxazole-4-carboxylate (10.4 g, 75 %) as a red oil.

LC-MS (Method A) 332.3/334.3 $[M+H]^+$; RT 3.06 min.

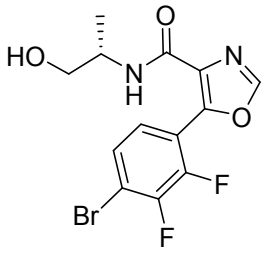
(b) Compound 26 (step 2) 5-(4-Bromo-2,3-difluorophenyl)-1,3-oxazole-4-carboxylic acid



Ethyl 5-(4-bromo-2,3-difluoro-phenyl)oxazole-4-carboxylate (8.4 g, 25.3 mmol) was dissolved in THF (100 mL) followed by addition of 2M sodium hydroxide (100 mL, 200 mmol). This was stirred at room temperature for 2 hours during which time the product precipitated. The THF was evaporated to leave the basic aqueous. The aqueous was acidified and extracted with ethyl acetate and dried over magnesium sulfate, filtered and evaporated to give a light brown solid (7.9 g, 100%)

LC-MS (Method A) 304.2/306.3 $[M+H]^+$; RT 2.39 min.

(c) Compound 26 (step 3) 5-(4-bromo-2,3-difluoro-phenyl)-N-[(1S)-2-hydroxy-1-methyl-ethyl]oxazole-4-carboxamide

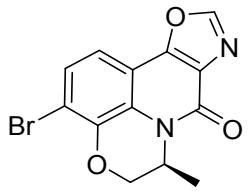


To a suspension of 5-(4-bromo-2,3-difluoro-phenyl)oxazole-4-carboxylic acid (1 g, 3.3 mmol) in dry DCM (15 mL) under N_2 was added oxalyl chloride (0.42 mL, 4.9 mmol) drop-wise at room temperature, followed by catalytic DMF (1 drop). This was allowed to stir for 1 h. The mixture was then evaporated to dryness to give 5-(4-bromo-2,3-difluoro-phenyl)oxazole-4-carbonyl chloride (1.06 g, 3.3 mmol) as a yellow powder. This was then diluted with dry DCM (75 mL) and treated with (2*S*)-(+)-2-aminopropan-1-ol (0.54 mL, 6.9 mmol) under N_2. This was allowed to stir at room temperature overnight. After which time the mixture was washed with saturated aqueous $NaHCO_3$ (3 x 30 mL) followed by brine (30 ml). The organic layer was then dried through a hydrophobic frit and evaporated to dryness to give 5-(4-bromo-2,3-difluoro-

phenyl)-N-[(1*S*)-2-hydroxy-1-methyl-ethyl]oxazole-4-carboxamide (1 g, 84%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.65 (ddd, *J* = 8.7, 6.5, 2.1 Hz, 1H), 7.42 (ddd, *J* = 8.6, 6.0, 2.0 Hz, 1H), 7.28–7.21 (m, 1H), 4.27–4.13 (m, 1H), 3.79-3.71 (m,1H), 3.68-3.62 (m, 1H), 2.57 (br s, 1H), 1.29 (d, *J* = 6.8 Hz, 3H); LC-MS (Method A) 361.2/363.2 $[M+H]^+$; RT 2.38 min.

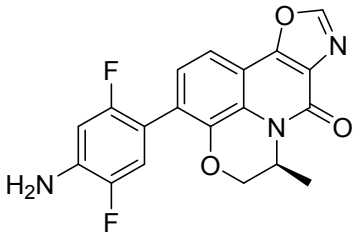
(d) Compound 27 (*S*)-3-Bromo-6-methyl-5,6-dihydro-8H-[1,4]oxazino[2,3,4-ij]oxazolo[4,5-c]quinolin-8-one



To a solution of 5-(4-bromo-2,3-difluoro-phenyl)-N-[(1S)-2-hydroxy-1-methyl-ethyl]oxazole-4-carboxamide (1 g, 2.8 mmol) ,18-crown-6 (0.82 g, 3.1 mmol) and potassium carbonate (1.91g, 13.9 mmol) in DMSO (25mL) was heated at 140 ^oC for 40 minutes. LCMS showed approx 70% product formation. The mixture was diluted with EA (200 ml) and washed with water (5 x 50 ml) and brine (50 ml). The organic extract was dried over Na_2SO_4 and solvent removed *in vacuo* to give a brown oil which was purified by flash chromatography eluting with 0 - 100% EtOAc in heptane to give (*S*)-3-bromo-6-methyl-5,6-dihydro-8H-[1,4]oxazino[2,3,4-ij]oxazolo[4,5-c]quinolin-8-one (400 mg, 45%)

^{1}H NMR (400MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.53–7.43 (m, 2H), 5.38-5.28 (m, 1H), 4.58 (dd, *J* = 11.3, 1.3 Hz, 1H), 4.22 (dd, *J* = 11.4, 2.4 Hz, 1H), 1.45 (d, *J* = 6.7 Hz, 3H). LC-MS (Method A) 321.3/323.3 $[M+H]^+$; RT 2.55 min.

(e) REDX06345 (S)-3-(4-amino-2,5-difluorophenyl)-6-methyl-5,6-dihydro-8H-[1,4]oxazino[2,3,4-ij]oxazolo[4,5-c]quinolin-8-one

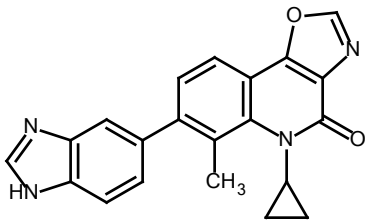


Prepared using 4-amno-2,5-difuorobenzeneboronic acid pinacol ester and (*S*)-3-Bromo-6-methyl-5,6-dihydro-8H-[1,4]oxazino[2,3,4-ij]oxazolo[4,5-c]quinolin-8-one and a similar procedure to that described in REDX05557

^{1}H NMR (400MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.32-7.23 (m, 1H), 7.08 (dd, J = 11.2, 6.4 Hz, 1H), 6.59 (dd, J = 10.7, 7.5 Hz, 1H), 5.36-5.25 (m, 1H), 4.42 (dd, 11.4, 1.3 Hz, 1H), 4.15 (dd, 11.4, 2.4 Hz, 1H), 3.95 (s, 2H), 1.45 (d, 6.6 Hz, 3H);

LC-MS (Method A) 370.4 $[M+H]^+$; RT 2 54 min.

REDX06530 – 7-(1H-benzimidazol-5-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



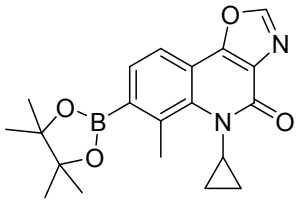
Prepared using 5-cyclopropyl-6-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one and *tert* butyl 5-bromobenzimidazole-1-carboxylate as

described in REDX04139 followed by deprotection of the Boc group using the method described in REDX07517

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.59 (s, 0.5H), 12.55 (s, 0.5H), 8.80 (s, 1H), 8.31 (d, *J* = 2.3 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.4Hz, 0.5H), 7.71 (m, 1H), 7.65 (d, *J* = 8.9 Hz, 0.5H), 7.56 (s, 0.5H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.4Hz, 0.5H), 7.27 (d, *J* = 8.4Hz, 0.5H), 3.59 (m, 1H), 1.26 m, 2H), 0.58 (m, 2H); LC-MS (Method D) 357.4 $[M+H]^+$; RT 1.54 min

REDX06615 - 7-(6-aminopyridazin-3-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

(a) Compound 10 5-cyclopropyl-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-oxazolo[4,5-c]quinolin-4-one

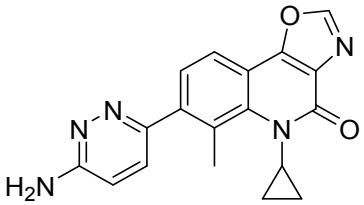


To a solution of 7-bromo-5-cyclopropyl-6-dimethyl-oxazolo[4,5-c]quinolin-4-one (1.6 g, 5.14 mmol) in 1,2-dimethoxyethane (30 mL) under N_2 was added potassium acetate (1.5 g, 15.42 mmol), bis(pinacolato)diboron (1.7 g, 6.68 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane complex (210 mg, 0.26 mmol). The resulting reaction mixture was heated to 75°C for 72 h. On cooling the reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 ml). The organic phase was separated and dried OVER $MgSO_4$, filtered and evaporated *in vacuo*. The resulting residue was purified by flash chromatography using a gradient of 0-100% EtOAc in DCM to give 5-

cyclopropyl-6-dimethyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one (1.6 g, 85 %) as a brown foam.

LC-MS (Method D) 367.5 $[M+H]^+$; RT 2.83 min

(b) 7-(6-aminopyridazin-3-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

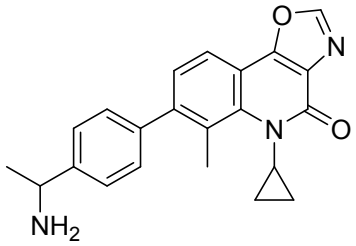


5-cyclopropyl-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one (300 mg, 0.82 mmol), 3-amino-6-bromopyridazine (0.15 mL, 1.23 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride dichloromethane complex (67 mg, 0.08 mmol), cesium carbonate (801 mg, 2.46 mmol) in 1,2-dimethoxyethane (2.5 mL) / water (0.65 mL) was heated in the microwave at 60 ^oC for 30 minutes under normal absorbance. After which time the mixture was diluted with MeOH and evaporated onto silica. This was then purified by ISCO chromatography using an eluent system of 0-40% DCM/MeOH. Evaporation of the fractions containing the desired compound left a brown solid. The brown solid was further purified by dissolving the desired compound in methanol (*note* impurities do not dissolve in neat methanol). Methanol was then evaporated to dryness, leaving 7-(6-aminopyridazin-3-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (6 mg, 2 %) as a yellow solid

1H NMR: (400MHz DMSO-d6): δ 8.79 (s, 1H) 7.83 (d, *J* =8.0 Hz, 1H) 7.51 (d, *J* =2.2 Hz, 1H) 7.45 (d, *J* = 2.2 Hz, 1H) 6.88 (d, *J* =7.9 Hz, 1H) 6.57 (d, J =8.7 Hz, 1H) 3.59-3.52 (m, 1H), 1.21 (m, 2H) 0.52 (m, 2H).

LCMS: 334.4 $[M+H]^+$; RT 1.38 min.

REDX06627 - 7-[4-(1-aminoethyl)phenyl]-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one

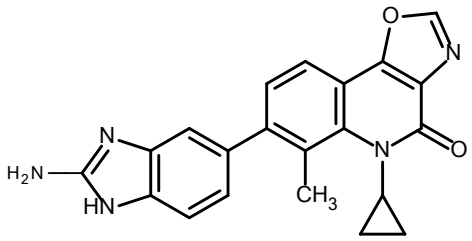


5-cyclopropyl-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one (198.93mg, 0.5400mmol) , 1-(4-bromophenyl)ethanamine (0.12mL, 0.8100mmol) , [1,1'-Bis(diphenylphosphino)ferrocene]Palladium(II) chloride dichloromethane complex (44.36mg, 0.0500mmol) , Cesium Carbonate (530.96mg, 1.63mmol) in 1,2-Dimethoxyethane (4.mL, 0.5400mmol) / Water (1mL) was heated in the microwave at 60°C for 30 minutes. The mixture was then diluted with MeOH and evaporated onto silica and then purified by column chromatography using an eluent system of 0-30% DCM/MeOH. The fractions containing the desired product were evaporated to dryness to give 7-[4-(1-aminoethyl)phenyl]-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (5mg, 0.0139mmol, 2.561% yield) as a beige solid

^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d,*J*= 2.8 Hz, 2H), 7.75 (d,*J*= 7.9 Hz, 1H), 7.52 (d,*J*= 7.9 Hz, 2H), 7.44 (d,*J*= 7.8 Hz, 2H), 7.21 (d,*J*= 7.9 Hz, 1H), 4.48 (q,*J*= 6.7 Hz, 1H), 3.53 (m, 1H), 2.44 (s, 3H), 1.61 (d,*J*= 6.8 Hz, 3H), 1.25 – 1.07 (m, 2H), 0.58 – 0.46 (m, 2H).

(ES^+, short BASIC): 1.63 min, m/z 360.4 $[M+H]^+$

REDX07125 – 7-(2-amino-1*H*-1,3-benzodiazol-5-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one



To a stirred solution of 6-bromo-1*H*-1,3-benzodiazol-2-amine (106 mg, 0.50 mmol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) in DCM (2 mL) was added Et_3N (0.1 mL, 0.72 mmol) followed by a solution of di-*tert*-butyl dicarbonate (123 mg, 0.56 mmol) in DCM (1 mL). The resulting reaction mixture was further stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the resulting residue purified by flash chromatography using a gradient of 0-80% EtOAc in Petroleum ether (40-60) to give an off-white solid of the desired Boc protected adducts as a mixture of isomers (80 mg, 51%)

LC-MS (Method B) 312.0/314.0 $[M+H]^+$; RT 2.56 min.

A mixture of the Boc protected adducts (80 mg, 0.26 mmol), 5-cyclopropyl-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazolo[4,5-c]quinolin-4-one (83 mg, 0.23 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (11 mg, 0.02 mmol), XPhos Pd G2 (18 mg, 0.02 mmol) and Cs_2CO_3 (222 mg, 0.68 mmol) in 1,2-dimethoxyethane (1 mL) and H_2O (0.25 mL) was irradiated with microwaves at 60 ^oC for 80 min. The reaction mixture was then dry loaded onto silica and purified by flash chromatography using a gradient of 0-100% EtOAc in Petroleum ether (40-60) to give an off white solid (70 mg) of the desired Suzuki adducts as a mixture of Boc protected isomers (70 mg, 66%).

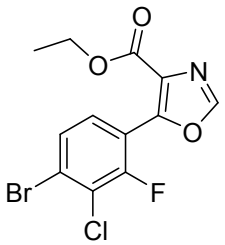
LC-MS (Method B) 472.1 $[M+H]^+$; RT 2.18/2.31 min.

To a stirred solution of the Suzuki adducts (70 mg, 0.15 mmol) in DCM (1 mL) was added TFA (0.25 mL, 3.27 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h and then quenched with saturated aq. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting residue was triturated with EtOAc and the resulting solid filtered and dried under vacuum to give 7-(2-amino-1*H*-1,3-benzodiazol-6-yl)-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one (23 mg, 42 %) as an off-white solid.

^1H NMR (400MHz, CD_3OD): δ ppm 8.53 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.43 (s, 1H), 7.37 (m, 2H), 3.66 (m, 1H), 2.58 (s, 3H), 1.32 (m, 2H), 0.68 (m, 2H); LC-MS (Method B) 372.1 $[M+H]^+$; RT 1.67 min.

REDX07368 - 7-(4-amino-2,5-difluoro-phenyl)-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one

(a) Compound 21 (step 1) 4-bromo-3-chloro-2-fluoro-benzoyl chloride



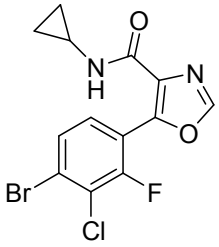
4-Bromo-3-chloro-2-fluoro-benzoic acid (11.9 g, 47.11 mmol) 4-bromo-3-chloro-2-fluoro-benzoic acid (11.9 g, 47.11 mmol) in DCM (60 mL) was treated with oxalyl chloride (5.98 mL, 70.67 mmol) followed by catalytic DMF (1 drop). The mixture was stirred for 1 h, then

evaporated and coevaporated from DCM (x3) and the resultant product was used immediately in the following reaction. Yield presumed quantitative.

Ethyl Isocyanoacetate (1.91 mL, 17.47 mmol) in THF (25 mL) was cooled to 0 °C. Triethylamine (6.64 mL, 47.66 mmol) was added dropwise followed by the addition of 4-bromo-3-chloro-2-fluoro-benzoyl chloride (4.3 g, 15.89 mmol) in THF (20 mL) over 5 min. The reaction was then allowed to warm to rt and stirred o/n. The mixture was diluted with ethyl acetate (250 mL) and washed with 1M HCl (2 x 100 mL), sat. $NaHCO_3$ (3 x 50 ml) and brine (50 mL). The organic layer was then dried over Na_2SO_4, filtered and evaporated to afford ethyl 5-(4-bromo-3-chloro-2-fluoro-phenyl)oxazole-4-carboxylate (4.58 g, 83 %) as a brown solid.

LC-MS (Method A) 347.9/349.9 $[M+H]^+$; RT 3.34 min.

(b) Compound 21 (step 2) 5-(4-bromo-3-chloro-2-fluoro-phenyl)-N-cyclopropyl-oxazole-4-carboxamide



Ethyl 5-(4-bromo-3-chloro-2-fluoro-phenyl)oxazole-4-carboxylate (4.6 g, 13.14 mmol) in 1,4-dioxane (150mL) was treated with lithium hydroxide hydrate (1.76 g, 73.47 mmol) (1 M aq) and stirred at rt o/n. The reaction mixture was then evaporated to remove dioxane, then diluted with 1M NaOH (aq. 50 mL) and washed with ethyl acetate (2 x 50 mL). The aqueous layer was then acidified with 1M HCl and extracted with ethyl acetate (2 x 150 mL) and the organic extracts were combined and washed with brine (100 mL). The combined organics

were then dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give 5-(4-bromo-3-chloro-2-fluoro-phenyl)oxazole-4-carboxylic acid as a pale yellow oil (3.54 g, 84%)

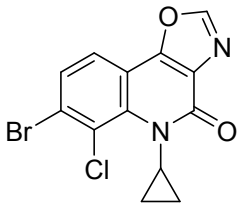
This was suspended in DCM (60 mL) and oxalyl chloride (1.4 mL, 16.57 mmol) was added, followed by one drop of DMF. The reaction mixture was then allowed to stir at rt for 1 h, until gas evolution ceased.

The solvent was removed from the reaction mixture and the residue was re-dissolved and coevaporated from DCM (x 3) to remove residual oxalyl chloride.

DCM (50 mL) was then added to the crude reaction mixture followed by cyclopropylamine (1.37mL, 19.81 mmol) dropwise over 5 min and stirred at rt for 1.5 h. The mixture was then diluted with DCM (100 mL) and washed with 0.5N HCl (2 x 50 mL) then sat.$NaHCO_3$ soln (3 x 50 mL) and brine (50 mL). Dried (Na_2SO_4) and evaporated to give 5-(4-bromo-3-chloro-2-fluoro-phenyl)-N-cyclopropyl-oxazole-4-carboxamide (3.68g, 10.234mmol, 92 % yield) as a yellow powder.

LC-MS (Method A) 38.9/360.9 $[M+H]^+$; RT 3.04 min.

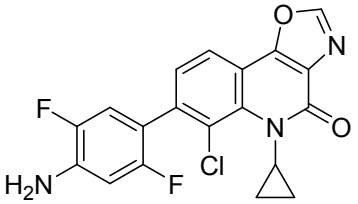
(c) Compound 21 (step 3) 7-Bromo-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one



To a solution of 5-(4-bromo-3-chloro-2-fluoro-phenyl)-*N*-cyclopropyl-oxazole-4-carboxamide (2.8 g, 7.84 mmol) in DMF (25 mL) was added potassium phosphate tribasic (5.0 g, 23.53 mmol) and the reaction mixture heated to 120 ^oC for 2 h. At this point the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic

layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude product. Further purification by flash chromatography eluting with a gradient (20 % to 75 % EtOAc in Petrol Ether) gave the 7-bromo-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one (1g, 38 %) as a light yellow solid. LC-MS (Method A) 339.0/341.0 $[M+H]^+$; RT 2.61 min.

(d) REDX07368 7-(4-amino-2,5-difluoro-phenyl)-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one



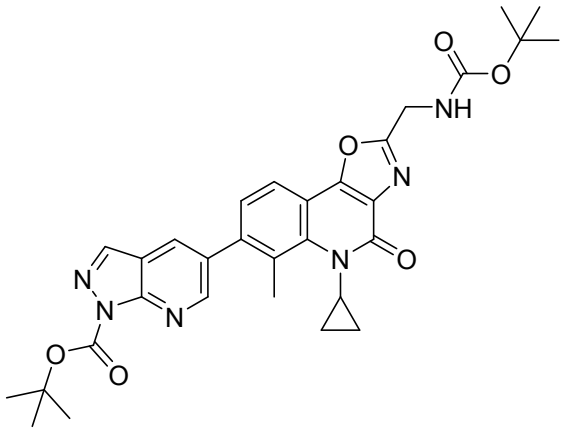
To a solution of 7-bromo-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one (38 mg, 0.11 mmol), 4-amino-2,5-difluorobenzeneboronic acid pinacol ester (37 mg, 0.15 mmol) and cesium carbonate (109 mg, 0.34 mmol) in a mixture of monoglyme (1 mL) and water (0.3 mL) was added 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (5 mg, 0.01 mmol) and XPhos Pd G2 (9 mg, 0.01 mmol). The reaction mixture was then heated to 60°C for 1 h using a microwave reactor. The reaction mixture was then evaporated onto silica and purified by flash chromatography using a gradient of 100% pet ether to 100% EtOAc. Product containing fractions were combined to yield 7-(4-amino-2,5-difluoro-phenyl)-6-chloro-5-cyclopropyl-oxazolo[4,5-c]quinolin-4-one (2 mg, 3.6 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.09 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.95 (dd, J = 11.0 Hz, 7.0 Hz, 1H), 6.61 (dd, J = 11.0 Hz, 7.0 Hz, 1H), 3.99 (m, 2H), 3.75 (m, 1H), 1.55 (m, 2H), 1.32 (m, 2H);

LC-MS (Method A) 388.4/390.4 $[M+H]^+$; RT 2.68 min.

REDX07473 – 2-(aminomethyl)-5-cyclopropyl-6-methyl-7-(1H-pyrazolo[3,4-b]pyridin-5-yl)oxazolo[4,5-c]quinolin-4-one

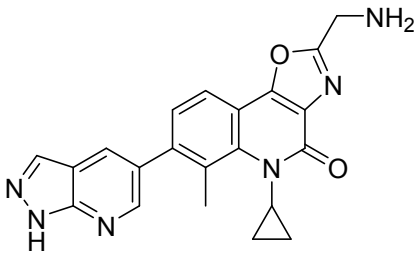
(a) *tert*-butyl 5-[2-[(tert-butoxycarbonylamino)methyl]-5-cyclopropyl-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-7-yl]pyrazolo[3,4-b]pyridine-1-carboxylate



Prepared using tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridine-1-carboxylate and *tert*-butyl N-({7-bromo-5-cyclopropyl-6-methyl-4-oxo-[1,3]oxazolo[4,5-c]quinolin-2- yl}methyl)carbamate as described for REDX04139.

LC-MS (Method E) 587.3, $[M+H]^+$; RT 2.91 min.

(b) 2-(aminomethyl)-5-cyclopropyl-6-methyl-7-(1H-pyrazolo[3,4-b]pyridin-5-yl)oxazolo[4,5-c]quinolin-4-one

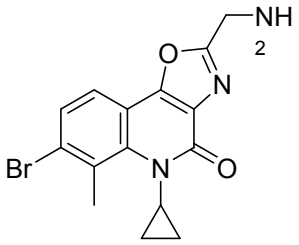


To a stirred solution of *tert*-butyl 5-[2-[(tert-butoxycarbonylamino)methyl]-5-cyclopropyl-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-7-yl]pyrazolo[3,4-b]pyridine-1-carboxylate (49 mg, 0.08 mmol) / *tert*-butyl *N*-[[5-cyclopropyl-6-methyl-4-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-yl)oxazolo[4,5-c]quinolin-2-yl]methyl]carbamate (41 mg, 0.08 mmol) in DCM (1 mL), was added trifluoroacetic acid (0.15 mL, 1.96 mmol) at rt. After 2h, the reaction mixture was put in the fridge overnight. This was then diluted with DCM and washed with saturated sodium bicarbonate, passed through a hydrophobic frit. The filtrate was evaporated to dryness. This was then purified by column chromatography, eluting with 0 - 5% MeOH/DCM to give the desired compound. 15 mg, 46%

^{1}H NMR (DMSO-d6) δ 8.63 (s, 1H) 8.35 (s, 1H), 8.26 (s, 1H), 7.83 (d, *J* =2.2 Hz, 1H) 7.42 (d, *J* =2.2 Hz, 1H), 4.11 (s, 2H), 3.62-3.59 (m, 1H), 1.28 (m, 2H) 0.58 (m, 2H). LC-MS (Method B) 387.1, $[M+H]^+$; RT 1.23 min.

REDX07517 – 2-(aminomethyl)-5-cyclopropyl-7-(1H-indazol-5-yl)-6-methyloxazolo[4,5-c]quinolin-4(5H)-one

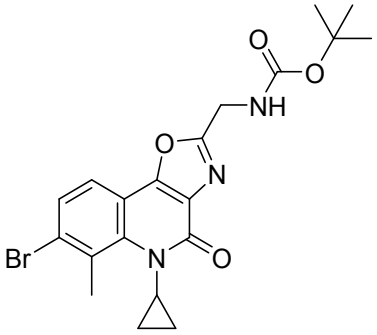
(a) Compound (44) 2-(aminomethyl)-7-bromo-5-cyclopropyl-6-methyl-[1 ,3]oxazolo[4,5-c]quinolin-4-one



To a solution of 2-(azidomethyl)-7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4- one (1.3 g, 3.47 mmol) in THF (20 mL)/H_2O (2 mL) was added triphenylphosphine (1.37 g, 5.21 mmol). This was heated to reflux for 1 h. The reaction mixture was evaporated to remove the THF. The remaining aq. was extracted with EtOAc followed by DCM and the combined organic extracts were dried over Na_2SO_4, filtered and evaporated to give a crude solid. The crude was purified by column chromatography using 0 to 7% methanolic ammonia (1 M) in DCM to yield 2-(aminomethyl)-7-bromo-5-cyclopropyl-6- methyl-[1 ,3]oxazolo[4,5-c]quinolin-4-one (1.05 g, 87 %) as a solid.

LC-MS (Method D) 348.0/350.0 $[M+H]^+$; RT 1.58 min

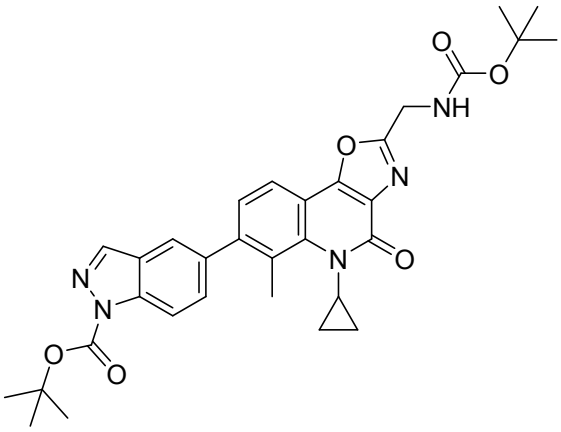
(b) Compound (45) tert-butyl N-({7-bromo-5-cyclopropyl-6-methyl-4-oxo-[1 ,3]oxazolo[4,5-c]quinolin-2- yl}methyl)carbamate



To a solution of 2-(aminomethyl)-7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4- one (1.05 g, 3.02 mmol) and NEt_3 (0.5 ml, 3.62 mmol) in DCM (15 ml) was added di-tert- butyl dicarbonate (723 mg, 3.32 mmol) in DCM (2 ml) and stirred at room temperature for 2 h. The reaction mixture was concentrated then purified by column chromatography, eluting with 0-80% EtOAc in petroleum ether (40-60) to give *tert*-butyl N-({7-bromo-5-cyclopropyl-6- methyl-4-oxo-[1 ,3]oxazolo[4,5-c]quinolin-2 yl}methyl)carbamate (1.0 g, 74 % yield) as a pale solid.

LC-MS (Method D) 448.4, 450.4 $[M+H]^+$; RT 3.37 min

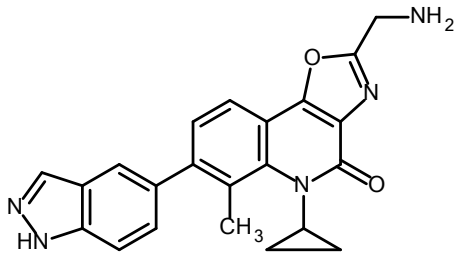
(c) **tert-butyl 5-(2-(((tert-butoxycarbonyl)amino)methyl)-5-cyclopropyl-6-methyl-4-oxo-4,5-dihydrooxazolo[4,5-c]quinolin-7-yl)-1H-indazole-1-carboxylate**



Prepared using *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate and *tert*-butyl N-({7-bromo-5-cyclopropyl-6-methyl-4-oxo-[1,3]oxazolo[4,5-c]quinolin-2- yl}methyl)carbamate as described for REDX04139.

LC-MS (Method E) 586.2, $[M+H]^+$; RT 3.42 min.

(d) 2-(aminomethyl)-5-cyclopropyl-7-(1H-indazol-5-yl)-6-methyloxazolo[4,5-c]quinolin-4(5H)-one

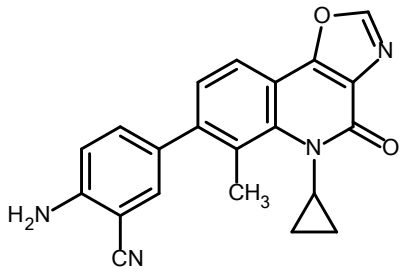


To a stirred solution of *tert*-butyl 5-[2-[(tert-butoxycarbonylamino)methyl]-5-cyclopropyl-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-7-yl]indazole-1-carboxylate (34 mg, 0.0600 mmol) / *tert*-butyl *N*-[[5-cyclopropyl-7-(1H-indazol-5-yl)-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-2-

yl]methyl]carbamate (28 mg, 0.06 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.1 mL, 1.31 mmol). This was stirred at rt for 1 h. The reaction mixture was diluted with DCM and washed with saturated sodium bicarbonate. The DCM extract was then dried over sodium sulfate, filtered and evaporated to dryness. The title compound was purified by column chromatography eluting with 0 - 5% 1M methanolic ammonia (15 mg, 67%).

^{1}H NMR (MeOD) *δ:* 13.5 (s, 1H), 8.40 (s, 1H), 7.88 (d, 1H), 7.76 (d, 1H), 7.65 (d, 1H), 7.44 (m, 1H), 7.32 (d, 1H), 4.12 (s, 2H), 3.70-3.66 (m, 1H), 2.20 (bs, 3H), 1.37-1.20 (m, 2H) 0.70-0.68 (m, 2H). LC-MS (Method E) 386.1, $[M+H]^+$; RT 4.95 min.

REDX07910 - 2-amino-5-(5-cyclopropyl-6-methyl-4-oxo-oxazolo[4,5-c]quinolin-7-yl)benzonitrile



Prepared using 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline and 7-bromo-5-cyclopropyl-6-methyl-oxazolo[4,5-c]quinolin-4-one as described for REDX04139.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.78 (s, 1H) 7.77 (d, *J* =8.0 Hz, 1H) 7.49 (d, *J* =2.2 Hz, 1H) 7.43 (dd, *J* =8.7,2.2 Hz, 1H) 7.28 (d, *J* =7.9 Hz, 1H) 6.91 (d, J =8.7 Hz, 1H) 6.30 (s, 2H) 3.59-3.52 (m, 1H) 1.27-1.20 (m, 2H) 0.51 (tt, *J* =5.5, 2.8 Hz, 2H) Methyl group under DMSO peak.

LC-MS (Method A): 2.35 min, m/z 355.0 $[M+H]^+$

Antibacterial susceptibility testing

Culturing and antibacterial susceptibility testing were performed in line with CLSI guidelines[1]. MICs were performed in triplicate and were determined by the broth microdilution method for routine testing and by the agar dilution method prior to determination of frequency of resistance.

References

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard–Ninth Edition M07-A9*. CLSI, Wayne, PA, USA, 2012.