Structural Requirements for Dihydrobenzoxazepinone Anthelmintics

Partridge, Frederick A.; Bataille, Carole J.R.; Forman, Ruth; Marriott, Amy E.; Forde-Thomas, Josephine; Häberli, Cécile; Dinsdale, Ria L.; O’Sullivan, James D.B.; Willis, Nicky J.; Wynne, Graham M.; Whiteland, Helen; Archer, John; Steven, Andrew; Keiser, Jennifer; Turner, Joseph D.; Hoffmann, Karl F.; Taylor, Mark J.; Else, Kathryn J.; Russell, Angela J.; Sattelle, David B.

Published in:
ACS Infectious Diseases

DOI:
10.1021/acsinfecdis.1c00025

Publication date:
2021

Citation for published version (APA):
Partridge, F. A., Bataille, C. J. R., Forman, R., Marriott, A. E., Forde-Thomas, J., Häberli, C., Dinsdale, R. L., O’Sullivan, J. D. B., Willis, N. J., Wynne, G. M., Whiteland, H., Archer, J., Steven, A., Keiser, J., Turner, J. D., Hoffmann, K. F., Taylor, M. J., Else, K. J., Russell, A. J., & Sattelle, D. B. (2021). Structural Requirements for Dihydrobenzoxazepinone Anthelmintics: Actions against Medically Important and Model Parasites: Trichuris muris, Brugia malayi, Heligmosomoides polygyrus, and Schistosoma mansoni. ACS Infectious Diseases, 7(5), 1260-1274. https://doi.org/10.1021/acsinfecdis.1c00025
Supporting Information

Structural requirements for dihydrobenzoxazepinone anthelmintics: actions against medically important and model parasites - *Trichuris muris*, *Brugia malayi*, *Heligmosomoides polygyrus* and *Schistosoma mansoni*

Short title: (70 characters) Dihydrobenzoxazepinone efficacy on human and model helminth parasites

Authors:
Frederick A Partridge¹, Carole JR Bataille², Ruth Forman³, Amy E Marriott⁴, Josephine Forde-Thomas⁵, Cécile Häberli⁶, Ria L Dinsdale², James DB O’Sullivan¹, Nicky J Willis², Graham M Wynne², Helen Whiteland⁵, John Archer⁴, Andrew Stevens⁴, Jennifer Keiser⁶, Joseph D Turner⁴, Karl F Hoffmann³, Mark J Taylor⁴, Kathryn J Else¹, Angela J Russell², and David B Sattelle¹

¹Centre for Respiratory Biology, UCL Respiratory, Division of Medicine, University College London, London, WC1E 6BT, United Kingdom
²Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Oxford, OX1 3TA, United Kingdom
³Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, United Kingdom
⁴Centre for Drugs and Diagnostics, Department of Tropical Disease Biology, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, United Kingdom
⁵Institute of Biological, Environmental and Rural Sciences (IBERS), Aberystwyth University, Aberystwyth, Wales, SY23 3DA, United Kingdom
⁶Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Socinstrasse 57, Basel, CH-4002, Switzerland.
⁷University of Basel, Petersplatz 1, Basel, CH-4001, Switzerland.
⁸Henry Royce Institute, The University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom
⁹Alzheimer’s Research UK UCL Drug Discovery Institute, University College London, Gower Street, London, WC1E 6BT, United Kingdom
¹⁰Centre for Neglected Tropical Diseases, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, United Kingdom
¹¹Department of Pharmacology, University of Oxford, Mansfield Road, Oxford, OX1 3QT, United Kingdom

* Corresponding authors: Email d.sattelle@ucl.ac.uk (DBS), kathryn.else@manchester.ac.uk (KJE), angela.russell@chem.ox.ac.uk (AJR)

¶ These authors contributed equally.
S1 File. Supporting information for synthetic chemistry

General Procedures .................................................................................................................. 3
Experimental data .................................................................................................................... 5
NMR Spectra .......................................................................................................................... 24
References ..................................................................................................................................61
Supplementary Figure 3 ......................................................................................................... 62
General Procedures

General Procedure 1

To a solution of the requisite aniline (1.0 eq.) in CH$_2$Cl$_2$ (6 mL/mmol) at room temperature was added the desired aldehyde (1.5 eq.) and AcOH (0.5 eq.). The resulting solution was then cooled to 0 °C before addition of NaBH(OAc)$_3$ (2.0 eq.). The mixture was warmed slowly to room temperature and stirred for 16 h before addition of CH$_2$Cl$_2$ (5 mL/mmol) and NaHCO$_3$ (sat. aq., 10 mL/mmol), and the aqueous layer extracted with CH$_2$Cl$_2$ (5x10 mL/mmol). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo and the crude residue was purified by column chromatography on silica gel to afford the desired methyl ester. A solution of LiAlH$_4$ (1.0 M in THF, 3.5 eq.) was added dropwise over a period of 5-10 min to an ice-cold solution of the requisite methyl ester (1.0 eq.) in THF (7 mL/mmol), and the reaction mixture was stirred for 1 h. NH$_4$Cl (sat. aq. sol, 3 mL/mmol) was then added and the aqueous layer extracted with EtOAc (3 x 35 mL/mmol), the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The resulting alcohol was used in the next step without further purification. To an ice-cold solution of desired alcohol in THF (2 mL/mmol) was added Et$_3$N (2.0 eq.), followed by chloroacetyl chloride (4.4 eq.). The reaction was warmed to room temperature and stirred for 16 h, at which time the crude reaction mixture was passed through a short pad of silica gel, eluted with EtOAc and the solution concentrated in vacuo. The crude residue was then dissolved in iPrOH (2 mL/mmol) before addition of NaOH (10 N, aq., 10 eq.). The reaction was stirred at room temperature for 2 h, diluted with CH$_2$Cl$_2$ (5 mL/mmol), washed with brine (ca 5 mL/mmol) and further extracted with CH$_2$Cl$_2$ (5 mL/mmol). The combined organic layers were dried (Na$_2$SO$_4$), concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel.

General Procedure 2
NaHCO₃ (1.5 M, aq., 3 eq.) was added to a solution of the bromide (1.0 eq.) and the boronic acid (1.3 eq.) in DMF (3 mL/mmol) in a microwave vial and the vessel was degassed with argon. The requisite Pd catalyst (5 mol%) was then added, the microwave vial was sealed and irradiated at 150 °C for 30 min. The reaction mixture was allowed to cool, diluted with EtOAc (5 mL/mmol), washed with 0.5 M aq. LiCl (3 x 3 mL/mmol). The combined organic layers were dried (Na₂SO₄), then concentrated in vacuo. Purification by column chromatography on silica gel (solvents as stated) afforded the desired product.

**General Procedure 3**

The requisite bromide (600 mg, 2.79 mmol, 1.0 eq.), K₂CO₃ (1.16 g, 8.37 mmol, 3.0 eq.), the requisite boronic acid (572 mg, 3.07 mmol, 1.1 eq.), and Pd(dppf)Cl₂ (100 mg, 0.140 mmol, 5 mol%) were added sequentially to a microwave vial equipped with a magnetic stirrer bar. The reaction vessel was fitted with a rubber septum and purged with N₂ for 5 min, before addition of a degassed solution of 1,4-dioxane/water (5:1, 8 mL) via syringe. The vial was then sealed and the reaction heated to 100 °C for 18 h. The mixture was cooled down, diluted with EtOAc (30 mL), and washed with a 50/50 solution of water and brine (2 x 30 mL). The organic phase was dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography on silica gel (solvents as stated) afforded the desired product.

**General Procedure 4** (Coppola et al., 2004)

To a solution of the requisite amide (1 eq.) in DMF (3 mL/mmol) was added the desired aryl bromide (1.3 eq.) followed by NaH (60% in oil, 1.3 eq.) portion-wise, and the resulting solution stirred for 18 h. The reaction was quenched with NH₄Cl (sat. aq. sol.), extracted with EtOAc (3 x 1 mL/mmol), dried (Na₂SO₄), then concentrated in vacuo. The compound was purified by flash column chromatography (silica gel).
Experimental data

3700 8-bromo-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 1, (4-bromo-2-((4-methylbenzyl)amino)phenyl)methanol (704 mg, 2.29 mmol) (obtained from the corresponding methyl-2-amino-4-bromobenzoate and benzaldehyde) afforded the title compound 3700 as a white solid (482 mg, 61%), after purification on silica gel (EtOAc:pentane, 1:9); mp = 155-157 °C (EtOAc); 1H NMR (500 MHz, CDCl3) δ 7.45 (d, J = 1.9 Hz, 1H), 7.36 (dd, J = 8.1, 1.8 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 5.04 (s, 2H), 4.45 (s, 2H), 4.04 (s, 2H), 2.29 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 168.3, 143.9, 137.6, 133.7, 131.9, 129.8, 129.5, 128.5, 127.9, 124.8, 123.6, 77.4, 77.4, 77.2, 76.9, 67.6, 67.5, 50.6, 21.2; m/z LRMS (ESI+): 370 [M+Na]+; HRMS (ESI+): calc for C17H17O2N81Br [M+H]+ 348.0417; found 348.0418.

3702 8-bromo-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one 68 (Zablocki et al., 2016)

Sodium azide (86 mg, 1.32 mmol, 1.5 eq.) was added over 45 min to an ice-cold solution of 7-bromochroman-4-one (200 mg, 0.881 mmol) in methanesulfonic acid (3 mL) and the resulting solution stirred at RT for 16 h. Conc. HCl (1 mL) was added, and the resulting solid filtered and washed with water, to afford the title compound 3702 as a beige solid (140 mg, 66%); 1H NMR (500 MHz, CDCl3) δ 7.89 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 1.9 Hz, 2H), 7.21 (d, J = 1.9 Hz, 1H), 6.56 (s, 1H), 4.43 – 4.38 (m, 2H), 3.52 (dd, J = 9.6, 5.0 Hz, 2H); 13C NMR (126 MHz, CDCl3) δ 169.0, 156.2, 133.8, 127.4, 126.1, 124.3, 121.8, 72.9, 41.9; m/z LRMS (ESI+): 243 [M+H]+; HRMS (EI): calc for C9H881BrNO2 (M+) 242.9718 found 242.9707.

3703 8-bromo-4-(4-methylbenzyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one
Following general procedure 4, amide 3702 (130 mg, 0.537 mmol) and 4-methylbenzyl bromide (199 mg, 1.07 mmol) afforded the title compound as a white solid (137 mg, 74%) after purification on silica gel (EtOAc:pentane, 1:9); mp = 64-66 ºC (EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 1.9 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.17 (s, 1H), 7.16 (d, J = 10.4 Hz, 2H), 4.77 (s, 2H), 4.16 (dd, J = 5.5, 4.6 Hz, 2H), 3.47 – 3.42 (m, 2H), 2.34 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.8, 154.6, 137.8, 133.8, 132.9, 129.7, 128.5, 126.8, 126.4, 125.9, 124.6, 50.9, 45.9, 21.3; m/z LRMS (ESI⁺): 370 [M+Na]+; HRMS (ESI⁺): calc. for C₁₇H₁₇O₂N₈1Br [M+H]+ 348.0417, found 348.0417.

3706 6-bromo-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 1, (2-bromo-6-((4-methylbenzyl)amino)phenyl)methanol (510 mg, 1.67 mmol) (obtained from the corresponding methyl 2-amino-6-bromobenzoate and 4-methylbenzaldehyde) afforded the title compound 3706 as a white solid (393 mg, 68%) after purification on silica gel (EtOAc:pentane, 1:9); mp = 121 ºC (EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.50 (dd, J = 6.5, 2.6 Hz, 1H), 7.24 (s, 1H), 7.26 – 7.21 (m, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 5.06 (s, 2H), 4.74 (s, 2H), 4.04 (s, 2H), 2.30 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.1, 144.1, 137.6, 133.7, 131.2, 130.7, 129.5, 129.4, 128.0, 125.3, 121.1, 77.4, 77.2, 76.9, 50.8, 21.2; m/z LRMS (ESI⁺): 370 [M(81Br)+Na]+; HRMS (ESI⁺): calc. for C₁₇H₁₇O₂N₈1Br [M+H]+ 348.0417 found 348.0417.

3827 8-bromo-1-(cyclohexylmethyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one
Following **general procedure 1**, ((4-bromo-2-((cyclohexylmethyl)amino)phenyl)methanol (310 mg, 0.863 mmol) (obtained from the corresponding methyl 2-amino-4-bromobenzoate and cyclohexane-carbaldehyde) afforded the title compound **3827** as an off white solid (262 mg, 90%) after purification on silica gel (EtOAc:pentane, 1:4); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 (d, \(J = 1.9\) Hz, 1H), 7.39 (dd, \(J = 8.0, 1.8\) Hz, 1H), 7.22 (d, \(J = 8.0\) Hz, 1H), 4.62 (s, 2H), 3.95 (s, 2H), 3.77 (d, \(J = 6.8\) Hz, 2H), 1.73 – 1.54 (m, 8H), 1.14 (td, \(J = 10.7, 9.0, 2.4\) Hz, 3H), 1.01 – 0.87 (m, 2H); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.3, 144.3, 132.2, 129.5, 128.2, 124.4, 123.7, 67.8, 67.7, 52.9, 36.8, 31.3, 26.3, 25.8; \(m/z\) LRMS (ESI\(^+\)): 362 [M+Na]\(^+\); HRMS (ESI\(^+\)): calc. for C\(_{16}\)H\(_{21}\)NO\(_2\)Br [M+H]\(^+\) 338.07502, found 338.07519.

**3829 1-benzyl-7-bromo-1,5-dihydropyrido[1,4]oxazepin-2(3H)-one**

Following **general procedure 1**, (2-(benzylamino)-5-bromophenyl)methanol (940 mg, 3.22 mmol) (obtained from the corresponding methyl 2-amino-5-bromobenzoate and benzaldehyde) afforded the title compound **3829** as a white solid (707 mg, 66%), after purification on silica gel (EtOAc:pentane, 1:9); mp = 115-116 °C (EtOAc); \(^1\)H NMR (500 MHz, MeOD) \(\delta\) 7.61 (dd, \(J = 8.6, 2.3\) Hz, 1H), 7.39 (d, \(J = 8.6\) Hz, 1H), 7.30 – 7.18 (m, 5H), 5.14 (s, 3H), 4.44 (s, 2H), 3.99 (s, 2H); \(^13\)C NMR (126 MHz, MeOD) \(\delta\) 170.3, 142.6, 138.2, 134.2, 134.2, 133.1, 129.7, 129.1, 128.8, 124.9, 120.8, 68.3, 68.1, 51.2, 49.5, 49.3, 49.2, 49.0, 48.8, 48.7, 48.5; \(m/z\) LRMS (ESI\(^+\)): 356 [M(\(^81\)Br)+Na]\(^+\) 354 ; HRMS (ESI\(^+\)): calc. for C\(_{16}\)H\(_{15}\)O\(_2\)N\(_{81}\)Br [M+H]\(^+\) 334.0260, found 334.0261.

**4119 7-bromo-1-(cyclopropylmethyl)-1,5-dihydropyrido[1,4]oxazepin-2(3H)-one**
Following general procedure 1, (5-bromo-2-((cyclopropylmethyl)amino)phenyl)methanol (280 mg, 0.833 mmol) (obtained from the corresponding methyl 2-amino-5-bromobenzoate and cyclopropane-carbaldehyde) afforded the title compound 4119 as a white solid (262 mg, 90%), after purification on silica gel ((EtOAc:pentane, 1:4); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (dd, $J = 8.6$, 2.4 Hz, 1H), 7.51 (d, $J = 2.3$ Hz, 1H), 7.18 (d, $J = 8.6$ Hz, 1H), 4.65 (s, 2H), 3.97 (s, 2H), 3.79 (d, $J = 7.2$ Hz, 2H), 1.10 – 0.95 (m, 1H), 0.49 – 0.37 (m, 2H), 0.28 – 0.19 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.9, 141.9, 133.4, 133.1, 132.0, 123.5, 119.6, 67.6, 67.4, 51.6, 10.2, 4.0; $m/z$ LRMS (ESI$^+$): 296 [M+Na]$^+$; HRMS (ESI$^+$): calc. for C$_{13}$H$_{15}$NO$_2$Br [M+H]$^+$ 296.0286, found 296.0284.

4118a 7-bromo-1-methyl-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 4, bromide 3593 (75 mg, 0.310 mmol) afforded the title compound 4118a as a white solid (262 mg, 90%), after purification on silica gel (EtOAc:pentane, 1:4); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (dd, $J = 8.6$, 2.3 Hz, 1H), 7.50 (d, $J = 2.3$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 1H), 4.60 (s, 2H), 4.02 (s, 2H), 3.41 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.3, 142.9, 133.3, 133.2, 131.0, 122.4, 119.3, 67.8, 67.5, 34.8; $m/z$ LRMS (ESI$^+$): 255 [M+H]$^+$.

3698 6-bromo-2-(4-methylbenzyl)-3,4-dihydroisoquinolin-1(2H)-one

Following general procedure 4, 6-bromo-3,4-dihydro-isoquinoline (570 mg, 2.52 mmol) and 4-methylbenzyl bromide (873 mg, 3.28 mmol) afforded the title compound 3698 as a white solid (130 mg, 98%) after purification on silica gel (EtOAc:pentane, 1:4); mp = 97-99 °C (EtOAc); $^1$H NMR (400
MHz, CDCl$_3$) δ 8.00 (d, $J = 8.3$ Hz, 1H), 7.33 (dd, $J = 2.0$, 1.0 Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 7.9$ Hz, 2H), 4.73 (s, 2H), 3.46 (dd, $J = 7.1$, 6.2 Hz, 2H), 2.90 (t, $J = 6.6$ Hz, 2H), 2.33 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.9, 140.0, 137.3, 134.2, 130.4, 130.3, 129.9, 129.4, 128.5, 128.2, 128.2, 126.4, 50.2, 45.1, 27.9, 21.2; m/z LRMS (ESI$^+$): 330 [M+H]$^+$; HRMS (EI$^+$): calc. for C$_{17}$H$_{16}$BrNO (M$^+$) requires 331.0395 found 331.0385.

3145 1-(cyclohexylmethyl)-8-(pyridin-3-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 3, bromide 3827 ((400 mg, 1.19 mmol) and 13-pyridyl boronic acid (190 mg, 1.54 mmol) afforded the title product 3145 (398 mg, 99%) as a yellow oil that solidified on standing after purification on silica gel (MeOH:CH$_2$Cl$_2$, 5%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.87 (s, 1H), 8.67 (s, 1H), 7.91 (dt, $J = 7.9$, 1.9 Hz, 1H), 7.52 – 7.41 (m, 3H), 4.73 (s, 2H), 4.02 (s, 2H), 3.88 (d, $J = 6.9$ Hz, 2H), 1.76 – 1.58 (m, 6H), 1.22 – 1.08 (m, 3H), 1.04 – 0.90 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.5, 149.3, 148.3, 143.8, 140.0, 135.6, 134.5, 131.6, 129.1, 125.1, 123.8, 119.7, 67.9, 67.9, 53.0, 36.8, 31.3, 26.3, 25.7; m/z LRMS (ESI$^+$): 337 [M+H]$^+$; HRMS (ESI$^+$): calc. for C$_{21}$H$_{25}$N$_2$O$_2$ [M+H]$^+$ 337.19105, found 337.19085.

3593 1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 1, title compound 3593 was obtained from o-aminobenzyl alcohol (1.00 g, 8.12 mmol) as an orange solid (621 mg, 38%), after purification on silica gel (EtOAc:pentane, 2:3); mp = 98-99 °C (EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.65 (s, 1H), 8.09 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.23 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.15 (td, $J = 7.5$, 1.2 Hz, 1H), 4.76 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.9, 136.7, 130.0, 129.4, 129.0, 125.2, 122.5, 64.4, 43.1; m/z LRMS (ESI$^+$): 164 [M+H]$^+$; HRMS (ESI$^+$): calc. for C$_9$H$_{10}$NO$_2$ [M+H]$^+$ 164.0701, found 164.0706.
Following general procedure 4, amide 3593 (100 mg, 0.612 mmol) and benzyl bromide (145 µL, 1.23 mmol) afforded the title compound as a white solid (43 mg, 28%) after purification on silica gel (EtOAc:pentane, 1:4); mp = 90-92 °C (EtOAc); 1H NMR (500 MHz, CDCl₃) δ 7.40 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H), 7.26 (s, 0H), 5.12 (s, 2H), 4.52 (s, 2H), 4.06 (s, 2H); 13C NMR (126 MHz, CDCl₃) δ 168.6, 142.7, 137.2, 130.7, 130.2, 129.6, 128.8, 127.9, 127.7, 126.8, 121.4, 68.1, 67.7, 50.9; m/z LRMS (ESI⁺): 276 [M+Na⁺]; HRMS (ESI⁺): calc. for C₁₆H₁₆NO₂ [M+H⁺] 254.1175, found 254.1176.

Following general procedure 2 using Pd(PPh₃)₄, bromide 3146 (Partridge et al., 2017) (50 mg, 0.144 mmol), phenylboronic acid (23 mg, 0.187 mmol) afforded the title compound 3596 as yellow solid (14 mg, 28%) after purification on silica gel (EtOAc:pentane, 1:9); mp = 102-105 °C (EtOAc); 1H NMR (500 MHz, CDCl₃) δ 7.61 (dd, J = 8.4, 2.2 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.51 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 8.4, 6.9 Hz, 2H), 7.37 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 5.11 (s, 2H), 4.58 (s, 2H), 4.11 (s, 2H), 2.30 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 168.6, 141.8, 139.7, 139.7, 137.4, 134.2, 129.9, 129.5, 129.2, 129.1, 128.7, 127.9, 127.9, 127.0, 121.8, 77.4, 77.2, 76.9, 68.3, 67.8, 50.6, 21.2; m/z LRMS (ESI⁺): 344 [M+H⁺]; HRMS (ESI⁺): calc. for C₂₃H₂₂NO₂ [M+H⁺] 344.1645, found 344.1643.
Following general procedure 2 using Pd(PPh$_3$)$_4$, bromide 3146 (50 mg, 0.144 mmol) and 4-methoxyphenylboronic acid (29 mg, 0.188 mmol) afforded the title compound 3599 as a yellow solid (11 mg, 21%) after purification on silica gel ((EtOAc:pentane, 1:9); mp = 48-50 °C (EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.53 – 7.47 (m, 2H), 7.46 (d, $J = 2.2$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 7.9$ Hz, 2H), 7.02 – 6.94 (m, 2H), 5.10 (s, 2H), 4.56 (s, 2H), 4.10 (s, 2H), 3.85 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.6, 159.6, 141.1, 139.3, 137.4, 134.2, 132.2, 129.9, 129.5, 128.7, 128.2, 128.1, 127.9, 121.8, 114.5, 77.4, 77.2, 76.9, 68.4, 67.8, 55.5, 50.6, 21.2; m/z LRMS (ESI$^+$): 396 [M+Na]+; HRMS (ESI$^+$): calcd. for C$_{24}$H$_{24}$NO$_3$ [M+H]$^+$ 374.1750, found 374.1749.

3600 7-(4-fluorophenyl)-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 2 using Pd(PPh$_3$)$_4$, bromide 3146 (50 mg, 0.144 mmol) and 4-fluorophenylboronic acid (26 mg, 0.188 mmol) afforded the title compound 3600 as a yellow solid (14 mg, 27%) after purification by flash column chromatography (EtOAc:pentane, 15%); mp = 127-129 °C (EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (d, $J = 2.2$ Hz, 1H), 7.34 (s, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 7.9$ Hz, 2H), 5.10 (s, 2H), 4.57 (s, 2H), 4.10 (s, 2H), 2.30 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.6, 163.8, 161.8, 141.7, 138.7, 137.4, 134.1, 130.0, 129.5, 129.1, 128.7, 128.6, 128.5, 127.9, 121.9, 116.1, 115.9, 77.4, 77.2, 76.9, 68.3, 67.8, 50.6, 21.2; m/z LRMS (ESI$^+$): 385 [M+Na]+; HRMS (ESI$^+$): calcd. for C$_{23}$H$_{21}$FNO$_2$ [M+H]$^+$ 362.1550, found 362.1546.
3601 1-(4-methylbenzyl)-7-(p-tolyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following **general procedure 2** using Pd(PPh₃)₄, bromide 3146 (50 mg, 0.144 mmol) and 4-tolylboronic acid (26 mg, 0.188 mmol) afforded the title compound 3601 as a pale yellow solid (167 mg, 32%) after purification on silica gel (EtOAc:pentane, 15%); mp = 100-101 °C (EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.49 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.26 (s, 6H), 7.19 – 7.14 (m, 2H), 7.08 (d, J = 7.9 Hz, 2H), 5.10 (s, 2H), 4.57 (s, 2H), 4.10 (s, 2H), 2.39 (s, 3H), 2.30 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.6, 141.5, 139.6, 137.8, 137.4, 136.8, 134.2, 129.9, 129.8, 129.5, 128.9, 128.4, 127.9, 126.9, 121.7, 68.4, 67.8, 50.6, 21.3, 21.2; m/z LRMS (ESI⁺): 380 [M+Na]⁺; HRMS (ESI⁺): calc. for C₂₄H₂₄NO₂ [M+H]⁺ 358.1801, found 358.1803.

3697 methyl 4-(1-(4-methylbenzyl)-2-oxo-1,2,3,5-tetrahydrobenzo[e][1,4]oxazepin-7-yl)benzoate

Following **general procedure 2** using Pd(dppf)Cl₂, bromide 3146 (200 mg, 0.578 mmol) and 4-methoxycarbonyl-phenylboronic acid (135 mg, 0.751 mmol), afforded the title compound 3697 as a pale yellow solid (51 mg, 22%) after purification on silica gel (EtOAc:pentane, 3:7); mp = 138-140 °C (EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 8.11 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.08 (d, J = 7.9 Hz, 2H), 5.12 (s, 2H), 4.59 (s, 2H), 4.11 (s, 2H), 3.94 (s, 3H), 2.30 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.8, 167.2, 144.3, 142.8, 138.6, 137.7, 134.3, 130.7, 130.4, 129.8, 129.7, 129.7, 129.1, 128.1, 127.2, 122.2, 52.6, 50.8,
21.5.; m/z LRMS (ESI\(^+\)) 424 [M+Na\(^+\)]; HRMS (ESI\(^+\)): calc. for C\(_{23}\)H\(_{24}\)NO\(_4\) [M+H\(^+\)] 402.1700, found 402.1701.

**3701 1-(4-methylbenzyl)-8-(pyridin-4-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one**

![Chemical structure of 3701](image)

Following general procedure 2 using Pd(dppf)Cl\(_2\), bromide 3700 (201 mg, 0.578 mmol) and 4-pyridinylboronic acid (106 mg, 0.867 mmol) afforded the title compound 3701 as a brown solid (44 mg, 24%) after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\); 2%); mp = 108-110 °C (MeOH); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.69 (d, \(J = 6.1\) Hz, 1H), 7.50 (d, \(J = 1.7\) Hz, 1H), 7.49 (dd, \(J = 7.7, 1.7\) Hz, 1H), 7.45 – 7.39 (m, 3H), 7.17 (d, \(J = 7.9\) Hz, 2H), 7.08 (d, \(J = 7.8\) Hz, 2H), 5.14 (s, 2H), 4.57 (s, 2H), 4.10 (s, 2H), 2.30 (s, 3H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.5, 150.7, 147.1, 143.5, 140.3, 137.6, 134.0, 131.5, 130.2, 129.6, 128.0, 125.3, 121.7, 120.1, 67.8, 67.8, 50.7, 21.3.; m/z LRMS (ESI\(^+\)) 345 [M+H\(^+\)]; HRMS (ESI\(^+\)): calc. for C\(_{22}\)H\(_{21}\)N\(_2\)O\(_2\) [M+H\(^+\)] 345.1578, found 345.1597

**3704 4-(4-methylbenzyl)-8-(pyridin-4-yl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one**

![Chemical structure of 3704](image)

Following general procedure 2 using Pd(dppf)Cl\(_2\), bromide 3703 (40 mg, 115 mmol) and 4-pyridinylboronic acid (18 mg, 0.150 mmol) afforded the title compound 3704 as a brown solid (37 mg, 93%) after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\); 2%); mp = 127-129 °C (MeOH); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.72 (s, 1H), 7.57 (s, 1H), 7.45 (dd, \(J = 8.1, 1.8\) Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 (d, \(J = 3.4\) Hz, 1H), 7.17 (d, \(J = 7.8\) Hz, 1H), 4.81 (s, 1H), 4.22 (t, \(J = 5.1\) Hz, 1H), 3.50 (t, \(J = 5.0\) Hz, 1H), 2.35 (s, 2H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 168.0, 154.6, 149.6, 142.4, 137.8, 133.8, 132.7, 129.7, 128.5, 127.5, 122.0, 120.1, 73.5, 50.9, 46.0, 21.3.; m/z LRMS (ESI\(^+\)) 345 [M+H\(^+\)]; HRMS (ESI\(^+\)): calc. for C\(_{22}\)H\(_{21}\)N\(_2\)O\(_2\) [M+H\(^+\)] 345.1578, found 345.1596.
**3705 1-(4-methylbenzyl)-7-(pyrimidin-5-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one**

Following **general procedure 2** using Pd(dppf)Cl₂, bromide 3146 (50 mg, 0.144 mmol) and pyrimidine-5-boronic acid (23 mg, 0.188 mmol) afforded the title compound 3705 as a pale yellow solid (15 mg, 31%) after purification on silica gel (EtOAc:pentane, 2:3); mp = 192-194 °C (EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 9.22 (s, 1H), 8.94 (s, 2H), 7.52 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 8.1 Hz, 3H), 7.09 (d, J = 7.9 Hz, 2H), 5.13 (s, 2H), 4.60 (s, 2H), 4.12 (s, 2H), 2.30 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.4, 158.0, 154.9, 143.4, 137.6, 133.9, 133.1, 132.6, 130.7, 129.6, 129.2, 128.6, 127.9, 122.5, 68.1, 67.9, 50.5, 21.3; m/z LRMS (ESI⁺): 346 [M+H]+; HRMS (ESI⁺): calc. for C₂₁H₂₀N₃O₂ [M+H]+ 346.1550 found 346.1547.

**3707 1-(4-methylbenzyl)-6-(pyridin-4-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one**

Following **general procedure 2** using Pd(dppf)Cl₂, bromide 3706 (60 mg, 0.173 mmol) and 4-pyridinylboronic acid (32 mg, 0.260 mmol) afforded the title compound 3707 as an orange solid (55 mg, 92%) after purification on silica gel (MeOH:CH₂Cl₂; 2%); mp = 134-136 °C (MeOH); ¹H NMR (500 MHz, CDCl₃) δ 8.68 (s, 2H), 7.47 (t, J = 7.9 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.26 (dd, J = 7.6, 1.2 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 5.13 (s, 2H), 4.40 (s, 2H), 4.20 (s, 2H), 2.29 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.2, 150.1, 147.3, 144.0, 141.2, 137.5, 133.9, 129.9, 129.5, 127.9, 127.7, 127.0,
124.3, 121.5, 67.9, 64.4, 50.8, 21.2; m/z LRMS (ESI⁺) 345 [M+H]⁺; HRMS (ESI⁺): calc. for C₂₂H₂₁N₂O₂ [M+H]⁺ requires 345.1598 found 345.1597.

3710 7-(benzylamino)-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Bromide 3146 (50 mg, 0.144 mmol), benzylamine (19 µL, 0.173 mmol), NaOtBu (28 mg, 0.289 mmol), XPhos (7 mg, 0.014 mmol) and Pd(OAc)₂ (2 mg, 0.007 mmol) were added sequentially to a vial and degassed before addition of degassed 1,4-dioxane (3 mL). The vial was sealed and heated to 110 ºC for 16 h. The reaction was cooled down to RT and filtered through celite, using EtOAc as an eluent, the filtrate was then concentrated in vacuo. Purification on silica gel (EtOAc:pentane, 3:7) afforded the title compound 3710 as a yellow oil (42 mg, 78%); ¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, J = 3.8 Hz, 4H), 7.32 – 7.27 (m, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 8.3, 3.1 Hz, 3H), 6.62 (dd, J = 8.7, 2.8 Hz, 1H), 6.51 (d, J = 2.7 Hz, 1H), 4.98 (s, 2H), 4.38 (s, 2H), 4.31 (s, 2H), 4.03 (s, 2H), 2.29 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.5, 146.8, 138.9, 137.2, 134.5, 132.5, 130.7, 129.3, 128.9, 128.1, 127.6, 127.6, 122.7, 114.0, 113.7, 50.6, 48.5, 21.2; m/z LRMS (ESI⁺) 373 [M+H]⁺; HRMS (ESI⁺): calc. for C₂₄H₂₅N₂O₂ [M+H]⁺ requires 373.1911, found 373.1907.

3824 1-(4-methylbenzyl)-7-(phenylamino)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Bromide 3146 (101 mg, 0.289 mmol), aniline (32 µL, 0.347 mmol), NaO'Bu (56 mg, 0.578 mmol), XPhos (14 mg, 0.029 mmol) and Pd(OAc)₂ (3 mg, 0.014 mmol) were added sequentially to a vial and degassed before addition of degassed 1,4-dioxane (3 mL). The vial was sealed and heated to 110 ºC for 16 h. The reaction was cooled down to RT and filtered through celite, using EtOAc as an eluent, the
filtrate was then concentrated *in vacuo*. Purification on silica gel (acetone: pentane, 3:7) afforded the title compound **3824** as a brown solid (41 mg, 40%); mp = 122-124 °C (CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.29 (dd, J = 8.5, 7.3 Hz, 2H), 7.15 (dd, J = 8.4, 2.1 Hz, 3H), 7.10 – 7.02 (m, 5H), 7.01 – 6.95 (m, 1H), 6.95 (d, J = 2.7 Hz, 1H), 5.02 (s, 2H), 4.42 (s, 2H), 4.07 (s, 2H), 2.29 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.5, 142.2, 142.2, 137.3, 135.1, 134.4, 130.8, 129.6, 129.4, 128.0, 122.7, 122.1, 118.8, 118.3, 118.2, 77.4, 77.2, 76.9, 50.6, 21.2; m/z LRMS (ESI⁺) 359 [M+H⁺]; HRMS (ESI⁺): calc. for C₂₃H₂₃N₂O₂ [M+H⁺] requires 359.1754, found 359.2904.

**3825 1-benzyl-7-(pyridin-4-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one**

![Structure](image)

Following **general procedure 2** using Pd(dppf)Cl₂, bromide **3829** (300 mg, 0.908 mmol) and 4-pyridinylboronic acid (144 mg, 1.17 mmol) afforded the title compound **3825** as a brown solid (96 mg, 32%) after purification on silica gel (MeOH:CH₂Cl₂, 2%); mp = 129-130 °C (MeOH); ¹H NMR (500 MHz, MeOD) δ 8.59 (d, J = 5.4 Hz, 1H), 7.89 (dd, J = 8.4, 2.3 Hz, 1H), 7.80 (d, J = 2.3 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.62 (d, J = 8.5 Hz, 1H), 7.32 – 7.23 (m, 3H), 5.22 (s, 1H), 4.59 (s, 2H), 4.05 (s, 1H); ¹³C NMR (126 MHz, MeOD) δ 170.5, 150.7, 149.1, 144.5, 138.3, 137.3, 131.8, 130.1, 129.8, 129.7, 129.0, 128.7, 123.7, 122.0, 68.7, 68.4; m/z LRMS (ESI⁺) 331 [M+H⁺⁺]; HRMS (ESI⁺⁺): calc. for C₂₁H₁₉N₂O₂⁺H [M+H⁺⁺] requires 331.1441, found 331.1439.

**4115 1-(4-methylbenzyl)-7-(pyridin-2-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one**

![Structure](image)
Bromide 3146 (110 mg, 0.328 mmol), 2-pyridyl-MIDA boronate (116 mg, 0.492 mmol), Cu(OAc)₂ (33 mg, 0.164 mmol), K₂CO₃ (227 mg, 1.64 mmol), XPhos (10 mg, 0.020 mmol) and Pd₂(db₃) (6 mg, 0.066 mmol) were added sequentially to a vial and degassed before addition of degassed DMF. The resulting suspension was degassed further for 5 min, the vial was sealed and heated to 100 °C for 16 h. The reaction was cooled down before addition of EtOAc (10 mL) and H₂O:brine (1:1, 30 mL). The organic phase was washed further with H₂O:brine (1:1, 2 x 30 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified on silica gel (MeOH:CH₂Cl₂, 3%) to afford the title product 4115 (113 mg, 99%) as a beige solid; ¹H NMR (400 MHz, CDCl₃) δ 8.67 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.01 (dd, J = 8.4, 2.2 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.79 – 7.70 (m, 1H), 7.69 (dt, J = 8.0, 1.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 7.3, 4.8, 1.3 Hz, 1H), 7.14 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 7.9 Hz, 2H), 5.11 (s, 2H), 4.58 (s, 2H), 4.09 (s, 2H), 2.26 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.5, 155.9, 149.9, 143.0, 137.7, 137.3, 137.0, 134.0, 129.9, 129.4, 129.1, 128.4, 127.9, 122.5, 121.7, 120.4, 68.2, 67.7, 50.3; m/z LRMS (ESI⁺) 345 [M+H⁺]; HRMS (ESI⁺): calc. for C₂₂H₂₁N₂O₂ [M+H⁺] requires 345.1598 found 345.1599.

4116 7-(2-methoxypyridin-4-yl)-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 3, 3146 (110 mg, 0.328 mmol) and 2-methoxypyridine boronic acid (55 mg, 0.36 mmol) afforded the title product 4116 (119 mg, 97%) as a light yellow oil that solidified on standing after purification on silica gel (EtOAc:pentane, 2:3); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (dd, J = 5.4, 0.7 Hz, 1H), 7.63 (dd, J = 8.4, 2.2 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 7.07 (dd, J = 5.5, 1.6 Hz, 1H), 6.91 (dd, J = 1.6, 0.7 Hz, 1H), 5.11 (s, 2H), 4.58 (s, 2H), 4.10 (s, 2H), 3.98 (s, 3H), 2.29 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.5, 165.1, 149.7, 147.5, 143.3, 137.5, 136.5, 134.0, 130.2, 129.5, 129.2, 128.6, 127.8, 122.0, 115.1,
108.4, 68.2, 67.9, 53.8, 50.5, 21.2; m/z LRMS (ESI\(^+\)) 375 [M+H]\(^+\); HRMS (ESI\(^+\)): calc. for \(\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2\) [M+H]\(^+\) requires 375.1709 found 375.1709.

**4117** 7-(2-aminopyridin-4-yl)-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure \(3\), \(3146\) (110 mg, 0.328 mmol) and 2-aminopyridine-4-boronic pinacol ester (79 mg, 0.361 mmol) afforded the title product **4117** (113 mg, 96%) as a light yellow oil that solidified on standing after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 4%); \(^1\)H NMR (400 MHz, MeOD) \(\delta\) 7.92 (dd, \(J = 5.5, 0.8\) Hz, 1H), 7.71 (dd, \(J = 8.4, 2.2\) Hz, 1H), 7.60 (d, \(J = 2.2\) Hz, 1H), 7.52 (d, \(J = 8.4\) Hz, 1H), 7.13 (d, \(J = 8.2\) Hz, 2H), 7.04 (dd, \(J = 8.4, 0.8\) Hz, 2H), 6.83 (dd, \(J = 5.5, 1.7\) Hz, 1H), 6.80 (dd, \(J = 1.6, 0.8\) Hz, 1H), 5.47 (s, 2H), 5.12 (s, 2H), 4.86 (s, 2H), 4.51 (s, 2H), 3.99 (s, 2H), 2.23 (s, 3H); \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 170.4, 161.4, 150.2, 148.6, 143.9, 138.6, 138.4, 135.3, 131.5, 133.0, 129.8, 129.5, 129.0, 123.3, 112.1, 107.4, 68.7, 68.4, 50.8, 25.0; m/z LRMS (ESI\(^+\)) 360 [M+H]\(^+\); HRMS (ESI\(^+\)): calc. for \(\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_2\) [M+H]\(^+\) requires 360.1712 found 360.1711.

**4118** 1-methyl-7-((pyridin-4-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure \(3\), 7-bromo-1-methyl-1,5-dihydrobenzo[e][1,4]oxazepin-3(2H)-one (30 mg, 0.118 mmol) and 4-pyridyl boronic acid hydrate (16 mg, 0.129 mmol) afforded the title product **4118** (22 mg, 74%) as a beige solid after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 2%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.72 – 8.66 (m, 2H), 7.74 (dd, \(J = 8.4, 2.2\) Hz, 1H), 7.63 (d, \(J = 2.2\) Hz, 1H), 7.56 – 7.46 (m, 2H), 7.36 (d, \(J = 8.4\) Hz, 1H), 4.73 (s, 2H), 4.08 (s, 2H), 3.48 (s, 3H); \(^{13}\)C NMR (126 MHz,
CDCl<sub>3</sub> δ 168.5, 150.5, 147.0, 144.6, 136.1, 129.8, 129.1, 128.7, 121.5, 121.4, 68.1, 67.8, 34.8; m/z LRMS (ESI<sup>+</sup>) 255 [M+H]<sup>+</sup>; HRMS (ESI<sup>+</sup>): calc. for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> requires 255.1134 found 255.1135.

4120 1-(cyclopropylmethyl)-7-(pyridin-4-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 3, 4119 (134 mg, 0.453 mmol) and 4-pyridyl boronic acid hydrate (61 mg, 0.498 mmol) afforded the title product 4120 (130 mg, 97%) as an orange oil that solidified on standing after purification on silica gel (MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 4%); <sup>1</sup>H NMR (500 MHz, DMSO) δ 8.69 (s, 2H), 8.01 (d, <i>J</i> = 2.2 Hz, 1H), 7.98 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 7.79 (d, <i>J</i> = 4.6 Hz, 2H), 7.66 (d, <i>J</i> = 8.4 Hz, 1H), 4.72 (s, 2H), 3.86 (s, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 2H), 0.98 (tt, <i>J</i> = 7.6, 4.7 Hz, 1H), 0.42 – 0.32 (m, 2H), 0.22 – 0.15 (m, 2H); <sup>13</sup>C NMR (126 MHz, DMSO) δ 167.3, 150.3, 145.6, 143.3, 134.8, 130.1, 128.7, 128.4, 122.7, 67.0, 66.8, 50.1, 10.0, 3.5; m/z LRMS (ESI<sup>+</sup>) 295 [M+H]<sup>+</sup>; HRMS (ESI<sup>+</sup>): calc. for C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> requires 295.1447 found 295.1448.

4122 1-(4-methylbenzyl)-7-(thiazol-5-yl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 3, 3146 (100 mg, 0.290 mmol) and thiazole-5-boronic pinacol ester (73 mg, 0.348 mmol) afforded the title product 4122 (98 mg, 97%) as an off white solid purification on silica gel (MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 4%); <sup>1</sup>H NMR (400 MHz, MeOD) δ 8.96 (s, 1H), 8.18 (s, 1H), 7.74 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 7.65 (d, <i>J</i> = 2.3 Hz, 1H), 7.53 (d, <i>J</i> = 8.5 Hz, 1H), 7.15 (d, <i>J</i> = 8.0 Hz, 2H), 7.06 (d, <i>J</i> = 8.2 Hz, 2H), 5.13 (s, 2H), 4.51 (s, 2H), 4.01 (s, 2H), 2.24 (s, 3H); <sup>13</sup>C NMR (101 MHz, MeOD) δ
7-(1-methyl-1H-pyrazol-5-yl)-1-(4-methylbenzyl)-1,5-dihydrobenzo[e][1,4]oxazepin-2(3H)-one

Following general procedure 3, 3146 (100 mg, 0.290 mmol) and 1-methylpyrazole-5- boronic acid (72 mg, 0.348 mmol) afforded the title product 4237 (96 mg, 95%) as a light orange oil that solidified on standing after purification on silica gel (MeOH:CH₂Cl₂, 4%); ¹H NMR (400 MHz, MeOD) δ 7.57 (d, J = 1.3 Hz, 2H), 7.47 (d, J = 2.0 Hz, 1H), 7.46 (t, J = 1.3 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 5.14 (s, 1H), 4.88 (s, 1H), 4.52 (s, 2H), 4.01 (s, 2H), 3.84 (s, 3H), 2.23 (s, 3H); ¹³C NMR (101 MHz, MeOD) δ 170.4, 143.9, 143.6, 139.4, 138.6, 135.3, 131.6, 131.4, 130.3, 130.2, 129.0, 123.4, 107.4, 68.5, 68.4, 37.7, 21.1; m/z LRMS (ESI⁺) 348 [M+H⁺]; HRMS (ESI⁺): calc. for C₂₁H₂₂N₃O₂ [M+H⁺] requires 348.1712 found 348.1713

2-(4-methylbenzyl)-6-(pyridin-4-yl)-3,4-dihydroisoquinolin-1(2H)-one

Following general procedure 2 using Pd(dppf)Cl₂, compound 3698 (50 mg, 0.151 mmol) and 4-pyridinylboronic acid (24 mg, 0.197 mmol), afforded the title compound as a brown solid (48 mg, 96%) after purification by flash column chromatography (MeOH:CH₂Cl₂, 5%); mp = 151-152 °C (MeOH); ¹H NMR (500 MHz, CDCl₃) δ 8.69 (d, J = 4.7 Hz, 2H), 8.26 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.1, 1.9 Hz, 1H), 7.52 (d, J = 6.1 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9
Hz, 2H), 4.78 (s, 2H), 3.52 (t, \( J = 6.6 \) Hz, 2H), 3.01 (t, \( J = 6.6 \) Hz, 2H), 2.34 (s, 3H); \(^{13}\text{C} \text{NMR} (126 MHz, CDCl\textsubscript{3}) \delta 164.1, 150.5, 147.5, 141.4, 139.0, 137.4, 134.3, 130.1, 129.5, 128.3, 125.9, 125.7, 121.8, 50.3, 45.3, 28.4, 21.3; \( m/z \) LRMS (ESI\(^{+}\)) 329 [M+H]\(^{+}\); HRMS (ESI\(^{+}\)): calc. for C\(_{22}\)H\(_{21}\)N\(_3\)O [M+H]\(^{+}\) requires 329.1648 found 329.1646.

4236 \( 2-(4\text{-methylbenzyl})-6-(\text{pyridin-3-yl})-3,4\text{-dihydroisoquinolin-1(2H)}\)-one

Following general procedure 3, 3698 (80 mg, 0.243 mmol) and 3-pyridyl boronic acid (33 mg, 0.267 mmol) afforded the title product 4236 (76 mg, 99%) as a brown oil that solidified on standing after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 4%); \(^1\text{H} \text{NMR} (400 MHz, Acetone) \delta 8.92 (d, \( J = 2.6 \) Hz, 1H), 8.60 (dd, \( J = 4.9, 1.6 \) Hz, 1H), 8.15 (d, \( J = 8.1 \) Hz, 1H), 8.11 – 8.03 (m, 1H), 7.71 (dd, \( J = 8.1, 1.9 \) Hz, 1H), 7.62 (t, \( J = 1.2 \) Hz, 1H), 7.48 (dd, \( J = 8.1, 4.7 \) Hz, 1H), 7.28 (d, \( J = 7.9 \) Hz, 2H), 7.17 (d, \( J = 7.9 \) Hz, 2H), 4.76 (s, 2H), 3.57 (dd, \( J = 7.1, 6.2 \) Hz, 2H), 3.08 (t, \( J = 6.6 \) Hz, 2H), 2.31 (s, 3H); \(^{13}\text{C} \text{NMR} (101 MHz, CDCl\textsubscript{3}) \delta 164.3, 148.9, 148.1, 141.0, 139.0, 137.3, 136.0, 134.8, 134.4, 132.2, 129.5, 129.3, 128.2, 128.2, 126.0, 125.7, 123.9, 50.3, 45.3, 28.3, 21.2; \( m/z \) LRMS (ESI\(^{+}\)) 329 [M+H]\(^{+}\); HRMS (ESI\(^{+}\)): calc. for C\(_{22}\)H\(_{21}\)N\(_3\)O [M+H]\(^{+}\) requires 329.1648 found 329.1647.

4237 \( 6-(1\text{-methyl-1H-pyrazol-5-yl})-2-(4\text{-methylbenzyl})-3,4\text{-dihydroisoquinolin-1(2H)}\)-one

Following general procedure 3, 3698 (80 mg, 0.243 mmol) and 1-methylpyrazole-5- boronic acid (34 mg, 0.267 mmol) afforded the title product 4237 (71 mg, 88%) as a brown oil after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 6%); \(^1\text{H} \text{NMR} (400 MHz, MeOD) \delta 8.07 (d, \( J = 8.0 \) Hz, 1H), 7.48 (dd, \( J = 2.0, 1.1 \) Hz, 1H), 7.44 (dd, \( J = 8.0, 1.7 \) Hz, 1H), 7.32 (t, \( J = 1.3 \) Hz, 1H), 7.19 (d, \( J = 7.8 \) Hz, 2H), 7.10 (d, \( J =
7.7 Hz, 2H), 6.39 (dd, J = 2.1, 1.0 Hz, 1H), 4.70 (s, 2H), 3.85 (d, J = 1.1 Hz, 3H), 3.51 – 3.43 (m, 2H), 2.94 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H). \(^{13}\)C NMR (101 MHz, MeOD) δ 165.7, 144.2, 140.6, 139.5, 138.4, 135.3, 135.1, 130.3, 130.1, 129.4, 129.0, 128.5, 128.2, 107.6, 46.5, 37.9, 28.7, 21.2; m/z LRMS (ESI\(^+\)) 332 [M+H]+; HRMS (ESI\(^+\)): calc. for C\(_{21}\)H\(_{22}\)N\(_3\)O [M+H]+ requires 332.1763 found 332.1762.

4238 6-(2-aminopyridin-4-yl)-2-(4-methylbenzyl)-3,4-dihydroisoquinolin-1(2H)-one

Following general procedure 3, 3698 (80 mg, 0.243 mmol) and 2-amino-pyridine-4-boronic pinacol ester (59 mg, 0.267 mmol) afforded the title product 4238 (79 mg, 95%) as a brown oil that solidified on standing after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 8%); \(^1\)H NMR (600 MHz, DMSO) δ 8.01 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 5.0 Hz, 1H), 7.62 (dd, J = 8.1, 1.8 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 6.81 (dd, J = 5.4, 1.7 Hz, 1H), 6.74 (dd, J = 1.6, 0.8 Hz, 1H), 6.01 (s, 2H), 4.68 (s, 2H), 3.49 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H), 2.28 (s, 3H); \(^{13}\)C NMR (151 MHz, DMSO) δ 163.0, 160.4, 148.5, 147.3, 141.4, 139.4, 136.3, 134.6, 129.1, 128.3, 127.6, 125.4, 124.8, 110.0, 105.2, 49.4, 45.1, 27.4, 20.7; m/z LRMS (ESI\(^+\)) 344 [M+H]+; HRMS (ESI\(^+\)): calc. for C\(_{22}\)H\(_{22}\)N\(_3\)O [M+H]+ requires 344.1763 found 344.1764.

4239 2-(4-methylbenzyl)-6-(thiazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one

Following general procedure 3, 3698 (80 mg, 0.243 mmol) and thiazole boronic acid (56 mg, 0.267 mmol) afforded the title product 4239 (78 mg, 97%) as a light orange oil that solidified on standing after purification on silica gel (MeOH:CH\(_2\)Cl\(_2\), 6%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.82 (s, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.16 (s, 1H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 7.37 (s, 1H), 7.24 (d, J = 14.2 Hz, 4H), 7.15 (d, J = 7.8 Hz, 2H), 4.76 (s, 2H), 3.50 (dd, J = 8.4, 4.8 Hz, 2H), 2.97 (t, J = 6.6 Hz, 2H), 2.34 (s,
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 164.0, 139.2, 137.4, 134.3, 129.6, 129.6, 129.5, 129.5, 128.3, 125.8, 125.5, 50.4, 45.2, 28.3, 21.3; $m/z$ LRMS (ESI$^+$) 335 [M+H]$^+$; HRMS (ESI$^+$): calc. for C$_{20}$H$_{19}$N$_2$OS [M+H]$^+$ requires 335.1218 found 335.1218.
NMR Spectra

3700
References

Coppola, G.M., Damon, R.E., Kukkola, P.J., Stanton, J.L., 2004. Amide derivatives and their use as inhibitors of 11-beta-hydroxysteroid dehydrogenase type 1. WO2004065351A1.

Partridge, F.A., Murphy, E.A., Willis, N.J., Bataille, C.J.R., Forman, R., Heyer-Chauhan, N., Marinič, B., Sowood, D.J.C., Wynne, G.M., Else, K.J., Russell, A.J., Sattelle, D.B., 2017. Dihydrobenz[e][1,4]oxazepin-2(3H)-ones, a new anthelmintic chemotype immobilising whipworm and reducing infectivity in vivo. PLoS Negl Trop Dis 11, e0005359. https://doi.org/10.1371/journal.pntd.0005359

Zablocki, J.A., Elzein, E., Li, X., Koltun, D.O., Parkhill, E.Q., Kobayashi, T., Martinez, R., Corkey, B., Jiang, H., Perry, T., Kalla, R., Notte, G.T., Saunders, O., Graupe, M., Lu, Y., Venkataramani, C., Guerrero, J., Perry, J., Osier, M., Strickley, R., Liu, G., Wang, W.-Q., Hu, L., Li, X.-J., El-Bizri, N., Hirakawa, R., Kahlig, K., Xie, C., Li, C.H., Dhall, A.K., Rajamani, S., Mollova, N., Soohoo, D., Lepist, E.-I., Murray, B., Rhodes, G., Belardinelli, L., Desai, M.C., 2016. Discovery of Dihydrobenzoxazepinone (GS-6615) Late Sodium Current Inhibitor (Late Na i), a Phase II Agent with Demonstrated Preclinical Anti-Ischemic and Antiarrhythmic Properties. Journal of Medicinal Chemistry acs.jmedchem.6b00939. https://doi.org/10.1021/acs.jmedchem.6b00939
**Supplementary Figure 3**

Supplementary Figure 3. Time course of *Brugia malayi* microfilariae motility scores taken every 24 hours for 6 consecutive days after exposure to compound OX02983. Error bars indicate mean plus or minus standard deviation.