Discovery of Indoline-2-carboxamide Derivatives as a New Class of Brain-Penetrant Inhibitors of *Trypanosoma Brucei*

Laura A. T. Cleghorn, Sébastien Albrecht, Laste Stojanovski, Frederick R. J. Simeons, Suzanne Norval, Robert Kime, Iain T. Collie, Lorna Campbell, Irene Hallyburton, Julie A. Frearson, Paul G. Wyatt, Kevin D. Read, Ian H. Gilbert*

Drug Discovery Unit, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, Dundee, DD1 5EH, UK

Ian H. Gilbert: author for correspondence: telephone +44 1382 386 240;

i.h.gilbert@dundee.ac.uk

Supporting Information
S1: Further Details of Chemistry Experimental Section

(*S*)-1-(2-(4-Chlorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (26)
Prepared using general procedure A, colourless solid, 65 mg, 38%; δ_H (500 MHz, *d*6-DMSO) 8.32 (d, *J* = 4.7 Hz, 1H, NH), 8.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 7.24 (d, *J* = 7.3 Hz, 1H, ArH), 7.19 (t, *J* = 7.3 Hz, 1H, ArH), 7.04 (t, *J* = 7.3 Hz, 1H, ArH), 6.97 (d, *J* = 8.1 Hz, 2H, ArH), 5.09 (d, *J* = 10.8 Hz, 1H, CH), 5.01 (d, *J* = 15.6 Hz, 1H, CH_2), 4.47 (d, *J* = 15.6, 1H, CH_2), 3.60 (dd, *J* = 16.2 and 10.8 Hz, 1H, CH_2), 3.12 (d, *J* = 16.2 Hz, 1H, CH_2), 2.64 (d, *J* = 4.7 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) = 171.0 (C=O), 166.0 (C=O), 156.9, 142.9, 129.6, 129.2, 129.1, 127.1, 124.6, 124.5, 123.8, 116.2 (ArC), 65.95, 59.6, 34.5, 25.9. LCMS (ES+): m/z (%) 345 $[M+H]^+$ t_R : 4.15 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H1_8ClN_2O_3$ + H] 345.1000 Found 345.0985.

1-(2-(Benzyloxy)acetyl)-*N*-methylindoline-2-carboxamide (28)
Prepared using general procedure A, colourless solid, 63 mg, 39%; δ_H (500 MHz, *d*6-DMSO) 8.17 (bs, 1H, NH), 7.42-7.32 (m, 6H, ArH), 7.24 (t, *J* = 7.5 Hz, 2H, ArH), 7.08 (td, *J* = 7.5 and 0.8 Hz, 1H, ArH), 4.65 (s, 3H, CH_3), 4.28 (d, *J* = 14.5 Hz, 1H, CH_2), 4.08 (d, *J* = 14.5 Hz, 1H, CH_2), 3.65 (m, 1H, CH_2), 3.12 (d, *J* = 16.7 Hz, 1H, ArH), 2.57 (s, 2H, CH_2). δ_C (125 MHz, *d*6-DMSO) = 171.1 (C=O), 167.9 (C=O0, 143.1, 137.8, 129.7, 128.2, 127.8, 127.6, 127.1, 124.4, 123.5, 116.3 (ArC), 72.2, 68.4, 59.6, 34.4, 25.7. LCMS (ES+): m/z (%) 325 $[M+H]^+$ t_R : 3.74 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{19}H_{21}N_2O_3$ +H] 325.1547 Found 325.1550.

1-(2-(4-Chloro-3-fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (29)
Prepared using general procedure A, colourless solid, 28 mg, 8%; δ_H (500 MHz, *d*6-DMSO) 8.33 (d, *J* = 4.4 Hz, 1H, NH), 8.00 (d, *J* = 8.0 Hz, 1H, ArH), 7.48 (t, *J* = 8.6 Hz, 1H, ArH), 7.25 (d, *J* = 7.4 Hz, 1H, ArH), 7.18 (t, *J* = 8.0 Hz, 1H, ArH), 7.11-7.08 (m, 1H, ArH), 7.05 (t, *J* = 7.4 Hz, 1H, ArH), 6.86 (d, *J* = 8.6 Hz, 1H, ArH), 5.09-5.04 (m, 2H, CH, CH_2), 4.50 (d, *J* = 15.7 Hz, 1H, CH_2), 3.60 (dd, *J* = 16.6 and 11.0 Hz, 1H, CH_2), 3.13 (d, *J* = 16.6 Hz, 1H, CH_2), 2.65 (d, *J* = 4.4 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.0, 165.6 (C=O), 158.3, 156.5, 142.8, 130.5, 129.6, 127.1, 124.5, 123.8, 116.2, 112.3, 103.8, 103.6 (ArC), 66.2, 59.6,

34.5, 25.9. LCMS (ES+): m/z (%) 363 $[M+H]^+$ t_R : 4.20 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{17}ClFN_2O_3$ +H] 363.0906 Found 363.0902

1-(2-(3,4-Dichlorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (30)
Prepared using general procedure A, colourless solid, 21 mg, 22%; δ_H (500 MHz, $CDCl_3$) 8.22 (bs, 1H, NH), 7.38 (d, *J* = 8.6 Hz, 1H, ArH), 7.39-7.32 (masked, 3H, ArH), 7.17 (t, *J* = 7.4 Hz, 1H, ArH), 7.07 (d, *J* = 3.0 Hz, 1H, ArH), 6.86 (d, *J* = 8.6 Hz, 1H, ArH), 5.80 and 4.76 (2 x bs, rotomer, 1H, CH_2), 5.33 and 5.01 (2 x bs, rotomer, 1H, CH_2), 3.72 (bs, 1H, CH_2), 3.31 (bs, 1H, CH_2), 2.78 (bd, rotomer, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.3 (C=O), 168.8 (C=O), 143.2, 140.0, 130.7, 130.0, 127.0, 124.9, 124.5, 123.5, 116.3 (ArC), 61.0, 40.8, 34.1, 25.8; LCMS (ES+): m/z (%) 379 $[M+H]^+$ t_R : 4.46 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{17}Cl_2N_2O_3$ + H] 379.0611 Found 379.0628

***N*-methyl-1-(2-phenoxyacetyl)indoline-2-carboxamide (31)**
Prepared using general procedure A, colourless solid, 49 mg, 16%; δ_H (500 MHz, $CDCl_3$) 8.20 (bs, 1H, NH), 7.35-7.32 (m, 4H, ArH), 7.15 (t, *J* = 7.5 Hz, 1H, ArH), 7.04 (t, *J* = 7.5 Hz, 1H, ArH), 6.98 (dd, *J* = 7.8 and 1.0 Hz, 1H, ArH), 5.80, 5.31, 5.06, 4.78 (4 x bs, rotomer, 3H, CH_2 and CH), 3.68 (bs, 1H, CH_2), 3.32 (bs, 1H, CH_2), 2.72 (bs, rotomer, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.1 (C=O), 166.3 (C=O), 158.0, 143.0, 129.6, 129.3, 127.1, 124.5, 123.7, 120.9, 116.2, 114.4 (ArC), 65.7, 59.6, 34.5, 25.8. LCMS (ES+): m/z (%) 311 $[M+H]^+$ t_R : 3.81 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{19}N_2O_3$ + H] 311.1390 Found 311.1398.

***N*-Methyl-1-(2-((tetrahydrofuran-3-yl)oxy)acetyl)indoline-2-carboxamide (32)**
1 : 1 mixture of diastereoisomers, colourless solid, 34 mg, 46%; δ_H (500 MHz, *d*6-DMSO) 8.05 (d, *J* = 7.1 Hz, 1H, ArH), 8.18 (bs, 1H, NH), 7.20 (m, 2H, ArH), 7.01 (t, *J* = 7.3 Hz, 1H, ArH), 4.97 (m, 1H, CH), 4.22 (m, 2H, CH_2), 3.88 (m, 1H, CH), 3.62-3.75 (m, 4H, 2 x CH_2), 3.54 (m, 1H, CH_2), 3.02 (d, *J* = 16.6 Hz, 1H, CH_2), 2.60 (bs, 3H, CH_3), 1.92 (m, 2H, CH_2); δ_C (125 MHz, *d*6-DMSO) 171.2, 167.9, 143.1, 129.7, 127.1, 124.5, 123.6, 116.4, 79.5, 72.0 (dia1), 71.9 (dia2), 67.6, 66.2, 59.8, 34.4, 31.9 (dia1), 31.8 (dia2), 25.8; LCMS (ES+): m/z (%) 305 $[M+H]^+$ t_R : 0.92 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{16}H_{20}N_2O_4$ + H] 305.1501 found 305.1486.

(*R*)-*N*-methyl-1-(2-((6-methylpyridin-3-yl)oxy)acetyl)indoline-2-carboxamide (33)
Prepared using general procedure A, colourless solid, 4 mg, 2%; δ_H (500 MHz, $CDCl_3$) 8.22 (d, *J* = 3.0 Hz, 1H, py-H), 7.26-7.24 (m, 2H, masked, ArH), 7.23-7.22 (m, 1H, masked, ArH), 7.18 (dd, *J* = 8.5 and 3.0 Hz, 1H, ArH), 7.14-7.05 (m, 2H, ArH), 5.82, 5.24, 5.12, 4.82 (4 x bs, rotomer, 3H, CH_2 and CH), 3.62 (bs, 1H, CH_2), 3.18 (bs, 1H, CH_2), 2.73 (bs, rotomer, 3H, CH_3), 2.50 (s, 3H, py-CH_3). HRMS (ES+) Calc. for $[C_{18}H_{20}N_2O_3$ + H] 326.1499 Found 326.1495.

***N*-Methyl-1-(2-(*p*-tolyoxy)acetyl)indoline-2-carboxamide (34)**
Prepared using general procedure A, colourless solid, 39 mg, 24%; δ_H (500 MHz, *d*6-DMSO) 8.30 (bs, 1H, NH), 8.03 (d, *J* = 7.9 Hz, 1H, ArH), 7.24 (d, *J* = 7.9 Hz, 1H, ArH), 7.19 (t, *J* = 7.9 Hz, 1H, ArH), 7.08 (d, *J* = 8.2 Hz, 2H, ArH), 7.02 (t, *J* = 7.2 Hz, 1H, ArH), 6.83 (d, *J* = 8.2 Hz, 2H, ArH), 5.09 (d, *J* = 10.0 Hz, 1H, CH), 4.91 (d, *J* = 15.5 Hz, 1H, CH_2), 4.42 (d, *J* = 15.5 Hz, 1H, CH_2), 3.60 (dd, *J* = 16.6 and 10.0 Hz, CH_2), 3.10 (d, *J* = 16.6 Hz, 1H, CH_2), 2.64 (d, *J* = 4.2 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3). LCMS (ES+): m/z (%) 325 $[M+H]^+$ t_R : 4.07 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{21}N_2O_3$ + H] 325.1547 Found 325.1549

1-(2-(4-Fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (35)
Prepared using general procedure A, colourless solid, 26 mg, 30%; δ_H (500 MHz, $CDCl_3$) 8.19 (bs, 1H, NH), 7.30-7.24 (m, 3H, ArH), 7.17 (t, *J* = 7.5 Hz, 1H, ArH), 7.01-6.97 (m, 2H, ArH), 6.92-6.89 (m, 2H, ArH), 5.74 and 5.04 (2 x bs, rotomer, 1H, CH_2), 5.25 and 4.70 (2 x bs, rotomer, 2H, CH_2), 3.66 (bs, 1H, CH_2), 3.27 (bs, 1H, CH_2), 2.75 (bd, rotomer, 3H, CH_3). LCMS (ES+): m/z (%) 329 $[M+H]^+$ t_R : 3.91 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{18}FN_2O_3 + H]$ 329.1296 Found 329.1295.

(*R*)-1-(2-(4-Fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (36)
Prepared using general procedure A, colourless solid, 70 mg, 85%; δ_H (500 MHz, $CDCl_3$) 8.23 (bs, 1H, NH), 7.28-7.36 (m, 3H, ArH), 7.16 (t, *J* = 7.5 Hz, 1H, ArH), 7.05-7.01 (m, 2H, ArH), 6.95-6.92 (m, 2H, ArH), 5.79, 5.30, 5.05, 4.74 (4 x bs, rotomer, 3H, CH_2 and CH), 3.70 (bs, 1H, CH_2), 3.32 (bs, 1H, CH_2), 2.75 (bs, rotomer, 3H, CH_3). LCMS (ES+): m/z (%) 329 $[M+H]^+$ t_R : 3.84 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{18}FN_2O_3 + H]$ 329.1296 Found 329.1297.

(*R*)-1-(2-(3,4-Difluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (37)
Prepared using general procedure A, colourless solid, 10 mg, 6%; δ_H (500 MHz, $CDCl_3$) 8.22 (bs, 1H, NH), 7.28-7.36 (m, 3H, ArH), 7.17 (t, *J* = 7.5 Hz, 1H, ArH), 7.12-7.08 (m, 2H, ArH), 6.82 (ddd, *J* = 11.6, 6.4 and 3.0 Hz, 1H, ArH), 5.79, 5.23, 5.04, 4.74 (4 x bs, rotomer, 3H, CH_2 and CH), 3.72 (bs, 1H, CH_2), 3.33 (bs, 1H, CH_2), 2.77 (bs, rotomer, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.1, 165.8 (C=O), 154.7, 142.8, 129.6, 127.1, 124.5, 123.8, 117.49, 117.4, 116.2, 110.8, 104.1, 104.0 (ArC), 66.3, 59.6, 34.4, 25.9. LCMS (ES+): m/z (%) 347 $[M+H]^+$ t_R : 3.91 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{17}F_2N_2O_3 + H]$ 347.1201 Found 347.1210.

N-methyl-1-(2-*d*5phenoxyacetyl)indoline-2-carboxamide (38)
Prepared using general procedure A, colourless solid, 95 mg, 44%; δ_H (500 MHz, $CDCl_3$) 8.23 (bs, 1H, NH), 7.32-7.26 (m, 2H, masked, ArH), 7.15 (t, *J* = 7.4 Hz, 1H, ArH), 5.79, 5.31, 5.11, 4.78 (4 x bs, rotomer, 3H, CH_2 and CH), 3.70 (bs, 1H, CH_2), 3.33 (bs, 1H, CH_2), 2.71 (bs, rotomer, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) = 171.1 (C=O), 166.3 (C=O), 157.9, 143.0, 129.6, 129.0, 128.7, 127.1, 124.5, 123.7, 116.2, 114.0 (ArC), 65.7, 59.6, 34.5, 25.9. LCMS (ES+): m/z (%) 316 $[M+H]^+$ t_R : 4.02 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{18}D_3N_2O_3 + H]$ 316.1735 Found 316.1726

***N*-Methyl-1-(2-(napthalen-1-yl)acetyl)indoline-2-carboxamide (39)**
Prepared using general procedure A, colourless solid, 31 mg, 22%; δ_H (500 MHz, *d*6-DMSO) 8.39 (d, *J* = 4.5 Hz, 1H, NH), 7.98 (d, *J* = 8.1 Hz, 1H, ArH), 7.96-7.91 (m, 2H, ArH), 7.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.53-7.51 (m, 2H, ArH), 7.46 (d, *J* = 8.1 Hz, 1H, ArH), 7.36 (d, *J* = 6.8 Hz, 1H, ArH), 7.23 (d, *J* = 7.7 Hz, 1H, ArH), 7.14 (t, *J* = 7.7 Hz, 1H, ArH), 7.01 (t, *J* = 7.3 Hz, 1H, ArH), 5.28 (dd, *J* = 10.8 and 2.5 Hz, 1H, CH), 4.30 (d, *J* = 16.8 Hz, 1H, CH_2), 3.90 (d, *J* = 16.7 Hz, 1H, CH_2), 3.67 (dd, *J* = 16.8 Hz and 11.0 Hz, 1H, CH_2), 3.12 (d, *J* = 16.7 Hz, 1H, CH_2), 2.70 (d, *J* = 4.5 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) = 171.6, 169.1, 143.4, 133.3, 132.3, 131.8, 129.9, 128.3, 128.1, 127.3, 127.0, 126.0, 125.4, 124.5, 123.3, 116.2, 60.9, 54.9, 34.3, 25.9. LCMS (ES+): m/z (%) 345 $[M+H]^+$ t_R : 4.23 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{22}H_{21}N_2O_2 + H]$ 345.1598 Found 345.1592

1-(2-(4-Chlorophenyl)acetyl)-*N*-methylindoline-2-carboxamide (40)
Prepared using general procedure A, colourless solid, 29 mg, 35%; δ_H (500 MHz, *d*6-DMSO) 8.32 (d, *J* = 4.2 Hz, 1H, NH), 8.04 (d, *J* = 8.2 Hz, 1H, ArH), 7.39 (d, *J* = 8.3 Hz, 3H, ArH), 7.26 (d, *J* = 8.3 Hz, 2H, ArH), 7.21 (d, *J*= 7.4 Hz, 1H, ArH), 7.15 (t, *J* = 7.4 Hz, 1H, ArH), 6.99 (t, *J* = 7.4 Hz, 1H, ArH), 5.12 (d, *J* = 8.5 Hz, 1H, CH), 3.80 (d, *J* = 16.2 Hz, 1H, CH), 3.57 (dd, *J* = 15.7 and 11.1 Hz, 1H, CH), 3.47 (d, *J* = 15.7 Hz, 1H, CH), 2.65 (d, *J* = 4.2 Hz, 3H, CH_3). LCMS (ES+): m/z (%) 329 $[M+H]^+$ t_R : 4.9 (20-95% MeCN, acidic);

1-(2-(4-Isopropylphenyl)acetyl)-*N*-methylindoline-2-carboxamide (41)
Prepared using general procedure A, colourless solid, 100 mg, 60%; δ_H (500 MHz, *d*6-DMSO) 8.28 (bs, 1H, NH), 8.06 (d, *J* = 8.0 Hz, 1H, ArH), 7.20 (d, *J* = 8.0 Hz, 4H, ArH), 7.13 (d, *J* = 8.0 Hz, 2H, ArH), 7.00 (t, *J* = 7.3 Hz, 1H, ArH), 5.08 (d, *J* = 10.0 Hz, 1H, CH), 3.69 (d, *J* = 15.7 Hz, 1H, CH_2), 3.57 (t, *J* = 10.0 Hz, 1H, CH_2), 3.44 (d, *J* = 15.7 Hz, 1H, CH_2), 3.04 (d, *J* = 14.3 Hz, 1H, CH_2), 2.88 (sep, *J* = 6.9 Hz, ^{i}PrCH), 2.65 (d, *J* = 4.5 Hz, 3H, $NHCH_3$), 1.20 (d, *J* = 6.9 Hz, 6H, 2 x ^{i}PrCH$_3$). δ_C (125 MHz, *d*6-DMSO) 171.4 (C=O), 169.5 (C=O), 146.5, 143.3, 132.3, 129.9, 129.5, 127.0, 126.1, 124.4, 123.3, 116.3, 60.9, 45.7, 40.9, 34.1, 33.1, 25.8, 23.9; LCMS (ES+): m/z (%) 337 $[M+H]^+$ t_R : 4.46 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{21}H_{25}N_2O_2$ + H] 337.1911 Found 337.1926

***N*-Methyl-1-(2-(4-(trifluoromethyl)phenyl)acetyl)indoline-2-carboxamide (42)**
Prepared using general procedure A, colourless solid, 41 mg, 45%; δ_H (500 MHz, *d*6-DMSO) 8.31 (d, *J* = 4.4 Hz, 1H, NH), 8.04 (d, *J* = 8.1 Hz, 1H, ArH), 7.70 (d, *J* = 8.1 Hz, 2H, ArH), 7.42 (d, *J* = 7.8 Hz, 2H, ArH), 7.22 (d, *J* = 7.8 Hz, 1H, ArH), 7.17 (t, *J* = 7.5 Hz, 1H, ArH), 7.02 (t, *J* = 7.5 Hz, 1H, ArH), 5.14 (d, *J* = 8.3 Hz, 1H, CH), 3.94 (d, *J* = 16.5 Hz, 1H, CH_2), 3.61 (t, *J* = 8.3, 2H, CH_2), 3.08 (d, *J* = 16.5 Hz, 1H, CH_2), 2.65 (d, *J* = 4.4 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.3 (C=O). 168.8 (C=O), 143.2, 140.0, 130.7, 130.0, 127.0, 124.9, 124.5, 123.5, 116.3 (ArC), 61.0, 40.8, 34.1, 25.8. LCMS (ES+): m/z (%) 363 $[M+H]^+$ t_R : 4.31 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{19}H_{18}F_3N_2O_2$ + H] 363.1315 Found 363.1308.

1-(2-(4-Fluorophenyl)acetyl)-*N*-methylindline-2-carboxamide (43)
Prepared using general procedure A, colourless solid, 10 mg, 13%; δ_H (500 MHz, *d*6-DMSO) 8.29 (d, *J* = 4.3 Hz, 1H, NH), 8.05 (d, *J* = 8.0 Hz, 1H, ArH), 7.28-7.26 (m, 2H, ArH), 7.21 (d, *J* = 7.3 Hz, 1H, ArH), 7.17-7.13 (m, 3H, ArH), 7.00 (t, *J* = 7.3 Hz, 1H, ArH), 5.11 (d, *J* = 8.7 Hz, 1H, CH), 3.78 (d, *J* = 16.0 Hz, 1H, CH), 3.59 (dd, *J* = 16.0 and 11.1 Hz, 1H, CH), 3.50 (d, *J* = 16.0 Hz, 1H, CH), 3.06 (d, *J* = 16.0 Hz, 1H, CH), 2.65 (d, *J* = 4.3 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.4 (C=O), 169.3 (C=O), 131.6, 131.5, 127.4, 127.0, 124.4, 123.4, 116.3, 114.9, 114.7, 109.7 (ArC), 60.93, 40.5, 34.1, 25.8; LCMS (ES+): m/z (%) 313 $[M+H]^+$ t_R : 3.95 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{18}FN_2O_2$ + H] 313.1347 Found 313.1347.

1-(2-(2,4-Difluorophenyl)acetyl)-*N*-methylindoline-2-carboxamide (44)
Prepared using general procedure A, colourless solid, 72 mg, 22%; δ_H (500 MHz, *d*6-DMSO) 8.30 (d, *J* = 4.3 Hz, 1H, NH), 8.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.38-7.32 (m, 1H, ArH), 7.25-7.20 (m, 2H, ArH), 7.15 (t, *J* = 7.5 Hz, 1H, ArH), 7.06 (td, *J* = 8.0 and 2.3 Hz, 1H, ArH), 7.02 (t, *J* = 7.5 Hz, 1H, ArH), 5.16 (d, *J* = 8.9 Hz, 1H, CH), 3.89 (d, *J* = 16.5 Hz, 1H, CH_2), 3.62 (dd, *J* = 15.6 and 11.1 Hz, 1H, CH_2), 3.46 (d, *J* = 16.5 Hz, 1H, CH_2), 3.08 (d, *J* = 15.6 Hz, 1H, CH_2), 2.66 (d, *J* = 4.4 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO)171.2 (C=O), 168.0 (C=O), 143.2, 133.2, 129.9, 127.0, 124.5, 123.4, 118.8, 118.7, 116.2, 111.11, 110.9, 103.4

(ArC), 60.9, 34.2, 31.8, 25.8; LCMS (ES+): m/z (%) 331 $[M+H]^+$ t_R : 3.94 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{17}F_2N_2O_2$ + H] 331.1253 Found 331.1254.

(*R*)-1-(2-(4-Chloro-3-fluorophenyl)acetyl)-*N*-methylindoline-2-carboxamide (45)
Prepared using general procedure A, colourless solid, 41 mg, 27%; δ_H (500 MHz, *d*6-DMSO) = 8.28 (d, *J* = 4.4 Hz, 1H, NH), 8.04 (d, *J* = 8.1 Hz, 1H, ArH), 7.55 (t, *J* = 8.1 Hz, 1H, ArH), 7.31 (d, *J* = 8.0 Hz, 1H, ArH), 7.22 (d, *J* = 7.4 Hz, 1H, ArH), 7.17 (t, *J* = 8.0 Hz, 1H, ArH), 7.11 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (t, *J* = 7.4 Hz, 1H, ArH), 5.13 (dd, *J* = 10.9 and 2.3 Hz, 1H, CH), 3.85 (d, *J* = 16.1 Hz, 1H, CH_2), 3.60 (dd, *J* = 16.6 and 10.9 Hz, 1H, CH_2), 3.51 (d, *J* = 16.1 Hz, 1H, CH_2), 3.07 (d, *J* = 16.6 Hz, 1H, CH_2), 2.64 (d, *J* = 4.4 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 171.2, 168.7, 157.7, 155.8, 143.1, 130.0, 127.2, 127.0, 124.5, 123.5, 118.3, 118.1, 116.4, 61.0, 34.1, 25.8. LCMS (ES+): m/z (%) 347$[M+H]^+$ t_R : 4.24 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H17ClFN_2O_2$ + H] 347.0957 Found 347.0981.

1-(2-(3,4-Difluorophenyl)acetyl-*N*-methylindoline-2-carboxamide (46)
Prepared using general procedure A, colourless solid, 24 mg, 15%; δ_H (500 MHz, *d*6-DMSO) 8.29 (d, *J* = 4.4 Hz, 1H, NH), 8.05 (d, *J* = 8.1 Hz, 1H, ArH), 7.40 (d, *J* = 8.6 Hz, 1H, ArH), 7.37 (d, *J* = 8.6 Hz, 1H, ArH), 7.33-7.30 (m, 1H, ArH), 7.21 (d, *J* = 7.5 Hz, 1H, ArH), 7.17 (t, *J* = 7.7 Hz, 1H, ArH), 7.08 (bs, 1H, ArH), 7.02 (t, *J* = 7.5 Hz, 1H, ArH), 5.13 (d, *J* = 10.9 Hz, 1H, CH), 3.82 (d, *J* = 16.1 Hz, 1H, CH_2), 3.59 (dd, *J* = 16.7 and 10.9 Hz, 1H, CH_2), 3.48 (d, *J* = 16.1 Hz, 1H, CH_2), 3.07 (d, *J* = 16.7 Hz, 1H, CH_2), 2.64 (d, *J* = 4.4 Hz, 3H, CH_3). LCMS (ES+): m/z (%) 331 $[M+H]^+$ t_R : 4.20 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{17}F_2N_2O_2$ + H] 331.1253 Found 331.1261

(*R*)-1-(2-(4-Fluorophenyl)acetyl)-*N*-methylindoline-2-carboxamide (47)
Prepared using general procedure A, colourless solid, 339 mg, 54%; δ_H (500 MHz, *d*6-DMSO) 8.28 (d, *J* = 4.4 Hz, 1H, NH), 8.05 (d, *J* = 8.1 Hz, 1H, ArH), 7.28-7.26 (m, 2H, ArH), 7.21 (d, *J* = 7.3 Hz, 1H, ArH), 7.17-7.13 (m, 2H, ArH), 7.01 (t, *J* = 7.3 Hz, 1H, ArH), 5.11 (d, *J* = 8.7 Hz, 1H, CH), 3.78 (d, *J* = 16.0 Hz, 1H, CH_2), 3.59 (dd, *J* = 16.5 and 11.3 Hz, 1H, CH_2), 3.47 (d, *J* = 16.0 Hz, 1H, CH_2), 3.06 (d, *J* = 16.5, 1H, CH_2), 2.65 (d, *J* = 4.4 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) = 171.4 (C=O), 169.3 (C=O), 131.6, 131.85, 131.2, 130.0, 127.0, 124.4, 123.4, 116.3, 114.9, 114.7 (ArC), 60.9, 34.1, 25.8. LCMS (ES+): m/z (%) 313 $[M+H]^+$ t_R : 3.90 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{18}FN_2O_2$ + H] 313.1347 Found 313.1335.

1-(2-(4-Chlorophenoxy)acetyl)-*N*,*N*-dimethylindoline-2-carboxamide (48)
Prepared using general procedure A, colourless solid, 31 mg, 57%; δ_H (500 MHz, *d*6-DMSO) 8.04 (d, *J* = 7.9 Hz, 1H, ArH), 7.33 (d, *J* = 8.8 Hz, 2H, ArH), 7.22 (d, *J* = 7.3 Hz, 1H, ArH), 7.17 (t, *J* = 7.9 Hz, 1H, ArH), 7.02 (t, *J* = 7.3 Hz, 1H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 5.63 (d, *J* = 11.0 Hz, 1H, CH), 4.98 (d, *J* = 15.8 Hz, 1H, CH_2-b), 4.36 (d, *J* = 15.8 Hz, 1H, CH_2-b), 3.70 (dd, *J* = 16.5 and 11.0 Hz, 1H, CH_2-a), 3.09. (s, 3H, CH_3), 3.08 (m, 1H, CH_2-a), 2.87 (s, 3H, CH_3); δ_C (125 MHz, *d*6-DMSO) 170.0, 166.0, 156.9, 143.3, 129.1, 129.0, 127.3, 124.6, 124.5, 123.7, 116.2, 115.9, 66.0, 57.6, 36.3, 35.6, 33.3; LCMS (ES+): m/z (%) 359 $[M+H]^+$ t_R : 0.43 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{19}H_{19}ClN_2O_3$ + H] 359.1162 found 359.1148.

1-(2-(4-Chlorophenoxy)acetyl)-*N*-ethylindoline-2-carboxamide (49)
Prepared using general procedure A, colourless solid, 31 mg, 57%; δ_H (500 MHz, *d*6-DMSO) 8.42 (m, 1H, NH), 8.02 (d, *J* = 7.8 Hz, 1H, ArH), 7.33 (d, *J* = 8.6 Hz, 2H, ArH), 7.24 (d, *J* = 7.3 Hz, 1H, ArH), 7.18 (t, *J* = 7.8 Hz, 1H, ArH), 7.02 (t, *J* = 7.3 Hz, 1H, ArH), 6.95 (d, *J* =

8.6 Hz, 2H, ArH), 5.06 (d, *J* = 11.0 Hz, 1H, CH), 5.00 (d, *J* = 15.6 Hz, 1H, CH_2), 4.43 (d, *J* = 15.6 Hz, 1H, CH_2), 3.60 (dd, *J* = 16.1 and 11.0 Hz, 1H, CH_2), 3.12 (m, 2H, CH_2), 3.09 (m, 1H, CH_2), 1.02 (t, *J* = 7.0 Hz, 3H, CH_3); δ_C (125 MHz, *d*6-DMSO) 170.6, 165.9, 156.9, 143.0, 129.6, 129.1, 127.1, 124.6, 124.5, 123.7, 116.2, 116.1, 65.9, 59.5, 34.6, 33.8, 14.5; LCMS (ES+): m/z (%) 359 $[M+H]^+$ t_R : 4.26 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{19}ClN_2O_3 + H]$ 359.1162 found 359.1170.

***N*-Butyl-1-(2-(4-chlorophenoxy)acetyl)indoline-2-carboxamide (50)**
Prepared using general procedure A, colourless solid, 32 mg, 55%; δ_H (500 MHz, *d*6-DMSO) 8.39 (m, 1H, NH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.32 (d, *J* = 8.6 Hz, 2H, ArH), 7.24 (d, *J* = 7.2 Hz, 1H, ArH), 7.18 (t, *J* = 7.7 Hz, 1H, ArH), 7.02 (t, *J* = 7.3 Hz, 1H, ArH), 6.95 (d, *J* = 8.6 Hz, 2H, ArH), 5.07 (d, *J* = 11.0 Hz, 1H, CH), 5.00 (d, *J* = 15.6 Hz, 1H, CH_2), 4.41 (d, *J* = 15.6 Hz, 1H, CH_2), 3.61 (dd, *J* = 16.4 and 11.0 Hz, 1H, CH_2), 3.05-3.13 (m, 3H, 2 x CH_2), 1.39-1.37 (m, 2H, CH_2), 1.24 (m, 1H, CH_2), 0.82 (t, *J* = 7.3 Hz, 3H, CH_3); δ_C (125 MHz, *d*6-DMSO) 170.5, 165.9, 156.9, 143.0, 129.6, 129.1, 127.2, 124.6, 124.5, 123.7, 116.2, 116.1, 66.0, 59.5, 34.7, 31.0, 19.5, 13.6; LCMS (ES+): m/z (%) 387 $[M+H]^+$ t_R : 4.60 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{21}H_{23}ClN_2O_3 + H]$ 387.1475 found 387.1476.

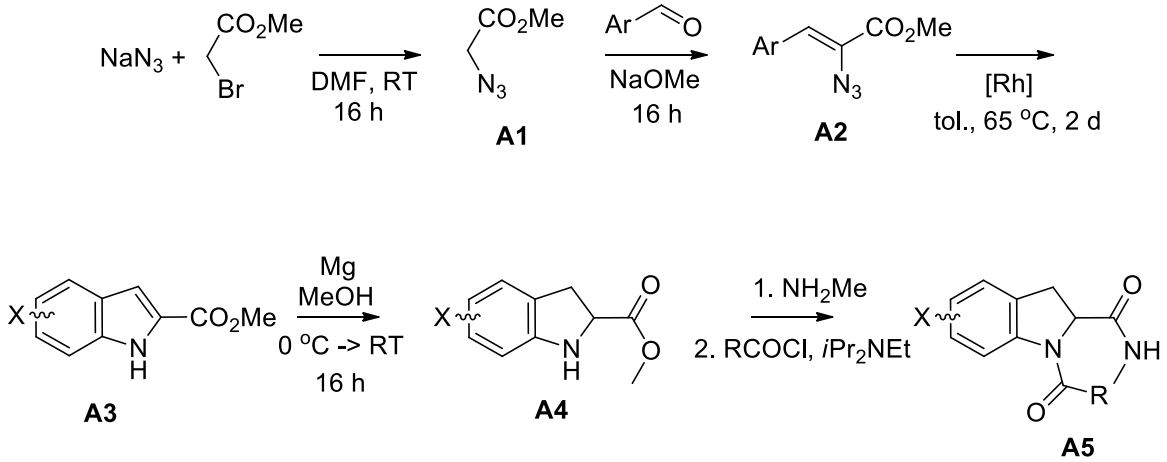
1-(2-(4-Chlorophenoxy)acetyl)-*N*-cyclopropylindoline-2-carboxamide (51)
Prepared using general procedure A, colourless solid, 33 mg, 59%; δ_H (500 MHz, *d*6-DMSO) 8.49 (m, 1H, NH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (d, *J* = 8.6 Hz, 2H, ArH), 7.23 (d, *J* = 7.1 Hz, 1H, ArH), 7.17 (t, *J* = 7.6 Hz, 1H, ArH), 7.02 (t, *J* = 7.3 Hz, 1H, ArH), 6.96 (d, *J* = 8.6 Hz, 2H, ArH), 5.01 (d, *J* = 11.1 Hz, 1H, CH), 4.96 (d, *J* = 15.6 Hz, 1H, CH_2), 4.41 (d, *J* = 15.6 Hz, 1H, CH_2), 3.57 (dd, *J* = 16.5 and 11.1 Hz, 1H, CH_2), 3.07 (d, *J* = 16.5 Hz, 1H, CH_2), 2.65 (m, 1H, CH), 0.63 (d, *J* = 7.1 Hz, 2H, CH_2), 0.43 (s, 2H, CH_2); δ_C (125 MHz, *d*6-DMSO) 171.8, 166.0, 156.9, 143.1, 129.5, 129.1, 127.2, 124.6, 124.5, 123.7, 116.2, 116.0, 66.0, 59.3, 34.5, 22.5, 5.7, 5.6; LCMS (ES+): m/z (%) 371 $[M+H]^+$ t_R : 4.26 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{20}H_{19}ClN_2O_3 + H]$ 371.1162 found 371.1164.

1-(2-(4-Chlorophenoxy)acetyl)-*N*-(2,2,2-trifluoroethyl)indoline-2-carboxamide (52)
Prepared using general procedure A, colourless solid, 33 mg, 53%; δ_H (500 MHz, *d*6-DMSO) 9.17 (m, 1H, NH), 8.02 (d, *J* = 7.8 Hz, 1H, ArH), 7.32 (d, *J* = 8.8 Hz, 2H, ArH), 7.26 (d, *J* = 7.4 Hz, 1H, ArH), 7.19 (t, *J* = 7.8 Hz, 1H, ArH), 7.04 (t, *J* = 7.4 Hz, 1H, ArH), 6.93 (d, *J* = 8.8 Hz, 2H, ArH), 5.20 (d, *J* = 11.0 Hz, 1H, CH), 5.02 (d, *J* = 15.6 Hz, 1H, CH_2), 4.38 (d, *J* = 15.6 Hz, 1H, CH_2), 3.66 (dd, *J* = 16.8 and 11.0 Hz, 1H, CH_2), 3.99 (m, 2H, CH_2), 3.08 (d, *J* = 16.8 Hz, 1H, CH_2); δ_F (470 MHz, *d*6-DMSO) -70.7; δ_C (125 MHz, *d*6-DMSO) 171.9, 165.9, 156.8, 142.9, 129.2, 129.1, 127.3, 124.7, 124.7 (q, *J* = 279.7 Hz), 124.6, 123.9, 116.2, 116.1, 65.8, 59.3, 34.6; LCMS (ES+): m/z (%) 413 $[M+H]^+$ t_R : 4.50 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{16}ClF_3N_2O_3 + H]$ 413.0880 found 413.0881.

1-(2-(4-Fluorophenoxy)acetyl)-*N*-*d*3methylindoline-2-carboxamide (53)
Prepared using general procedure A, colourless solid, 39 mg, 24%; δ_H (500 MHz, *d*6-DMSO) 8.28 (bs, 1H, NH), 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 7.24 (d, *J* = 7.3 Hz, 1H, ArH), 7.20 (t, *J* = 7.6 Hz, 1H, ArH), 7.14-7.11 (m, 2H, ArH), 7.04 (t, *J* = 7.3 Hz, 1H, ArH), 6.97-6.94 (m, 2H, ArH), 5.09 (d, *J* = 10.0 Hz, 1H, CH), 4.97 (d, *J* = 15.5 Hz, 1H, CH_2), 4.45 (d, *J* = 15.5 Hz, 1H, CH_2), 3.60 (dd, *J* = 16.3 and 10.0 Hz, 1H, CH_2), 3.12 (d, *J* = 16.3 Hz, 1H, CH_2). δ_C (125 MHz, *d*6-DMSO) = 171.1 (C=O), 166.2 (C=O), 154.3, 142.9, 129.6, 127.1, 124.5, 123.7, 116.2, 115.8, 115.7, 115.6 (ArC), 66.3, 59.6, 34.46. LCMS (ES+): m/z (%) 332 $[M+H]^+$ t_R :

3.89 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{15}D_3FN_2O_3$ + H] 332.1484 Found 332.1471

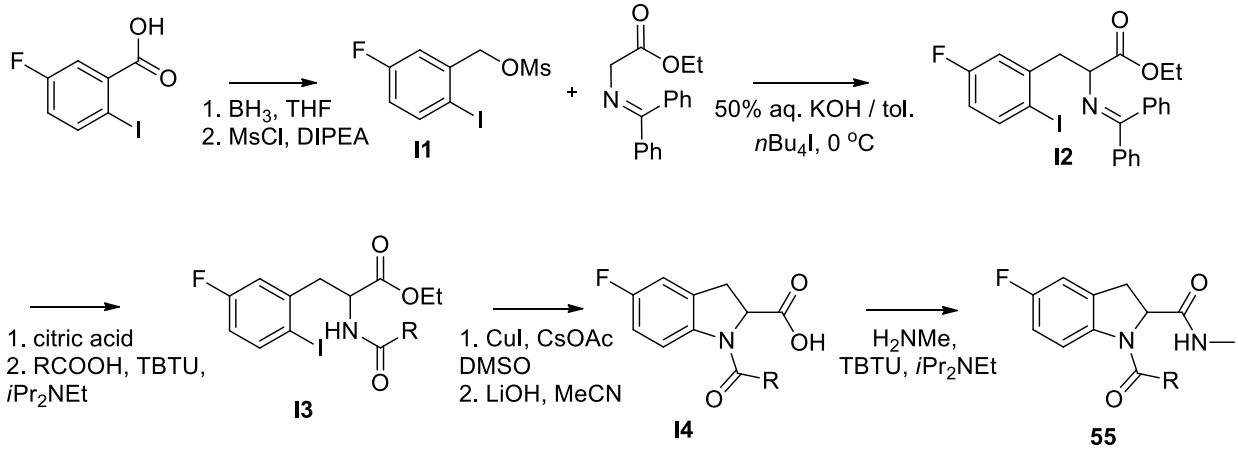
General Procedure B: *Preparation of substituted indolines* (Scheme 2a)



Methyl bromoacetate (3.2 mL, 34.8 mmol) was added drop-wise to a solution of sodium azide (2.1 g, 32.4 mmol) in DMF (8 mL) at 0 °C, under argon, the reaction was slowly warmed up to RT over a 16 h period, quenched with brine and extracted with Et_2O (2x). The organics were dried over Na_2SO_4, filtered, concentrated in-vacuo to give methyl azidoacetate **A1** as a colourless oil which was used without further purification (can be stored in the freezer during several weeks). A solution of methyl azidoacetate **A1** (8.01 mmol, 3 eq) and aldehyde (2.6 mmol, 1 eq) in THF (2 mL) was added drop-wise to a solution of sodium methoxide (0.5 g, 3.5 eq) in MeOH (7 mL) at -10°C under argon. The reaction mixture was stirred at -10 °C for 3 h and was poured into a water-ice bath, the precipitate was filtered, washed with water (3x) and freeze-dried overnight to give the desired vinylazide **A2** as a colourless solid. A solution **A2** (0.71 mmol) in toluene (0.8 mL) in presence of $Rh_2(O_2CC_3F_7)_4$ (37 mg, 5 % mol) was heated at 65 °C for 48 h. The reaction mixture was cooled to RT and was diluted with CH_2Cl_2 before quenching with sat. aq. $NaHCO_3$. The mixture was then filtered through a hydrophobic frit and concentrated to dryness to give the methyl 2-carboxyindole **A3**. Mg turnings (300 mg, 10 eq) were added to a solution of **A3** (1.23 mmol) in MeOH (15 mL) in one portion at 0°C under argon. The reaction mixture was allowed to warm up slowly to RT over a 16 h period. The reaction mixture was diluted with CH_2Cl_2 and cooled down to 0 °C before adding aq. 2 *N* HCl until pH<5. The resulting mixture was then poured into a sat. aq. Na_2CO_3 solution at 0 °C (until pH>9). The precipitate was filtered off and washed with a mixture of CH_2Cl_2 and water. The filtrate was extracted with CH_2Cl_2 (3x) and the organics were dried over Na_2SO_4, filtered through a hydrophobic frit and concentrated in-vacuo to give indoline **A4**. The crude **A4** and $MeNH_2$ (10 eq, 2 M in THF) were stirred at RT under argon for 16 h. After concentration to dryness, the crude was reacted with the acid chloride (1.1 eq) and iPr$_2$NEt (2 eq) in CH_2Cl_2 (0.1 M) at RT under Ar for 2 h. The reaction mixture was then diluted with CH_2Cl_2, neutralized with sat. aq. $NaHCO_3$ and filtered through a hydrophobic frit. Excess solvent was removed in-vacuo and column chromatography eluenting with 0-100 % EtOAc in hexanes or 0-20 % MeOH (20 %)/CH_2Cl_2 in CH_2Cl_2) afforded the title compound **A5**.

1-(2-(4-Chlorophenoxy)acetyl)-5-fluoro-*N*-methylindoline-2-carboxamide (54)
Prepared using general procedure B, colourless solid, 30 mg, 7%; δ_H (500 MHz, *d*6-DMSO) 8.32 (d, *J* = 4.2 Hz, 1H, NH), 7.98 (dd, *J* = 8.7 and 4.9 Hz, 1H, ArH), 7.33 (d, *J* = 8.7 Hz, 2H, ArH), 7.12 (d, *J* = 7.8 Hz, 1H, ArH), 7.01 (t, *J* = 8.7 Hz, 1H, ArH), 6.95 (d, *J* = 8.7 Hz, 2H, ArH), 5.11 (d, *J* = 10.8 Hz, 1H, CH), 4.99 (d, *J* = 15.5 Hz, 1H, CH_2), 4.46 (d, *J* = 15.5 Hz, 1H, CH_2), 3.59 (dd, *J* = 16.8 and 10.8 Hz, 1H, CH_2), 3.11 (d, *J* = 16.8 Hz, 1H, CH_2), 2.63 (d, *J* = 4.2 Hz, 3H, CH_3); δ_F (470 MHz, *d*6-DMSO) -119.2; δ_C (125 MHz, *d*6-DMSO) 170.8, 165.8, 158.7 (d, *J* = 239.6 Hz), 156.9, 139.3, 132.2 (d, *J* = 7.5 Hz), 129.1, 124.6, 117.0 (d, *J* = 7.7 Hz), 116.3, 113.3 (d, *J* = 23.2 Hz), 111.9 (d, *J* = 23.9 Hz), 65.9, 60.0, 34.4, 25.9; LCMS (ES+): m/z (%) 363 $[M+H]^+$ t_R : 4.18 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{16}Cl_2N_2O_3 + H]$ 363.0912 found 363.0911.

5-Fluoro-1-(2-(4-fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (55)
General Procedure: *Preparation of 5-fluoro substituted indolines* (Scheme 2b)[1-3]



1 M BH_3 in THF (7.1 mL, 7.1 mmol, 1.25 eq.) was added drop-wise to a solution of acid (1.5 g, 5.64 mmol) in THF (11.3 mL) at 0 °C under argon. The reaction mixture was allowed to warm up slowly to RT overnight then quenched by slow addition of water at 0 °C. The organic and aqueous phases were partitioned and the aqueous phase was extracted with EtOAc (2 x). The organics were washed with brine and dried over Na_2SO_4, filtered through a hydrophobic frit and concentrated under reduced pressure to give the crude alcohol (1.24 g). Mesyl chloride (460 µL, 5.94 mmol, 1.2 eq.) was added drop-wise to a solution of the crude alcohol and *i*Pr_2NEt (1.7 mL, 9.76 mmol, 2 eq.) in THF (25 mL) at 0 °C, under argon. The reaction mixture was stirred at 0 °C for 2 h and was quenched with brine, extracted with EtOAc, washed with brine and dried over Na_2SO_4. After filtration through a hydrophobic frit, the organics were evaporated to dryness to give the title compound **I1**. To a solution of the crude mesylate **I1** (519 mg, 1.57 mmol), *N*-(diphenylmethylene)glycine ethyl ester (440 mg, 1.65 mmol, 1.05 eq.), TBAI (29 mg, 5% mol) in toluene (4 mL) was added a solution of aq. 50% KOH (1.7 mL) at 0 °C under argon. The biphasic solution was vigorously stirred and allowed to warm up slowly to RT overnight. The reaction mixture was diluted in EtOAc and the organics and aqueous phases were partitioned. The aqueous phase was extracted with EtOAc (3 x) and the organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the title compound **I2**. **I2** was dissolved in THF (8 mL) and a 1 M aq. citric acid solution (8 mL) was added at 0 °C under argon, the reaction mixture was stirred at RT for 3 h then cooled to 0 °C and neutralized by addition of solid Na_2CO_3 until pH >8. The resulting mixture was extracted with CH_2Cl_2, washed with sat. aq. Na_2CO_3 solution and dried over Na_2SO_4. After filtration through a hydrophobic frit, the solvents were evaporated and the mixture re-dissolved in CH_2Cl_2 (12 mL) and added to a solution of 4-

fluorophenoxyacetic acid (235 mg, 1.38 mmol, 1.15 eq), *i*Pr_2NEt (501 µL, 2.87 mmol, 2.4 eq) and TBTU (462 mg, 1.44 mmol, 1.2 eq) in CH_2Cl_2 (12 mL) stirred at RT under argon for 30 min. This resulting mixture was stirred at RT overnight and was then quenched with sat. aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 x) and washed with brine. The organics were dried over Na_2SO_4, filtered through a hydrophobic frit and concentrated in-vacuo. Purification by flash column chromatography eluting with EtOAc in hexanes 0-100% afforded the desired amide **I3** (350 mg, 46% from the commercially available acid).

Ethyl 3-(5-fluoro-2-iodophenyl)2-(2-(4-fluorophenoxy)acetamido)propanoate I3
d_H (500 MHz, $CDCl_3$) 1.24 (t, *J* = 7.2 Hz, 3H, CH_3), 3.17 (dd, *J* = 14.1 and 8.5 Hz, 1H, CH_2), 3.33 (dd, *J* = 14.1 and 6.0 Hz, 1H, CH_2), 4.21 (m, 2H, CH_2), 4.39 (d, *J* = 15.0 Hz, 1H, CH_2), 4.44 (d, *J* = 15.0 Hz, 1H, CH_2), 4.96 (ddd, *J* = 8.5, 8.4 and 6.0 Hz, 1H, CH), 6.72 (td, *J* = 8.4 and 3.0 Hz, 1H, ArH), 6.84 (m, 2H, ArH), 6.95 (dd, *J* = 9.3 and 2.9 Hz, 1H, ArH), 6.99 (m, 2H, ArH), 7.07 (d, *J* = 8.4 Hz, 1H, NH), 7.74 (dd, *J* = 8.7 and 5.7 Hz, 1H, ArH); d_F (470 MHz, $CDCl_3$) -121.9, -113.5; LCMS (ES+): m/z (%) 490 $[M+H]^+$ t_R : 4.89 (20-95% MeCN, acidic).

CsOAc (412 mg, 2.15 mmol, 3 eq.) and CuI (150 mg, 0.79 mmol, 1.1 eq.) were successively added to a solution of amide **I3** (350 mg, 0.72 mmol) in DMSO (3.6 mL) at RT under argon. The reaction mixture was stirred at RT for 1.5 h and was quenched with brine, extracted with CH_2Cl_2 (3 x), washed with brine and dried over Na_2SO_4. Excess solvent was removed *in vacuo* to afford the indoline, that was used in the next step without further purification. 1 *N* aq. LiOH (0.8 mL, 0.8 mmol, 1.1 eq.) was added to a solution of the crude indoline in THF (5 mL) at RT, under argon, the reaction mixture stirred at RT for 1h, cooled to 0 °C, quenched 1 *N* aq. HCl and extracted with EtOAc (3 x). The organics were dried over Na_2SO_4, filtered, excess solvent removed in-vacuo to give the crude acid **I4**. *i*Pr_2NEt (300 µL, 1.72 mmol, 2.4 eq.) and TBTU (275 mg, 0.86 mmol, 1.2 eq.) were added to a solution **I4** dissolved in CH_2Cl_2 (10 mL) at RT, under argon and the reaction mixture stirred at RT for 30 min and $MeNH_2$ in MeOH (2M, 0.9 mL, 1.8 mmol, 2.4 eq.) added. This resulting mixture was stirred for a 1h, quenched with sat. aq. $NaHCO_3$ solution, extracted with CH_2Cl_2 (2 x) and washed with brine. The organics were dried over Na_2SO_4, filtered and excess solvent removed in-vacuo. Flash column chromatography eluenting with MeOH (20%)/CH_2Cl_2 in CH_2Cl_2 gradient 0-100% afforded the title compound **55** (135 mg, 55% from amide **I3**).d_H (500 MHz, *d*6-DMSO) 8.32 (d, *J* = 4.4 Hz, 1H, NH), 7.99 (dd, *J* = 8.7 and 4.9 Hz, 1H, ArH), 7.12 (m, 3H, ArH), 7.01 (m, 1H, ArH), 6.94 (m, 2H, ArH), 5.11 (d, *J* = 10.7 Hz, 1H, CH), 4.95 (d, *J* = 15.6 Hz, 1H, CH_2), 4.43 (d, *J* = 15.6 Hz, 1H, CH_2), 3.59 (dd, *J* = 16.8 and 10.7 Hz, 1H, CH_2), 3.11 (d, *J* = 16.8 Hz, 1H, CH_2), 2.63 (d, *J* = 4.4 Hz, 3H, CH_3); d_F (470 MHz, *d*6-DMSO) -123.7, -119.2; d_C (125 MHz, *d*6-DMSO) 170.9, 166.0, 158.7 (d, *J* = 239.6 Hz), 156.7 (d, *J* = 236.5 Hz), 154.3, 139.3, 132.2 (d, *J* = 9.2 Hz), 117.0 (d, *J* = 8.4 Hz), 115.7 (d, *J* = 22.9 Hz), 115.7 (d, *J* = 8.6 Hz), 113.3 (d, *J* = 22.5 Hz), 111.9 (d, *J* = 24.5 Hz), 66.2, 60.0, 34.4, 25.9; LCMS (ES+): m/z (%) 347 $[M+H]^+$ t_R : 4.09 (20-95% MeCN, acidic); HRMS (ES+) Calc. for [$C_{18}H_{16}F_2N_2O_3$ + H] 347.1207 found 347.1201.

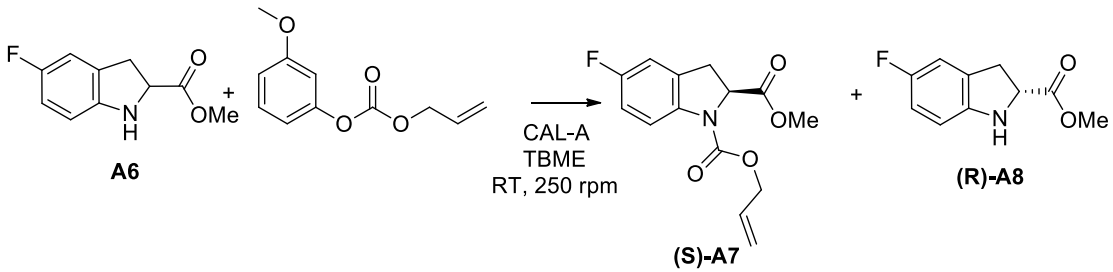
5,6-Difluoro-1-(2-(4-fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (57)
Prepared using general procedure B, colourless solid, 10 mg. 10%; δ_H (500 MHz, *d*6-DMSO) 8.35 (bs, 1H, NH), 7.94 (m, 1H, ArH), 7.36 (t, *J* = 8.7 Hz, 1H, ArH), 7.12 (t, *J* = 8.2 Hz, 2H, ArH), 6.94 (m, 2H, ArH), 5.14 (d, *J* = 10.2 Hz, 1H, CH), 4.97 (d, *J* = 15.6 Hz, 1H, CH_2), 4.44 (d, *J* = 15.6 Hz, 1H, CH_2), 3.57 (m, 1H, CH_2), 3.09 (d, *J* = 16.8 Hz, 1H, CH_2), 2.63 (m, 3H, CH_3); δ_F (470 MHz, *d*6-DMSO) -143.8 (d, *J* = 21.9 Hz), -139.3 (d, *J* = 21.8 Hz), -123.6; δ_C

(125 MHz, *d*6-DMSO) 170.6, 166.5, 156.7 (d, *J* = 235.9 Hz), 154.2, 139.1, 126.2, 115.7 (d, *J* = 22.8), 115.7 (d, *J* = 8.4 Hz), 113.5 (d, *J* = 19.1 Hz), 105.3 (d, *J* = 23.3 Hz), 66.1, 60.3, 34.1, 25.9; LCMS (ES+): m/z (%) 365 $[M+H]^+$ t_R : 4.09 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{15}F_3N_2O_3 + H]$ 365.1113 found 365.1092.

5,7-Difluoro-1-(2-(4-fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (58)
Prepared using general procedure B, colourless solid, 7 mg, 4%; δ_H (500 MHz, *d*6-DMSO) 8.13 (m, 1H, NH), 7.12 (m, 3H, ArH), 7.06 (d, *J* = 7.4 Hz, 1H, ArH), 6.92 (bs, 2H, ArH), 5.10 (d, *J* = 9.5 Hz, 1H, CH), 4.96 (d, *J* = 15.2 Hz, 1H, CH_2), 4.81 (d, *J* = 15.2 Hz, 1H, CH_2), 3.53 (s, 1H, CH_2), 3.11 (d, *J* = 16.7 Hz, 1H, CH_2), 2.57 (d, *J* = 4.4 Hz, 3H, NCH_3); δ_F (470 MHz, *d*6-DMSO); -123.4, -115.2 (d, *J* = 5.6 Hz, 2 F); δ_C (75 MHz, *d*6-DMSO) 170.2, 166.6, 156.8 (d, *J* = 236.2 Hz), 153.9 (d, *J* = 2.0 Hz), 137.4, 115.8 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 23.3 Hz), 108.2 (dd, *J* = 23.9 and 3.0 Hz), 103.2 (dd, *J* = 27.4 and 25.2 Hz), 67.2, 62.8, 34.5, 25.8; LCMS (ES+): m/z (%) 365 $[M+H]^+$ t_R : 4.02 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{15}F_3N_2O_3 + H]$ 365.1113 found 365.1120.

1-(2-(4-Chlorophenoxy)acetyl)-4,5,6-trifluoro-*N*-methylindoline-2-carboxamide (59)
Prepared using general procedure B, beige solid, 38 mg, 8%; δ_H (500 MHz, *d*6-DMSO) 8.40 (bs, 1H, NH), 7.81 (bs, 1H, ArH), 7.33 (d, *J* = 8.5 Hz, 2H, ArH), 6.96 (d, *J* = 8.5 Hz, 2H, ArH), 5.21 (d, *J* = 9.9 Hz, 1H, CH), 5.02 (d, *J* = 15.8 Hz, 1H, CH_2), 4.48 (d, *J* = 15.8 Hz, 1H, CH_2), 3.61 (m, 1H, CH_2), 3.21 (d, *J* = 16.6 Hz, 1H, CH_2), 2.64 (s, 3H, CH_3); δ_F (470 MHz, *d*6-DMSO) -167.4 (t, *J* = 21.7 Hz), -139.3 (d, *J* = 21.7 Hz), -135.5 (d, *J* = 20.7 Hz); δ_C (125 MHz, *d*6-DMSO) 170.1, 166.7, 156.8, 129.1, 124.8, 116.3, 113.4 (d, *J* = 19.0 Hz), 101.0 (d, *J* = 23.4 Hz), 65.9, 60.4, 30.6, 25.9; LCMS (ES+): m/z (%) 399 $[M+H]^+$ t_R : 0.42 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{18}H_{14}ClF_3N_2O_3 + H]$ 399.0723 found 399.0731.

General Procedure C: Lipase-catalysed kinetic resolution to generate single enantiomers of substituted indolines (Scheme 3).



3-methoxyphenyl allyl carbonate (1.547 g, 2-2.5 eq) was added to a suspension of crude compound rac-**A6** (753 mg) and lipase CAL-A (CLEA, Aldrich) (380 mg) in TBME (30 mL) at RT, under argon, the mixture was stirred at RT at 250 rpm, the reaction was monitored by LCMS until the conversions were around 50 % (approximately 5 h), filtered and the filtrate concentrated in-vacuo. Column chromatography eluting with 0-50 % EtOAc in Hexane

afforded (*R*)-**A8** (269 mg). **A8** and H_2NMe (10 eq, 2 M in THF) were stirred at RT under argon for 16 h. After concentration to dryness, the crude was reacted with the acid chloride (1.1 eq) and $i Pr_2NEt$ (2 eq) in CH_2Cl_2 (0.1 M) at RT under argon for 2 h and worked up as described in general procedure B.

5-Bromoindoline-2-carboxylic acid
N-Bromosuccinimide (1 mol eq.) was added portion wise to a solution of indoline-2-carboxylic acid (1 mol eq.) in DMF (anhydrous, 2 $mLmmol^{-1}$) at 0 °C, the reaction was allowed to warm to rt and stirred for 2h, stopped, partitioned between EtOAc and H_2O, the organic layer was dried over $MgSO_4$, filtered and excess solvent removed in-vacuo to give the title compound (83 % yield). The material was used without further purification. δ_H (500 MHz, $CDCl_3$) 7.81 (s, 1H, OH), 7.16 (s, 1H, ArH), 7.12 (d, *J* = 8.2 Hz, 1H, ArH), 6.31 (d, *J* = 8.2 Hz, 1H, ArH), 4.19 (dd, *J* = 10.7 and 5.1 Hz, 1H, CH), 3.21 (dd, *J* = 16.4 and 10.7 Hz, 1H, CH_2), 3.10 (dd, *J* = 16.4 and 5.1 Hz, 1H, CH_2), 2.55 (s, 1H, NH); LCMS (ES+): m/z (%) 242 and 244 ^{79}Br and ^{81}Br $[M+H]^+$ t_R : 3.80 (20-95% MeCN, acidic).

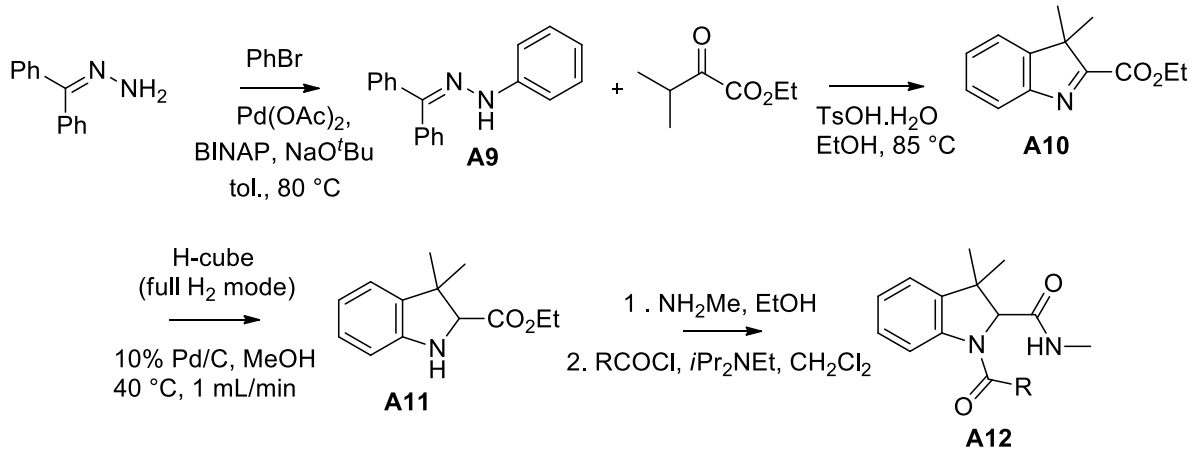
5-Bromo-1-(2-(4-fluorophenoxy)acetyl)-*N*-methylindoline-2-carboxamide (60)
Prepared from 5-bromoindoline-2-carboxylic acid using general procedure A, colourless solid, 56 mg, 14 %; δ_H (500 MHz, *d*6-DMSO) 8.33 (bs, 1H, NH), 7.95 (d, *J* = 8.3 Hz, 1H, ArH), 7.45 (s, 1H, ArH), 7.38 (d, *J* = 8.3 Hz, 1H, ArH), 7.12 (t, *J* = 8.9 Hz, 2H, ArH), 6.94 (dd, *J* = 8.9 and 4.4 Hz, 2H, ArH), 5.11 (d, *J* = 10.0 Hz, 1H, CH), 4.97 (d, *J* = 15.7 Hz, 1H, CH), 4.44 (d, *J* = 15.7 Hz, 1H, CH), 3.60 (dd, *J* = 16.7 and 10 Hz, 1H, CH), 3.12 (d, *J* = 16.7 Hz, 1H, CH), 2.63 (d, *J* = 4.2 Hz, 3H, CH_3). LCMS (ES+): m/z (%) 408 and 410 ^{79}Br and ^{81}Br $[M+H]^+$ t_R : 5.6 (5-95% MeCN, basic);

General Procedure D: Suzuki Coupling
5-Bromoindoline-2-carboxylic acid (1 mol. eq.) was dissolved in a mixture of toluene:EtOH (7:3, 10 mL/mmol), degassed with argon, K_3PO_4 (3 mol. eq.), boronic acid (1 mol. eq.) were added followed by bis-(tri-*tert*-butyl phosphine)Pd(0) (0.01 mol. eq.), the reaction mixture was heated at 120 °C for 15 min in a μW reactor, filtered through a celite pad, dissolved in EtOAc and washed with H_2O. Column chromatography eluting with ether afforded the desired product.

1-(2-(4-Fluorophenoxy)acetyl)-*N*-methyl-5-phenylindoline-2-carboxamide (61)
Prepared using general procedure D, colourless solid, 11 mg, 23%; δ_H (500 MHz, $CDCl_3$) 8.10 (bs, 1H, NH), 7.40 (dd, *J* = 8.2 and 1.1 Hz, 2H, ArH), 7.29 (t, *J* = 7.4 Hz, 4H, ArH), 7.20 (t, *J* = 7.4 Hz, 1H, ArH), 6.87-6.84 (m, 2H, ArH), 6.79-6.76 (m, 2H, ArH), 5.67 and 4.58 (2 x bs, rotomer, 1H, CH_2), 5.16 and 4.92 (2 x bs, rotomer, 2H, CH_2), 3.58 (bs, rotomer, 1H, CH), 3.19 (bs, rotomer, 1H, CH), 2.60 (bs, rotomer, 3H, CH_3); LCMS (ES+): m/z (%) 405 $[M+H]^+$ t_R : 4.42 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{24}H_{21}FN_2O_3 + H]$ 405.1609 found 405.1610.

1-(2-(4-Fluorophenoxy)acetyl)-*N*-methyl-5-(pyridine-4-yl)indoline-2-carboxamide (62)
Prepared using general procedure D, colourless solid, 10 mg, 31%; δ_H (500 MHz, $CDCl_3$) 8.68 (d, *J* = 6.1 Hz, 2H, ArH), 7.61-7.58 (m, 2H, ArH), 7.49 (dd, *J* = 4.6 and 1.6 Hz, 2H, ArH), 7.47-7.45 (m, 1H, ArH), 7.05-7.02 (m, 2H, ArH), 6.96-6.93 (m, 2H, ArH), 5.79 and 5.14 (2 x bs, rotomer, 1H, CH_2), 5.34 and 4.52 (2 x bs, rotomer, 2H, CH_2), 3.78-3.72 (m, 2H, CH_2), 2.90 (d, *J* = 5.0 Hz, 3H, CH_3); LCMS (ES+): m/z (%) 406 $[M+H]^+$ t_R : 4.21 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{23}H_{20}FN_3O_3 + H]$ 406.1561 found 406.1572.

1-(2-(4-Chlorophenoxy)acetyl-*N*,3,3-trimethylindoline-2-carboxamide (63)



Benzophenone hydrazone (205 mg, 1.04 mmol, 1.1 eq.), bromobenzene (0.1 mL, 0.95 mmol), $Pd(OAc)_2$ (5.3 mg, 2.5 % mol), (±)-BINAP (22.2 mg, 3.75 % mol) were dissolved in toluene (2.1 mL) in a test tube fitted with a septum and stirred at RT until homogenous. The septum was removed and NaO^tBu (140 mg, 1.45 mmol, 1.4 eq.) added, followed by additional toluene (1 mL), the reaction vessel was recapped with a septum and purged with argon and heated at 85 °C for 18 h, stopped, cooled to RT, diluted with Et_2O and filtered through a celite pad, the filtrate concentrated in-vacuo to afford the crude hydrazone **A9**. **A9** (0.95 mmol), ethyl pyruvate (220 µL, 1.49 mmol, 1.5 eq.), $TsOH.H_2O$ (570 mg, 3 mmol, 3 eq.) were dissolved in EtOH (7 mL) and the solution was heated at 85 °C for 21 h. The reaction mixture was then cooled to RT, diluted with EtOAc and neutralized with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc, washed with brine and the combined organics were dried over Na_2SO_4, filtered and concentrated in-vacuo. Purification with column chromatography eluting with 0-10% EtOAc in hexanes to afford the title compound **A10** (75 mg, 35%) as a beige solid. **A10** (70 mg, 0.32 mmol) was hydrogenated on a H-Cube (1 mL/min, Full H_2 mode) in MeOH (8 mL) using a 10% Pd/C cartridge. The resulting solution was concentrated in-vacuo, the residue dissolved in EtOH (4 mL) and $MeNH_2$ (2M in MeOH, 1.6 mL, 10 eq.) added at RT, under argon and stirred for 16 h, concentrated in-vacuo and the crude was reacted with iPr$_2$NEt (110 µL, 0.63 mmol, 2 eq.), acid chloride (55 mg, 0.27 mmol, 1.1 eq.) in CH_2Cl_2 (4 mL) for 3 h, diluted with CH_2Cl_2, neutralized with sat. aq. $NaHCO_3$, filtered, concentrated in-vacuo, the residue was purified by flash chromatography eluting with MeOH (20%) in CH_2Cl_2-CH_2Cl_2 0-30% to afford the desired compound **A12** (39 mg, 33%). δ_H (500 MHz, *d*$_6$-DMSO) 8.34 (bs, 1H, NH), 8.01 (d, J = 7.3 Hz, 1H, ArH), 7.33 (d, J = 8.2 Hz, 2H, ArH), 7.22 (m, 1H, ArH), 7.18 (m, 1H, ArH), 7.05 (t, J = 7.3 Hz, 1H, ArH), 6.91 (d, J = 8.2 Hz, 2H, ArH), 4.99 (d, J = 15.5 Hz, 1H, CH_2), 4.63 (s, 1H, CH), 4.39 (d, J = 15.5 Hz, 1H, CH_2), 2.64 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); δ_C (125 MHz, *d*$_6$-DMSO) 168.9, 165.8, 156.8, 141.7, 139.3, 129.1, 127.4, 124.7, 123.9, 122.0, 116.2, 115.7, 70.9, 66.1, 44.3, 31.8, 25.5, 22.6; LCMS (ES+): m/z (%) 373 $[M+H]^+$ t_R : 4.33; HRMS (ES+) Calc. for $[C_{20}H_{21}ClN_2O_3 + H]$ 373.1319 found 373.1307.

1-(2-(4-Chlorophenoxy)acetyl)-*N*-methylpyrrolidine-2-carboxamide (64)

Prepared using general procedure A, pale orange solid, 150 mg, 51%; δ_H (500 MHz, $CDCl_3$) 7.29-7.26 (m, 2H, ArH), 6.91-6.88 (m, 2H, ArH), 6.83 (bs, 1H, NH), 4.68 (d, J = 1.3 Hz, 2H, CH), 4.62 (dd, J = 8.2 and 2.2 Hz, 1H, CH), 3.63 (ddd, J = 9.9, 8.2 and 3.4 Hz, 1H, CH), 3.55-3.50 (m, 1H, CH), 2.75 (d, J = 4.9 Hz, 3H, CH_3), 2.47-2.42 (m, 1H, CH), 2.24 (m, 1H, CH), 2.05-2.00 (m, 1H, CH), 1.90-1.85 (m, 1H, CH); δ_C (125 MHz, *d*$_6$-DMSO) 175.0, 169.3,

158.4, 130.4, 127.3, 117.4, 67.7, 62.0, 47.4, 30.6, 26.6, 25.8; LCMS (ES+): m/z (%) 297 $[M+H]^+$ t_R : 3.30 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{14}H_{17}N_2O_3Cl + H]$ 297.1000 Found 297.0987.

2-(4-Chlorophenoxy)-*N*-(2-(methylamino)-2-oxoethyl)-*N*-phenylacetamide (65)

Prepared using general procedure A, colourless solid, 91 mg, 27%; δ_H (500 MHz, *d*6-DMSO) 7.93 (bs, 1H, NH), 7.56 (d, *J* = 7.5 Hz, 2H, ArH), 7.48 (t, *J* = 7.5 Hz, 2H, ArH), 7.29 (d, *J* = 8.8 Hz, 2H, ArH), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 4.48 (s, 2H, CH_2), 4.20 (s, 2H, CH_2), 2.60 (d, *J* = 4.3 Hz, 3H, CH_3). δ_C (125 MHz, *d*6-DMSO) 167.8 (C=O), 166.7 (C=O), 156.7, 141.2, 129.7, 129.0, 128.3, 127.7, 124.5, 116.2 (ArC), 65.6, 52.3, 25.5. LCMS (ES+): m/z (%) 333 $[M+H]^+$ t_R : 4.09 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{17}H_{18}ClN_2O_3 + H]$ 333.1000 Found 333.0997.

(*R*)-2-(2-(4-Fluorophenoxy)acetyl)-*N*-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (66)

Prepared from (R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using general procedure A, colourless solid, 56 mg, 33%; δ_H (500 MHz, *d*6-DMSO) 7.27-7.22 (m, 2H, ArH), 7.15-7.13 (m, 1H, ArH), 7.03-6.98 (m, 2H, ArH), 6.94-6.92 (m, 2H, ArH), 6.87-6.84 (m, 1H, ArH), 6.12 (d, *J* = 4.9 Hz, 1H, NH), 5.09 (t, *J* = 6.2 Hz, 1H, CH), 4.85 (d, *J* = 6.2 Hz, 1H, CH), 4.74-4.72 (m, 1H, CH), 4.60 (t, *J* = 13.8 Hz, 1H, CH), 3.41 (dd, *J* = 15.9 and 5.4 Hz, 1H, CH), 3.03 (dd, *J* = 15.9 and 6.6 Hz, 1H, CH), 2.65 (d, *J* = 4.9 Hz, 3H, CH_3), 2.57 (d, *J* = 4.9 Hz, 1H, CH); δ_C (125 MHz, *d*6-DMSO) 170.4, 168.5 (ArC), 153.6, 133.6, 132.1, 128.4, 127.9, 127.6, 127.2, 126.7, 126.4, 125.5 (ArC), 68.2, 53.2, 45.5, 29.5, 26.3; LCMS (ES+): m/z (%) 359 $[M+H]^+$ t_R : 5.1 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{20}FN_2O_3 + H]$ 343.1452 Found 343.1436.

1-(2-(4-Chlorophenoxy)acetyl)-*N*-methyl-1,2,3,4-tetrahydroquinoline-2-carboxamide (67)

Prepared from 1,2,3,4-tetrahydroquinoline-3-carboxylic acid using general procedure A, colourless solid, 14 mg, 8%; δ_H (500 MHz, $CDCl_3$) 7.24-7.23 (m, 3H, ArH), 7.20-7.18 (m, 3H, ArH), 6.69-6.66 (m, 2H, ArH), 6.58 (bs, 1H, NH), 5.07 (t, *J* = 8.7 Hz, 1H, CH), 4.88 (d, *J* = 14.5 Hz, 1H, CH), 4.62 (d, *J* = 14.5 Hz, 1H, CH), 2.78 (d, *J* = 4.9 Hz, 3H, CH_3), 2.72 (dt, *J* = 14.6 and 4.1 Hz, 1H, CH), 2.33-2.29 (m, 2H, CH), 2.21-2.15 (m, 1H, CH); δ_C (125 MHz, *d*6-DMSO) 170.6, 168.8 (C=O), 156.2, 135.5, 129.4, 128.1, 127.2, 126.6, 124.2, 115.8 (ArC), 66.8, 56.6, 41.0, 26.5, 25.9; LCMS (ES+): m/z (%) 359 $[M+H]^+$ t_R : 5.1 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{20}ClN_2O_3 + H]$ 359.1157 Found 359.1142.

***N*-Methyl-1-(2-phenoxyacetyl)-1,2,3,4-tetrahydroquinoline-3-carboxamide (68)**

Prepared from 1,2,3,4-tetrahydroquinoline-3-carboxylic acid using general procedure A, colourless solid, 10 mg, 6%; δ_H (500 MHz, $CDCl_3$) 7.25-7.22 (m, 3H, ArH), 6.99 (t, *J* = 7.3 Hz, 1H, ArH), 6.82 (bs, 1H, NH), 4.87 (s, 2H, CH_2), 4.22 (bs, 1H, CH), 3.77 (t, *J* = 10.0 Hz, 1H, CH_2), 3.12-3.07 (m, 1H, CH_2), 2.99-2.94 (m, 1H, CH_2), 2.81 (d, *J* = 4.8 Hz, 3H, CH_3), 2.77-2.73 (m, 1H, CH_2). LCMS (ES+): m/z (%) 325 $[M+H]^+$ t_R : 3.97 (20-95% MeCN, acidic); HRMS (ES+) Calc. for $[C_{19}H_{21}N_2O_3 + H]$ 325.1547 Found 325.1554

S2: Details of receptors screened at the NIMH Psychoactive Drug Screening Program

All compounds tested (**1**, **27**, **35** and **47**) did not show significant inhibitor against any of the receptors screened. Significant inhibition is considered > 50%. In cases where negative inhibition (-) is seen, this represents a stimulation of binding. The receptors screened were 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1e, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT5a, 5-HT6, 5-HT7, Alpha1A, Alpha1B, Alpha1D, Alpha2A, Alpha2B, Alpha2C, Beta1, Beta2, Beta3, BZP rat Brain site, D1, D2, D3, D4, D5, DAT, DOR, GABBA, H1, H2, H3, KOR, M1, M2, M3, M4, M5, MOR, NET, PBR, SERT, Sigma1 and Sigma2

1. Ooi, T.; Uematsu, Y.; Maruoka, K. Highly enantioselective alkylation of glycine methyl and ethyl ester derivatives under phase-transfer condiditons: it synthetic advantage. *Tetrahedron Lett.* **2004**, *45*, 1675-1678.
2. Kitamura, M.; Arimura, Y.; Shirakawa, S.; Maruoka, K. Combinatorial approach for the design of new, simplified chiral phase-transfer catalysts with high catalytic performance for practical asymmetric synthesis of alpha-alkyl-alpha-amino acids. *Tetrahedron Lett.* **2008**, *49*, 2026-2030.
3. Ooi, T.; Kameda, M.; Maruoka, K. Design of N-spiro C-2-symmetric chiral quaternary ammonium bromides as novel chiral phase-transfer catalysts: Synthesis and application to practical asymmetric synthesis of alpha-amino acids. *J. Am. Chem. Soc.* **2003**, *125*, 5139-5151.