

## Supporting Information

# Synthesis and antitumor effect in vitro and in vivo of substituted 1,3-dihydroindole-2-ones.

*Mette K. Christensen, Kamille D. Erichsen, Christina Trojel-Hansen, Jette Tjørnelund, Søren J. Nielsen, Karla Frydenvang, Tommy N. Johansen, Birgitte Nielsen, Maxwell Sehested, Peter Buhl Jensen, Martins Ikaunieks, Andrei Zaichenko, Einars Loza, Ivars Kalvinsh, and Fredrik Björkling.*

## Table of contents

	page
Experimentals	S2
General procedures	S2
Preparations and spectroscopic data of compounds <b>3-39</b>	S2
X-Ray Crystallographic Analysis of compound <b>39</b>	S13
Data Collection and Reduction compound <b>39</b>	S13
Structure Solution and Refinement compound <b>39</b>	S13
References	S15

## Experimentals

Reaction conditions and yields were not optimized.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance 300 spectrometer (300 MHz). Chemical shifts are reported in parts per million ( $\delta$ ) and referenced according to deuterated solvent for  $^1\text{H}$  spectra ( $\text{CDCl}_3$ , 7.26;  $\text{CD}_3\text{OD}$ , 3.31;  $(\text{CD}_3)_2\text{SO}$ , 2.50) and  $^{13}\text{C}$  spectra ( $\text{CDCl}_3$ , 77.23;  $\text{CD}_3\text{OD}$ , 49.00;  $(\text{CD}_3)_2\text{SO}$ , 39.52). The value of a multiplet, either defined doublet (d), triplet (t), double doublet (dd), double triplet (dt), quartet (q) or not (m) at the approximate mid point is given unless a range is quoted. (bs) indicates a broad singlet. The purity of the compounds was determined using an LC-MS (Bruker Esquire 3000+ ESI Iontrap with an Agilent 1200 HPLC-system) and was confirmed to be  $\geq 95\%$  for all compounds. HRMS was carried out on a Micromass *Q-ToF micro* mass spectrometer. The HPLC system for the semipreparative resolution of **39** consisted of a Jasco 880 pump, a Rheodyne 7125 injector, equipped with a 5 mL loop, and a Shimadzu SPD-6A UV detector, connected to a Hitachi-D2000 Chromato-integrator. A HPLC system for determination of the elution order of (*S*)-**38** and (*R*)-**38** consisting of a Dionex Ultimate 3000 pump, a TSP AS-3000 autosampler, and a Dionex Ultimate 3000 photodiode array detector was controlled by Chromeleon software v. 6.80.

### General Procedure A: Grignard reaction to form tertiary alcohols of general formula II, followed by Friedel-Crafts reaction with phenol.

To a stirred solution of isatin derivative I in dry THF under nitrogen at  $-78^\circ\text{C}$  was added 3 eq. of Grignard reagent. After 30 min, the dry-ice bath was removed and the reaction was left to reach rt over 4 to 14 h.<sup>7</sup> Excess Grignard reagent was quenched with water, and the reaction mixture was acidified with 1N HCl or saturated  $\text{NH}_4\text{Cl}$ -solution, extracted with  $\text{EtOAc}$  ( $\times 2$ ), dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by chromatography (1% MeOH in DCM or mixtures of petroleum ether and  $\text{EtOAc}$ ) to afford racemic tertiary alcohol II.

To a solution of tertiary alcohol of general formula II in dichloroethane was added phenol (5 eq.) and p-TSA (7.5 eq.). The reaction mixture was heated to  $90^\circ\text{C}$  for 2–4 h and then cooled to rt. The solid (mainly p-TSA) was filtered off and washed with dichloroethane or DCM. The solution was concentrated and the residue was purified by chromatography (1% MeOH in DCM or mixtures of petroleum ether and  $\text{EtOAc}$ ) to afford racemic compounds of general formula III.

### General Procedure B: HPLC purification on Daicel Chiralcel-OD column to yield pure enantiomers of general formula III.

Racemic compound of general formula III was dissolved in EtOH or EtOH/heptane mixtures and purified by HPLC on a Daicel Chiralcel-OD column ( $250 \times 20$  mm ID, 10 micron) to yield pure enantiomers of general formula III.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-phenylindolin-2-one (3).** Preparation of **3** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and phenylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-phenylindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.19 (bs, 1H), 7.39–7.24 (m, 5H), 7.05–6.91 (m, 2H), 6.81 (s, 1H). Yield 55%.

Product **3**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.47 (bs, 1H), 9.49 (bs, 1H), 7.37–7.25 (m, 3H), 7.18–7.12 (m, 2H), 7.09–7.00 (m, 2H), 6.96 (m, 2H), 6.72 (m, 2H). HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{13}\text{F}_2\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 360.0812; found, 360.0899. Yield 83%.

**(*RS*)-6,7-Difluoro-3-(4-fluorophenyl)-3-(4-hydroxyphenyl)indolin-2-one (4).** Preparation of **4** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 4-fluorophenylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-(4-fluorophenyl)-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.22 (bs, 1H), 7.31 (dd,  $J = 5.0, 8.9$  Hz, 2H), 7.16 (t,  $J = 9.0$  Hz, 2H), 7.04–6.91 (m, 2H), 6.88 (s, 1H). Yield 93%.

Product **4**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.49 (bs, 1H), 9.50 (bs, 1H), 7.22–7.11 (m, 4H), 7.10–6.99 (m, 2H), 6.95 (m, 2H), 6.72 (m, 2H). HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{12}\text{F}_3\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 378.0718; found, 374.0774. Yield 89%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-*p*-tolylindolin-2-one (5).** Preparation of **5** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and *p*-tolylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-*p*-tolylindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.19 (bs, 1H), 7.13 (m, 4H), 7.05–6.88 (m, 2H), 6.73 (s, 1H). Yield 86%.

Product **5**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.28 (bs, 1H), 7.11 (m, 4H), 7.06 (m, 2H), 6.93–6.78 (m, 2H), 6.72 (m, 2H), 5.47 (bs, 1H), 2.31 (s, 3H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{F}_2\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 374.0969; found, 374.0955. Yield 85%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (6).** Preparation of **6** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 4-methoxyphenylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy 3-(4-methoxyphenyl)indolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.12 (bs, 1H), 7.20 (m, 2H), 7.04–6.91 (m, 2H), 6.89 (m, 2H), 6.71 (s, 1H), 3.33 (s, 3H). Yield 86%.

Product **6**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.42 (bs, 1H), 9.47 (bs, 1H), 7.04 (m, 4H), 6.94 (d,  $J = 8.7$  Hz, 2H), 6.89 (d,  $J = 8.9$  Hz, 2H), 6.72 (d,  $J = 8.9$  Hz, 2H), 3.72 (s, 3H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{F}_2\text{NO}_3$  [ $\text{M}+\text{Na}$ ], 390.0918; found, 390.0902. Yield 92%.

**6,7-Difluoro-3-(4-hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (enantiomer 1) (6).**

Preparation of enantiomer 1 of compound **6** was performed according to general procedure B (heptane:EtOH 70:30, 15 mL/min) using racemic compound **6** as starting material.  $t_R$  (Chiralcel OD-H 250 × 4.6 mm ID, 5 micron, heptane:EtOH 70:30, 0.6 mL/min): 10.5 min. HRMS  $m/z$  calcd for  $C_{21}H_{15}F_2NO_3$  [M+Na], 390.0918; found, 390.0902. Yield 37%.

**6,7-Difluoro-3-(4-hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (enantiomer 2) (6).**

Preparation of enantiomer 2 of compound **6** was performed according to general procedure B (heptane:EtOH 70:30, 15 mL/min) using racemic compound **6** as starting material.  $t_R$  (Chiralcel OD-H 250 × 4.6 mm ID, 5 micron, heptane:EtOH 70:30, 0.6 mL/min): 15.6 min. HRMS  $m/z$  calcd for  $C_{21}H_{15}F_2NO_3$  [M+Na], 390.0918; found, 390.0883. Yield 40%.

**(RS)-3-(4-Ethoxyphenyl)-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (7).** Preparation of **7** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 4-ethoxyphenylmagnesium bromide.

(RS)-3-(4-Ethoxyphenyl)-6,7-difluoro-3-hydroxyindolin-2-one:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  11.13 (bs, 1H), 7.18 (m, 2H), 7.00 (m, 2H), 6.87 (m, 2H), 6.71 (s, 1H), 3.99 (q,  $J = 7.0$  Hz, 2H), 1.30 (t,  $J = 7.0$  Hz, 3H). Yield 62%.

Product **7**:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.66 (bs, 1H), 7.15 (m, 2H), 7.06 (m, 2H), 6.95–6.85 (m, 2H), 6.83 (m, 2H), 6.72 (m, 2H), 6.20 (bs, 1H), 4.01 (q,  $J = 7.1$  Hz, 2H), 1.40 (t,  $J = 7.1$  Hz, 3H). HRMS  $m/z$  calcd for  $C_{22}H_{17}F_2NO_3$  [M+Na], 404.1074; found, 404.049. Yield 85%.

**(RS)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-(4-propoxyphenyl)indolin-2-one (8).**

Preparation of **8** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 4-propoxyphenylmagnesium bromide.

(RS)-6,7-Difluoro-3-hydroxy-3-(4-propoxyphenyl)indolin-2-one:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.41 (bs, 1H), 7.79 (m, 2H), 7.49 (m, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 6.09 (s, 1H), 4.38 (t,  $J = 6.5$  Hz, 2H), 2.20 (m, 2H), 1.45 (t,  $J = 7.4$ , 3H). Yield 40%.

Product **8**:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.67 (bs, 1H), 7.13 (m, 2H), 7.05 (m, 2H), 6.87 (m, 2H), 6.81 (m, 2H), 6.70 (m, 2H), 6.28 (bs, 1H), 3.87 (q,  $J = 6.5$  Hz, 2H), 1.78 (m, 2H), 1.01 (t,  $J = 7.5$  Hz, 3H). HRMS  $m/z$  calcd for  $C_{23}H_{19}F_2NO_3$  [M+Na], 418.1231; found, 404.1245. Yield 94%.

**(RS)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-[4-(pentyloxy)phenyl]indolin-2-one (9).**

Preparation of **9** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 4-(pentyloxy)phenylmagnesium bromide.

(RS)-6,7-Difluoro-3-hydroxy-3-[4-(pentyloxy)phenyl]-indolin-2-one:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10. (bs, 1H), 7.79 (m, 2H), 7.49 (m, 1H), 7.40 (m, 1H), 7.34 (m, 2H), 6.09 (s, 1H), 4.42 (t,  $J = 6.5$  Hz, 2H), 2.50 (m, 2H), 1.85 (m, 4H), 1.36 (t,  $J = 7.1$  Hz, 3H). Yield 80%.

Product **9**:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.77 (bs, 1H), 7.13 (m, 2H), 7.04 (m, 2H), 6.87 (m, 2H), 6.81 (m, 2H), 6.69 (m, 2H), 6.30 (bs, 1H), 3.91 (q,  $J = 6.4$  Hz, 2H), 1.76 (m, 2H), 1.39 (m, 4H), 0.92 (t,  $J = 6.7$  Hz, 3H). HRMS  $m/z$  calcd for  $C_{25}H_{23}F_2NO_3$  [M+Na], 446.1544; found, 446.1621. Yield 59%.

**(*RS*)-6,7-Difluoro-3-(3-hydroxyphenyl)-3-(4-methoxyphenyl)indolin-2-one (10).**

Preparation of **10** was performed according to general procedure A (step 1) using 6,7-difluoroindoline-2,3-dione and 3-methoxyphenylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-(3-methoxyphenyl)indolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.19 (bs, 1H), 7.21 (t,  $J = 7.9$  Hz, 1H), 6.94 (m, 3H), 6.86 (m, 1H), 6.82 (bs, 1H), 6.70 (m, 1H), 3.73 (s, 3H). Yield 85%.

6,7-Difluoro-3-hydroxy-3-(3-methoxyphenyl)indolin-2-one (1.0 mmol) was suspended in DCM, cooled to  $-78$  °C under  $\text{N}_2$ , followed by dropwise addition of  $\text{BBr}_3$  (2.0 mmol). The reaction mixture was gradually allowed to reach rt and stirred overnight, quenched with water, extracted three times with diethyl ether. The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by chromatography (1% MeOH in DCM) to afford 6,7-difluoro-3-hydroxy-3-(3-hydroxyphenyl)indolin-2-one.  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.15 (bs, 1H), 9.38 (bs, 1H), 7.09 (t,  $J = 7.9$  Hz, 1H), 6.96 (m, 2H), 6.75 (m, 1H), 6.72 (bs, 1H), 6.65 (m, 1H). Yield 93%.

To a suspension of 6,7-difluoro-3-hydroxy-3-(3-hydroxyphenyl)indolin-2-one in dichloroethane was added anisol (5 eq.) and p-TSA (7.5 eq.). The reaction mixture was heated to  $90$  °C for 4 h and then cooled to rt. The solid (mainly p-TSA) was filtered off and washed with DCM. The filtrate was concentrated and the residue was purified by chromatography (1% MeOH in DCM) to afford compound **10**.  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.47 (bs, 1H), 9.38 (bs, 1H), 7.16–7.00 (m, 5H), 6.90 (m, 2H), 6.67 (m, 1H), 6.58 (m, 1H), 6.54 (m, 1H), 3.73 (s, 3H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{F}_2\text{NO}_3$  [ $\text{M}+\text{H}$ ], 368.1098; found, 368.1094. Yield 69%.

**(*RS*)-3-(3,4-Difluorophenyl)-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (11).**

Preparation of **11** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and 3,4-difluorophenylmagnesium bromide.

(*RS*)-3-(3,4-Difluorophenyl)-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.73 (bs, 1H), 8.11 (m, 1H), 8.03 (bs, 1H), 7.72 (m, 1H), 7.49 (m, 2H), 6.99 (bs, 1H). Yield 60%.

Product **11**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.04 (bs, 1H), 7.20–7.00 (m, 4H), 7.00–6.84 (m, 3H), 6.77 (m, 2H), 5.12 (bs, 1H). HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{11}\text{F}_4\text{NO}_2$  [ $\text{M}+\text{H}$ ], 374.0804; found, 374.0797. Yield 98%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-(thiophen-2-yl)indolin-2-one (12).** Preparation of **12** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and thiophen-2-ylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-(thiophen-2-yl)indolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.23 (bs, 1H), 7.52 (dd,  $J = 1.3, 5.1$  Hz, 1H), 7.16 (m, 1H), 7.06 (m, 1H), 7.05 (s, 1H), 6.95 (dd,  $J = 3.56, 5.1$  Hz, 1H), 6.71 (dd,  $J = 1.3, 3.6$  Hz, 1H). Yield 41%.

Product **12**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.55 (bs, 1H), 9.53 (bs, 1H), 7.51 (d,  $J = 5.5$  Hz, 1H), 7.16 (m, 1H), 7.08 (m, 1H), 7.0–6.9 (m, 4H), 6.70 (m, 2H). HRMS  $m/z$  calcd for  $\text{C}_{18}\text{H}_{11}\text{F}_2\text{NO}_2\text{S}$  [ $\text{M}+\text{H}$ ], 344.0558; found, 344.0557. Yield 66%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-(pyridin-4-yl)indolin-2-one (13).** Preparation of **13** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and pyridin-4-ylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-(pyridin-4-yl)indolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.37 (bs, 1H), 8.53 (m, 2H), 7.27 (m, 2H), 7.08 (s, 1H), 7.06–6.9 (m, 2H). Yield 43%.

Product **13**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.87 (bs, 1H), 8.99 (bs, 3H), 7.69 (bs, 2H), 7.68–7.40 (m, 4H), 7.27 (m, 2H). HRMS  $m/z$  calcd for  $\text{C}_{19}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_2$  [ $\text{M}+\text{H}$ ], 339.0945; found, 339.0928. Yield 18%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-(pyridin-3-yl)indolin-2-one (14).** Preparation of **14** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and pyridin-3-ylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-(pyridin-3-yl)indolin-2-one:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.61 (bs, 1H), 8.37 (m, 1H), 8.15 (1H, bs), 7.69 (m, 1H), 7.16 (m, 1H), 6.89 (m, 1H), 6.73 (m, 1H), 5.23 (s, 1H). Yield 10%. Product **14**: MS [ $\text{M}+\text{K}$ ] $^+$  = 380.20. HRMS  $m/z$  calcd for  $\text{C}_{19}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_2$  [ $\text{M}+\text{H}$ ], 339.0945; found, 339.0943. Yield 10%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-propylindolin-2-one (15).** Preparation of **15** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and *n*-propylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-propylindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.00 (bs, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.01 (s, 1H), 1.74 (m, 2H), 1.1–0.9 (m, 2H), 0.78 (t,  $J$  = 7.3 Hz, 3H). Yield 37%.

Product **15**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.20 (bs, 1H), 9.38 (bs, 1H), 7.04 (m, 4H), 6.69 (m, 2H), 2.13 (m, 2H), 1.21 (m, 2H), 1.02 (m, 2H), 0.83 (m, 3H). HRMS  $m/z$  calcd for  $\text{C}_{17}\text{H}_{15}\text{F}_2\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 326.0969; found, 326.0996. Yield 96%.

**(*RS*)-6,7-Difluoro-3-(4-hydroxyphenyl)-3-pentylindolin-2-one (16).** Preparation of **16** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and *n*-pentylmagnesium bromide.

(*RS*)-6,7-Difluoro-3-hydroxy-3-pentylindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.00 (bs, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.01 (s, 1H), 1.76 (m, 2H), 1.35–0.8 (m, 6H), 0.78 (t,  $J$  = 6.7 Hz, 3H). Yield 46%.

Product **16**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.21 (bs, 1H), 9.39 (bs, 1H), 7.04 (m, 4H), 6.70 (m, 2H), 2.20 (m, 2H), 1.18 (m, 4H), 1.00 (m, 1H), 0.9–0.65 (m, 4H). HRMS  $m/z$  calcd for  $\text{C}_{19}\text{H}_{19}\text{F}_2\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 354.1282; found, 354.1290. Yield 80%.

**(*RS*)-3-Cyclopentyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (17).** Preparation of **17** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and cyclopentylmagnesium bromide.

(*RS*)-3-Cyclopentyl-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.98 (bs, 1H), 7.15 (m, 1H), 6.94 (m, 1H), 2.31 (m, 1H), 1.7–1.3 (m, 7H), 1.15 (m, 1H). Yield 42%.

Product **17**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.21 (bs, 1H), 9.38 (bs, 1H), 7.12 (m, 3H), 7.01 (m, 1H), 6.69 (m, 2H), 2.97 (m, 1H), 1.6–1.2 (m, 7H), 0.94 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_2\text{NO}_2$   $[\text{M}+\text{H}]$ , 330.1306; found, 330.1312. Yield 57%.

**(*RS*)-3-Cyclohexyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (18).** Preparation of **18** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and cyclohexylmagnesium chloride.

(*RS*)-3-Cyclohexyl-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.98 (bs, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 1.9–1.4 (m, 6H), 1.25–0.85 (m, 4H), 0.67 (m, 1H). Yield 55%.

Product **18**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.19 (bs, 1H), 9.39 (bs, 1H), 7.12 (m, 3H), 7.03 (m, 1H), 6.70 (m, 2H), 2.33 (m, 1H), 1.7–0.8 (m, 9H), 0.71 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_2\text{NO}_2$   $[\text{M}+\text{H}]$ , 344.1462; found, 344.1453. Yield 93%.

**3-Cyclohexyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (enantiomer 1) (18).**

Preparation of enantiomer 1 of compound **18** was performed according to general procedure B (heptane:ethanol 70:30, 7 mL/min). Starting material: racemic compound **18**.  $t_{\text{R}}$  (Chiralcel OD-H 250  $\times$  4.6 mm ID, 5 micron, heptane:ethanol 70:30, 0.6 mL/min): 8.9 min. HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_2\text{NO}_2$   $[\text{M}+\text{H}]$ , 344.1462; found, 344.1448, Yield 39%.

**3-Cyclohexyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (enantiomer 2) (18).**

Preparation of enantiomer 2 of compound **18** was performed according to general procedure B (heptane:ethanol 70:30, 7 mL/min). Starting material: racemic compound **18**.  $t_{\text{R}}$  (Chiralcel OD-H 250  $\times$  4.6 mm ID, 5 micron, heptane:ethanol 70:30, 0.6 mL/min): 14.5 min. HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_2\text{NO}_2$   $[\text{M}+\text{Na}]$ , 366.1282; found, 366.1275. Yield 34%.

**(*RS*)-3-Cycloheptyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (19).** Preparation of **19** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.99 (bs, 1H), 7.06 (m, 1H), 6.94 (m, 1H), 2.06 (m, 1H), 1.91 (m, 1H) 1.8–1.1 (m, 10H), 0.78 (m, 1H). Yield 42%.

Product **19**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.16 (bs, 1H), 9.39 (bs, 1H), 7.08 (m, 4H), 6.70 (m, 2H), 2.53 (m, 1H), 1.7–1.15 (m, 11H), 0.84 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{21}\text{F}_2\text{NO}_2$   $[\text{M}+\text{H}]$ , 358.1619; found, 358.1622. Yield 90%.

**(*RS*)-3-Cyclooctyl-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (20).** Preparation of **20** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and cyclooctylmagnesium bromide.

(*RS*)-3-Cyclooctyl-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.01 (bs, 1H), 7.08 (m, 1H), 6.94 (m, 1H), 6.00 (s, 1H), 2.03 (m, 1H), 1.8–1.2 (m, 13 H), 0.85 (m, 1H). Yield 28%.

Product **20**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.16 (bs, 1H), 9.40 (bs, 1H), 7.11 (m, 3H), 7.02 (m, 1H), 6.70 (m, 2H), 2.64 (m, 1H), 1.65–1.15 (m, 13H), 0.89 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{23}\text{F}_2\text{NO}_2$   $[\text{M}+\text{H}]$ , 372.1775; found, 372.1755. Yield 43%.

**(*RS*)-3-(Cyclohexylmethyl)-6,7-difluoro-3-(4-hydroxyphenyl)indolin-2-one (21).**

Preparation of **21** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and cyclohexylmethylmagnesium bromide.

(*RS*)-3-(Cyclohexylmethyl)-6,7-difluoro-3-hydroxy-indolin-2-one:  $^1\text{H}$ -NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.00 (bs, 1H), 7.10 (m, 1H), 6.98 (m, 1H), 5.95 (s, 1H), 1.75 (d, 2H), 1.6–1.4 (m, 4H), 1.32 (m, 1H), 1.02 (m, 4H), 0.82 (m, 2H). Yield 42%.

Product **21**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  11.19 (bs, 1H), 9.37 (bs, 1H), 7.07 (m, 2H), 7.05 (m, 2H), 6.67 (d, 2H), 2.12 (m, 2H), 1.6–1.4 (m, 4H), 1.25 (m, 1H), 1.1–0.7 (m, 6H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{21}\text{F}_2\text{NO}_2$   $[\text{M}+\text{Na}]$ , 380.1438; found, 380.1403. Yield 67%.

**(*RS*)-3-Benzyl-6,7-difluoro-3-(4-hydroxyphenyl)indoline-2-one (22).** Preparation of **22** was performed according to general procedure A using 6,7-difluoroindoline-2,3-dione and benzylmagnesium chloride.

(*RS*)-3-Benzyl-6,7-difluoro-3-hydroxyindolin-2-one:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.86 (bs, 1H), 7.3–6.7 (m, 7H), 6.33 (1H, bs), 3.10 (dd, 2H). Yield 85%.

Product **22**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.99 (bs, 1H), 9.44 (s, 1H), 7.18 (m, 3H), 7.08 (m, 3H), 6.99 (m, 1H), 6.89 (m, 2H), 6.74 (m, 2H), 3.50 (dd, 2H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{F}_2\text{NO}_2$   $[\text{M}+\text{Na}]$ , 374.0969; found, 374.0957. Yield 82%.

**(*RS*)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)indolin-2-one (23).** Preparation of **23** was performed according to general procedure A using indoline-2,3-dione and 4-fluorophenylmagnesium bromide.

(*RS*)-3-(4-Fluorophenyl)-3-hydroxy-indolin-2-one:  $^1\text{H}$ -NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.42 (bs, 1H), 7.29 (m, 3H), 7.14 (m, 3H), 6.98 (t,  $J = 7.5$  Hz, 1H), 6.90 (d,  $J = 7.5$  Hz, 1H), 6.69 (s, 1H). Yield 67%.

Product **23**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.71 (bs, 1H), 9.45 (bs, 1H), 7.22 (m, 2H), 7.15 (m, 4H), 7.01 (m, 1H), 6.94 (m, 3H), 6.70 (m, 2H). HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{14}\text{FNO}_2$   $[\text{M}+\text{Na}]$ , 342.0906; found, 342.0886. Yield 95%.

**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)indolin-2-one (24).** Preparation of **24** was performed according to general procedure A using indoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-indolin-2-one:  $^1\text{H}$ -NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.19 (bs, 1H), 7.22 (d,  $J = 7.0$  Hz, 3H), 7.17 (m, 1H), 6.92 (m, 1H), 6.77 (d,  $J = 7.5$  Hz, 1H), 5.77 (s, 1H). Yield 26%.

Product **24**:  $^1\text{H}$  NMR ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.36 (bs, 1H), 9.32 (bs, 1H), 7.28 (d,  $J = 7.5$  Hz, 1H), 7.23 (m, 1H), 7.10 (m, 2H), 7.02 (m, 1H), 6.87 (d,  $J = 7.2$  Hz, 1H), 6.68 (m, 2H), 2.46 (m, 1H), 1.7–1.15 (m, 11H), 0.84 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{23}\text{NO}_2$   $[\text{M}+\text{Na}]$ , 344.1626; found, 344.1645. Yield 63%.



**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-7-methylindolin-2-one (25).** Preparation of **25** was performed according to general procedure A using 7-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-7-methylindolin-2-one:  $^1\text{H-NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.24 (bs, 1H), 7.05 (d,  $J = 7.4$  Hz, 1H), 7.01 (d,  $J = 7.4$  Hz, 1H), 6.85 (t,  $J = 7.4$  Hz, 1H), 5.73 (s, 1H), 2.17 (s, 3H), 2.07 (m, 1H), 1.80 (m, 1H), 1.72 (m, 1H), 1.6–1.15 (m, 9H), 0.75 (m, 1H). Yield 14%.

Product **25**:  $^1\text{H NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.39 (bs, 1H), 9.31 (bs, 1H), 7.09 (m, 3H), 7.05 (d,  $J = 7.4$  Hz, 1H), 6.93 (t,  $J = 7.4$  Hz, 1H), 6.67 (m, 2H), 2.46 (m, 1H), 2.21 (s, 3H), 1.7–1.2 (m, 9H), 0.84 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{25}\text{NO}_2$  [ $\text{M}+\text{H}$ ], 336.1964; found, 336.1940. Yield 68%.

**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-7-(trifluoromethyl)indolin-2-one (26).**

Preparation of **26** was performed according to general procedure A using 7-(trifluoromethyl)indoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-7-(trifluoromethyl)indolin-2-one:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  10.72 (bs, 1H), 7.50 (m, 2H), 7.12 (t,  $J = 7.7$  Hz, 1H), 6.03 (s, 1H), 2.2–1.1 (m, 12H), 0.80 (m, 1H). Yield 26%.

Product **26**:  $^1\text{H NMR}$  ( $(\text{CD}_3)_2\text{SO}$ )  $\delta$  10.90 (bs, 1H), 9.41 (bs, 1H), 7.56 (m, 2H), 7.20 (t,  $J = 7.5$  Hz, 1H), 7.09 (m, 2H), 6.71 (m, 2H), 2.55 (m, 1H), 1.7–1.15 (m, 11H), 0.86 (m, 1H). HRMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{22}\text{F}_3\text{NO}_2$  [ $\text{M}+\text{Na}$ ], 390.1681; found, 390.1662. Yield 49%.

**(*RS*)-3-(4-(hydroxyphenyl)-3-(1*H*-imidazol-1-yl)-7-(trifluoromethyl)indolin-2-one (27).**

Preparation of **27** was performed according to general procedure A (step 1) using 7-(trifluoromethyl)indoline-2,3-dione and (4-(benzyloxy)phenyl)magnesium bromide followed by two additional steps (see below).

(*RS*)-3-(4-(Benzyloxy)phenyl)-3-hydroxy-7-(trifluoromethyl)indolin-2-one:  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  10.85 (bs, 1H), 7.55 (d,  $J = 8.7$  Hz, 1H), 7.5–7.28 (m, 6H), 7.18 (m, 3H), 6.98 (m, 2H), 6.75 (s, 1H), 5.08 (s, 2H). Yield 69%.

Imidazole (204 mg, 3 mmol) was dissolved in DCM (dried), cooled to 0 °C, and thionylchloride (55  $\mu\text{L}$ , 0.75 mmol) was added with stirring. After 30 min 3-(4-(benzyloxy)phenyl)-3-hydroxy-7-(trifluoromethyl)indolin-2-one (200 mg, 0.5 mmol) was added. After a further 2 h the reaction mixture was extracted with  $\text{H}_2\text{O}$ , brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by chromatography (1% MeOH in DCM) to afford 3-(4-(benzyloxy)phenyl)-3-(1*H*-imidazol-1-yl)-7-(trifluoromethyl)indolin-2-one.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  11.59 (bs, 1H), 7.82 (d,  $J = 7.4$  Hz, 1H), 7.69 (d,  $J = 8.3$  Hz, 1H), 7.59 (s, 1H), 7.5–7.2 (m, 6H), 7.15–6.95 (m, 6H), 5.10 (s, 2H). Yield 81%.

3-(4-(benzyloxy)phenyl)-3-(1*H*-imidazol-1-yl)-7-(trifluoromethyl)indolin-2-one (184 mg, 0.36 mmol) was dissolved in MeOH (10 mL) and the solution bubbled through with  $\text{N}_2$  for 2 minutes. 10% Pd/C (60 mg) was added. The flask was fitted with a septum and a  $\text{N}_2$ -filled balloon, carefully evacuated and filled with  $\text{N}_2$ . The  $\text{N}_2$ -filled balloon was substituted with a  $\text{H}_2$ -filled balloon, the flask was then carefully evacuated and filled with  $\text{H}_2$  twice and the reaction mixture vigorously stirred at rt for 4h. The flask was the carefully evacuated and

filled with N<sub>2</sub> twice, the reaction mixture filtered through Celite, concentrated and purified by flash chromatography (1%–5% MeOH in DCM) to yield product **27**. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 11.53 (bs, 1H), 9.79 (bs, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.56 (bs, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.10 (bs, 1H), 7.01 (m, 3H), 6.80 (m, 2H). HRMS *m/z* calcd for C<sub>18</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub> [M+Na], 382.0779; found, 382.0772. Yield 38%.

**(*RS*)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)-5,7-dimethylindolin-2-one (28).**

Preparation of **28** was performed according to general procedure A using 5,7-dimethylindoline-2,3-dione and 4-fluorophenylmagnesium bromide.

(*RS*)-3-(4-Fluorophenyl)-3-hydroxy-5,7-dimethylindolin-2-one: <sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.36 (bs, 1H), 7.28 (m, 2H), 7.13 (m, 2H), 6.88 (bs, 1H), 6.73 (bs, 1H), 5.59 (s, 1H), 2.20 (s, 3H), 2.18 (s, 3H). Yield 63%.

Product **28**: <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.63 (bs, 1H), 9.42 (bs, 1H), 7.15 (m, 4H), 6.95 (m, 2H), 6.86 (bs, 1H), 6.82 (bs, 1H), 6.70 (m, 2H), 2.21 (s, 3H), 2.20 (s, 3H). HRMS *m/z* calcd for C<sub>20</sub>H<sub>18</sub>FNO<sub>2</sub> [M+H], 348.1400; found, 348.1406. Yield 95%.

**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-5,7-dimethylindolin-2-one (29).** Preparation of **29** was performed according to general procedure A using 5,7-dimethylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-5,7-dimethylindolin-2-one: <sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.13 (bs, 1H), 6.86 (bs, 1H), 6.81 (bs, 1H), 5.66 (s, 1H), 2.21 (s, 3H), 2.13 (s, 3H), 2.07 (m, 1H), 1.87 (m, 1H), 1.71 (m, 1H), 1.65–1.15 (m, 9H), 0.76 (m, 1H). Yield 34%.

Product **29**: <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.28 (bs, 1H), 9.31 (bs, 1H), 7.10 (m, 2H), 6.90 (bs, 1H), 6.85 (bs, 1H), 6.68 (m, 2H), 2.46 (m, 1H), 2.26 (s, 3H), 2.17 (s, 3H), 1.7–1.1 (m, 11H), 0.85 (m, 1H). HRMS *m/z* calcd for C<sub>23</sub>H<sub>27</sub>NO<sub>2</sub> [M+Na], 372.1939; found, 372.1938. Yield 60%.

**(*RS*)-3-Cycloheptyl-5-fluoro-3-(4-hydroxyphenyl)-7-methylindolin-2-one (30).**

Preparation of **30** was performed according to general procedure A using 5-fluoro-7-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-5-fluoro-3-hydroxy-7-methylindolin-2-one: <sup>1</sup>H-NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.30 (bs, 1H), 6.88 (m, 2H), 5.88 (s, 1H), 2.18 (s, 3H), 2.02 (m, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.65–1.15 (m, 9H), 0.79 (m, 1H). Yield 35%.

Product **30**: <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.45 (bs, 1H), 9.35 (bs, 1H), 7.10 (m, 2H), 6.95 (m, 2H), 6.69 (m, 2H), 2.46 (m, 1H), 2.21 (s, 3H), 1.7–1.2 (m, 11H), 0.86 (m, 1H). HRMS *m/z* calcd for C<sub>22</sub>H<sub>24</sub>FNO<sub>2</sub> [M+Na], 376.1689; found, 378.1696. Yield 57%.

**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-6,7-dimethylindolin-2-one (31).** Preparation of **31** was performed according to general procedure A using 6,7-dimethylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-6,7-dimethylindolin-2-one: <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.16 (bs, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.62 (s, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 2.05 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.6–1.15 (m, 9H), 0.75 (m, 1H). Yield 28%.

Product **31**: <sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO) δ 10.30 (bs, 1H), 9.29 (bs, 1H), 7.10 (m, 2H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.66 (m, 2H), 2.45 (m, 1H), 2.22 (s, 3H), 2.12 (s, 3H),

1.7–1.15 (m, 11H), 0.84 (m, 1H). HRMS  $m/z$  calcd for  $C_{23}H_{27}NO_2$  [M+H], 350.2120; found, 350.2097. Yield 72%.

**(*RS*)-3-Cycloheptyl-6-fluoro-3-(4-hydroxyphenyl)-7-methylindolin-2-one (32).**

Preparation of **32** was performed according to general procedure A using 6-fluoro-7-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-6-fluoro-3-hydroxy-7-methylindolin-2-one:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.56 (bs, 1H), 7.16 (m, 1H), 6.71 (m, 1H), 2.84 (m, 1H), 2.18 (s, 3H), 2.3–1.3 (m, 11H), 0.88 (m, 1H). Yield 27%.

Product **32**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.62 (bs, 1H), 9.35 (bs, 1H), 7.10 (m, 3H), 6.80 (m, 1H), 6.68 (m, 2H), 2.47 (m, 1H), 2.14 (s, 3H), 1.7–1.1 (m, 11H), 0.84 (m, 1H). HRMS  $m/z$  calcd for  $C_{22}H_{24}FNO_2$  [M+Na], 376.1689; found, 376.1689. Yield 57%.

**(*RS*)-6-Chloro-3-cycloheptyl-3-(4-hydroxyphenyl)-7-methylindolin-2-one (33).**

Preparation of **33** was performed according to general procedure A using 6-chloro-7-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-6-chloro-3-cycloheptyl-3-hydroxy-7-methylindolin-2-one:  $^1H$ -NMR ( $(CD_3)_2SO$ )  $\delta$  10.48 (bs, 1H), 7.07 (d,  $J = 7.9$  Hz, 1H), 7.01 (d,  $J = 7.9$  Hz, 1H), 5.85 (s, 1H), 2.21 (s, 3H), 2.04 (m, 1H), 1.90 (m, 1H), 1.71 (m, 1H), 1.6.1-1.1 (m, 9H), 0.79 (m, 1H). Yield 36%.

Product **33**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.62 (bs, 1H), 9.35 (bs, 1H), 7.09 (m, 4H), 6.69 (m, 2H), 2.25 (s, 3H), 1.7–1.15 (m, 12H), 0.85 (m, 1H). HRMS  $m/z$  calcd for  $C_{22}H_{24}ClNO_2$  [M+H], 370.1574; found, 370.1532. Yield 65%.

**(*RS*)-7-Chloro-3-cycloheptyl-3-(4-hydroxyphenyl)-6-methylindolin-2-one (34).**

Preparation of **34** was performed according to general procedure A using 7-chloro-6-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-7-chloro-3-cycloheptyl-3-hydroxy-6-methylindolin-2-one:  $^1H$ -NMR ( $(CD_3)_2SO$ )  $\delta$  10.55 (bs, 1H), 7.09 (d,  $J = 7.4$  Hz, 1H), 6.92 (d,  $J = 7.4$  Hz, 1H), 5.90 (s, 1H), 2.29 (s, 3H), 2.06 (m, 1H), 1.90 (m, 1H), 1.71 (m, 1H), 1.6–1.15 (m, 9 H), 0.75 (m, 1H). Yield 42%.

Product **34**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.69 (bs, 1H), 9.36 (bs, 1H), 7.15 (d,  $J = 7.6$  Hz, 1H), 7.08 (m, 2H), 7.01 (d,  $J = 7.6$  Hz, 1H), 6.69 (m, 2H), 2.47 (m, 1H), 2.33 (s, 3H), 1.7–1.2 (m, 11 H), 0.85 (m, 1H). HRMS  $m/z$  calcd for  $C_{22}H_{24}ClNO_2$  [M+Na], 392.1393; found, 392.1369. Yield 56%.

**(*RS*)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (35).**

Preparation of **35** was performed according to general procedure A using 6-methoxy-7-methylindoline-2,3-dione and 4-fluorophenylmagnesium bromide.

(*RS*)-3-(4-Fluorophenyl)-3-hydroxy-6-methoxy-7-methylindolin-2-one:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.42 (bs, 1H), 7.29 (m, 2H), 7.12 (m, 2H), 6.90 (d,  $J = 8.2$  Hz, 1H, ), 6.56 (d,  $J = 8.2$  Hz, 1H), 6.51 (s, 1H), 3.77 (s, 3H), 2.09 (s, 3H). Yield 82%.

Product **35**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.71 (bs, 1H), 9.41 (bs, 1H), 7.15 (m, 4H), 6.95 (m, 3H), 6.69 (m, 2H), 6.59 (d,  $J = 8.3$  Hz, 1H), 3.76 (s, 3H), 2.09 (s, 3H). HRMS  $m/z$  calcd for  $C_{22}H_{18}FNO_3$  [M+H], 364.1349; found, 364.1336. Yield 94%.

**(*RS*)-3-Cyclopentyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (36).**

Preparation of **36** was performed according to general procedure A using 6-methoxy-7-methylindoline-2,3-dione and cyclopentylmagnesium bromide.

(*RS*)-3-Cyclopentyl-3-hydroxy-6-methoxy-7-methylindolin-2-one: MS  $[M+Na]^+ = 284.0$   $[M-H]^+ = 260.0$ . Yield 27%.

Product **36**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.39 (bs, 1H), 9.27 (bs, 1H), 7.13 (m, 2H), 7.05 (d,  $J = 8.3$  Hz, 1H), 6.66 (m, 2H), 6.58 (d,  $J = 8.3$  Hz, 1H), 3.78 (s, 3H), 2.92 (m, 1H), 2.06 (s, 3H), 1.6–1.2 (m, 7H), 0.86 (m, 1H). HRMS  $m/z$  calcd for  $C_{21}H_{23}NO_3$   $[M+Na]$ , 360.1576; found, 360.1593. Yield 56%.

**(*RS*)-3-Cyclohexyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (37).**

Preparation of **37** was performed according to general procedure A using 6-methoxy-7-methylindoline-2,3-dione and cyclohexylmagnesium chloride.

(*RS*)-3-Cyclohexyl-3-hydroxy-6-methoxy-7-methylindolin-2-one:  $^1H$ -NMR ( $(CD_3)_2SO$ )  $\delta$  10.19 (bs, 1H), 7.00 (d,  $J = 8.2$  Hz, 1H), 6.51 (d,  $J = 8.2$  Hz, 1H), 5.52 (s, 1H), 3.75 (s, 3H), 2.01 (s, 3H), 1.95–1.4 (m, 6H), 1.25–0.85 (m, 4H), 0.63 (m, 1H). Yield 51%.

Product **37**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.38 (bs, 1H), 9.28 (bs, 1H), 7.13 (m, 2H), 7.07 (d,  $J = 8.2$  Hz, 1H), 6.67 (m, 2H), 6.61 (d,  $J = 8.2$  Hz, 1H), 3.79 (s, 3H), 2.27 (m, 1H), 2.05 (s, 3H), 1.58 (m, 3H), 1.41 (m, 2H), 1.13 (m, 3H), 0.93 (m, 1H), 0.68 (m, 1H). HRMS  $m/z$  calcd for  $C_{22}H_{25}NO_3$   $[M+H]$ , 352.1913; found, 352.1914. Yield 94%.

**(*RS*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (38).**

Preparation of **38** was performed according to general procedure A using 6-methoxy-7-methylindoline-2,3-dione and cycloheptylmagnesium bromide.

(*RS*)-3-Cycloheptyl-3-hydroxy-6-methoxy-7-methylindolin-2-one:  $^1H$ -NMR ( $(CD_3)_2SO$ )  $\delta$  10.21 (bs, 1H), 7.00 (d,  $J = 8.3$  Hz, 1H), 6.49 (d,  $J = 8.3$  Hz, 1H), 5.58 (s, 1H), 3.75 (s, 3H), 2.08 (m, 1H), 2.01 (s, 3H), 1.88 (m, 1H), 1.73 (m, 1H), 1.55 (m, 1H), 1.50–1.20 (m, 8H), 0.75 (m, 1H). Yield 35%.

Product **38**:  $^1H$  NMR ( $(CD_3)_2SO$ )  $\delta$  10.38 (bs, 1H), 9.28 (bs, 1H), 7.13 (m, 2H), 7.07 (d,  $J = 8.2$  Hz, 1H), 6.67 (m, 2H), 6.61 (d,  $J = 8.2$  Hz, 1H), 3.79 (s, 3H), 2.27 (m, 1H), 2.05 (s, 3H), 1.58 (m, 3H), 1.41 (m, 2H), 1.13 (m, 3H), 0.93 (m, 1H), 0.68 (m, 1H). HRMS  $m/z$  calcd for  $C_{23}H_{27}NO_3$   $[M+Na]$ , 388.1889; found, 388.1936. Yield 90%.

**(*S*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (enantiomer 1) [(*S*)-38].**

Preparation of enantiomer 1 of compound **38** was performed according to general procedure B (heptane:EtOH 70:30, 7 mL/min) using racemic compound **38** as starting material.  $t_R$  (Chiralcel OD-H column  $10 \times 4.0$  and  $250 \times 4.6$  mm ID, 5 micron, heptane:2-PrOH:TFA 80:20:0.1, 0.8 mL/min): 6.4 min.

**(*R*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (enantiomer 2) [(*R*)-38].**

Preparation of enantiomer 2 of compound **38** was performed according to general procedure B (heptane:EtOH 70:30, 7 mL/min) using racemic compound **38** as starting material.  $t_R$  (Chiralcel OD-H column  $10 \times 4.0$  and  $250 \times 4.6$  mm ID, 5 micron, heptane:2-PrOH:TFA 80:20:0.1, 0.8 mL/min): 7.6 min.

**(2*R*,3'*RS*)-4'-(3'-Cycloheptyl-6'-methoxy-7'-methyl-2'-oxoindolin-3'-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (39).** Compound **38** (211 mg, 0.58 mmol) was dissolved in DCM, (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (176 mg, 0.75 mmol) was added followed by EDC (166 mg, 0.87 mmol) and DMAP (catalytic amount), left at rt for 7 days, concentrated and the residue was purified by flash chromatography (petroleum ether:EtOAc 10:1) to afford **39** (195 mg, 58%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  8.95 (bs, 1H), 7.61 (m, 2H), 7.47 (d, *J* = 9.0, Hz, 2H), 7.44 (m, 3 H), 7.08 (m, 3H), 6.58 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.66 (m, 3H), 2.63 (m, 1H), 2.10 (s, 3H), 1.75–1.2 (m, 11H), 0.90 (m, 1H).

**(2*R*,3'*S*)-4'-(3'-Cycloheptyl-6'-methoxy-7'-methyl-2'-oxoindolin-3'-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (diastereomer 1) 39.** Preparation of diastereomer 1 of compound **39** was performed using a Chiralcel OD-H guard column (10 × 4.0 mm ID, 5 micron) connected to a Chiralcel OD-H column (250 × 4.6 mm ID, 5 micron) (heptane:2-PrOH 95:5, 0.7 mL/min) using diastereomeric compound **39** as starting material. *t<sub>R</sub>*: 11.5 min..

**(2*R*,3'*R*)-4'-(3'-Cycloheptyl-6'-methoxy-7'-methyl-2'-oxoindolin-3'-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (diastereomer 2) 39.** Preparation of diastereomer 2 of compound **39** was performed using a Chiralcel OD-H guard column (10 × 4.0 mm ID, 5 micron) connected to a Chiralcel OD-H column (250 × 4.6 mm, ID 5 micron) (heptane:2-PrOH 95:5, 0.7 mL/min) using diastereomeric compound **39** as starting material. *t<sub>R</sub>*: 16.3 min.

**(*S*)-3-Cycloheptyl-3-(4-hydroxyphenyl)-6-methoxy-7-methylindolin-2-one (enantiomer 1) (*S*)-38.** An analytical amount of diastereomer 1 of **39** was dissolved in MeOH, 2 M NaOH was added and the reaction mixture was stirred at 40 °C over night. After evaporation *in vacuo* the residue was dissolved in EtOH. *t<sub>R</sub>* (Chiralcel OD-H column 10 × 4.0 and 250 × 4.6 mm ID, 5 micron, heptane:2-PrOH:TFA 80:20:0.1, 0.8 mL/min): 6.4 min.

**X-Ray Crystallographic Analysis of (2*R*,3'*S*)-4'-(3'-cycloheptyl-6-methoxy-7-methyl-2-oxoindolin-3-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (diastereomer 1) 39.** Colorless single crystals were obtained from a solution in hexane. Crystal data: C<sub>33</sub>H<sub>34</sub>F<sub>3</sub>NO<sub>5</sub>, Mr 581.6, monoclinic, space group *C*2 (No. 5), *a* = 16.4137(8) Å, *b* = 11.9810(10) Å, *c* = 15.781(2) Å,  $\beta$  = 104.936(6)°, *V* = 2998.5(5) Å<sup>3</sup>, *Z* = 4, *D<sub>c</sub>* = 1.288 Mg/m<sup>3</sup>, *F*(000) = 1224,  $\mu$ (MoK $\alpha$ ) = 0.098 mm<sup>-1</sup>, crystal size 0.54 x 0.43 x 0.46 mm.

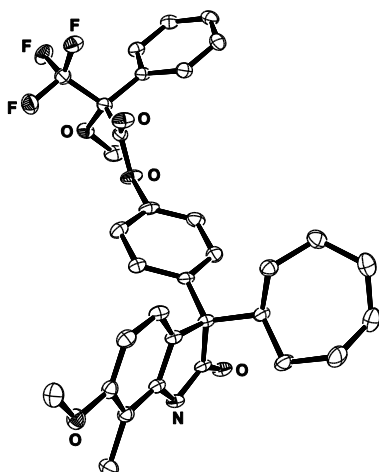
### Data Collection and Reduction.

A single crystal was mounted and immersed in a stream of nitrogen gas [*T* = 122(1) K]. Data were collected, using graphite-monochromated MoK $\alpha$  radiation ( $\lambda$  = 0.71073 Å) on a KappaCCD diffractometer. Data collection and cell refinement were performed using COLLECT<sup>1</sup> and DIRAX<sup>2</sup> Data reduction was performed using EvalCCD.<sup>3</sup> Correction for absorption was performed using Gaussian integration<sup>4</sup> as included in maXus.<sup>5</sup>

### Structure Solution and Refinement.

Positions of all non-hydrogen atoms were found by direct methods<sup>6,7</sup> Full-matrix least-squares refinements<sup>8</sup> were performed on *F*<sup>2</sup>, minimizing  $\sum w(F_o^2 - kF_c^2)^2$ , with anisotropic displacement parameters of the non-hydrogen atoms. The position of hydrogen atoms were located in subsequent difference electron density maps and were included in calculated

position with fixed isotropic displacement parameters ( $U_{iso} = 1.2U_{eq}$  for CH, CH<sub>2</sub> and  $U_{iso} = 1.5U_{eq}$  for CH<sub>3</sub>), except for the hydrogen atom bonded to NH. The position of this hydrogen atom was refined with fixed isotropic displacement parameters ( $U_{iso} = 1.2U_{eq}$  for NH). Refinement (385 parameters, 6867 unique reflections) converged at  $R_F = 0.026$ ,  $wR_F^2 = 0.069$  [6698 reflections with  $F_o > 4\sigma(F_o)$ ;  $w^{-1} = (\sigma^2(F_o^2) + (0.0407P)^2 + 0.9226P)$ , where  $P = (F_o^2 + 2F_c^2)/3$ ;  $S = 1.062$ ]. The residual electron density varied between -0.15 and 0.30 e Å<sup>-3</sup>. Absolute configuration could not be identified based on the structure determination (Flack parameter = 0.0(3)<sup>9</sup>), but the stereochemistry could be identified relative to the known stereochemistry of the Mosher's ester. Complex scattering factors for neutral atoms were taken from International Tables for Crystallography as incorporated in SHELXL97<sup>8,10</sup>. Crystallographic data for (2*R*,3'*S*)-4'-(3'-cycloheptyl-6-methoxy-7-methyl-2-oxoindolin-3-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate Fractional atomic coordinates, list of anisotropic displacement parameters and a complete list of geometrical data have been deposited in Cambridge Crystallographic Data Centre (No. CCDC 779154). Copies of the data can be obtained, free of charge, on application to the director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).



**Figure 1.** Perspective drawing (ORTEP-3)<sup>11</sup> of compound (2*R*,3'*S*)-4'-(3'-cycloheptyl-6-methoxy-7-methyl-2-oxoindolin-3-yl)phenyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate. Displacement ellipsoids of the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms have been left out for clarity.

## References

1. COLLECT, data collection software; Nonius BV: Delft, The Netherlands, **1999**.
2. Duisenberg, A. J. M. Indexing in single-crystal diffractometry with an obstinate list of reflections. *J. Appl. Crystallogr.* **1992**, *25*, 92-96.
3. Duisenberg, A. J. M. Reflections on area detectors : ab initio calculation of single-crystal x-ray reflection contours. Ph.D. Thesis, University of Utrecht, The Netherlands, **1998**.
4. Coppens, P. Evaluation of absorption and extinction in single-crystal structure analysis. In *Crystallographic Computing*; Ahmed, F. R., Hall, S. R., Huber, C. P. Eds.; Munksgaard: Copenhagen, **1970**, 255-270.
5. Mackay, S.; Gilmore, C. J.; Edwards, C.; Stewart, N.; Shankland, K. *maXus* Computer Program for the Solution and Refinement of Crystal Structures; Bruker Nonius: The Netherlands, Mac-Science: Japan, & The University of Glasgow, **1999**.
6. Sheldrick, G. M. Phase annealing in SHELX-90: direct methods for larger structures. *Acta Crystallogr.* **1990**, *A46*, 467-473.
7. Sheldrick, G. M. SHELXS97; Program for the Solution of Crystal Structures; University of Göttingen: Göttingen, Germany, **1997**.
8. Sheldrick, G. M. SHELXL97, Program for Crystal Structure Refinement; University of Göttingen: Göttingen, Germany, **1997**.
9. Flack H. D. On enantiomorph-polarity estimation. *Acta Crystallogr.* **1983**, *A39*, 876-881.
10. International Tables for Crystallography; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, **1995**; Vol. C, Tables 4.2.6.8 and 6.1.1.4.
11. Farrugia, L. J. ORTEP-3 for Windows - a version of ORTEP-III with a Graphical User Interface (GUI). *J. Appl. Crystallogr.* **1997**, *30*, 565.