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Supporting Information

Investigation of Squaramide Catalysts in the Aldol Reaction En Route to Funapide

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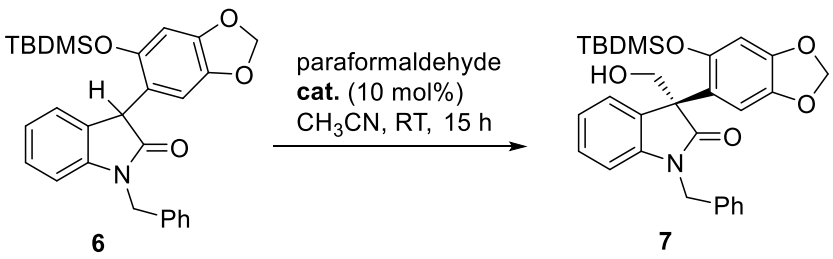
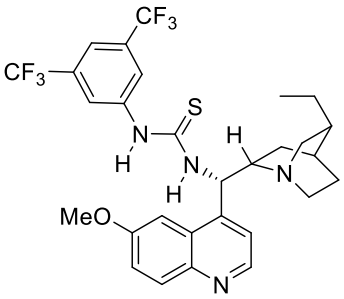
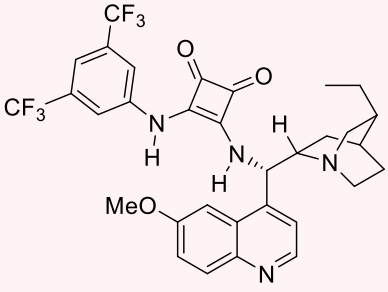


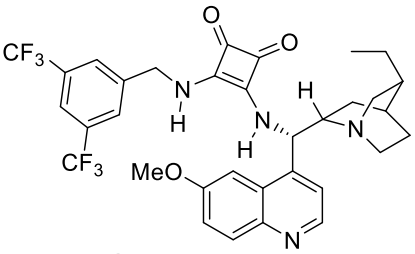
6 **7**



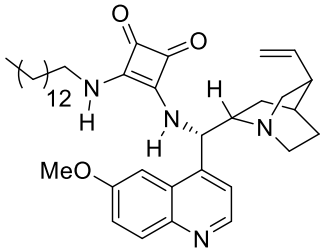
dhQN-1
59% conv., 45% *ee*



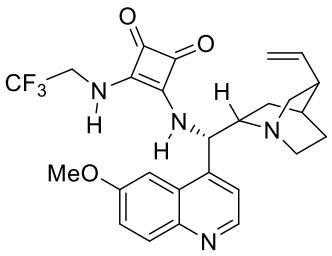
dhQN-2
67% conv., 66% *ee*



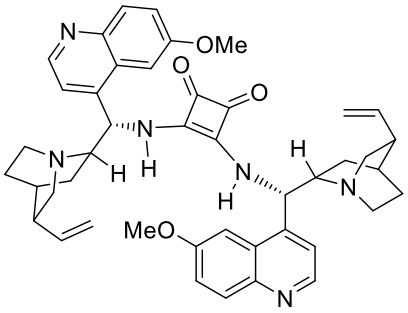
dhQN-3
n.d. conv., 23% *ee*



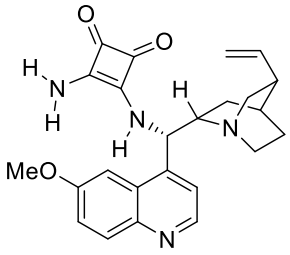
11% conv., 23% *ee*



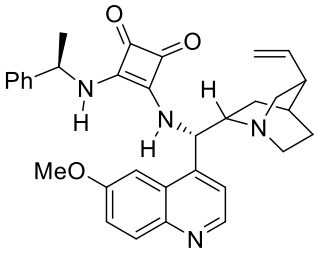
39% conv., 22% *ee*



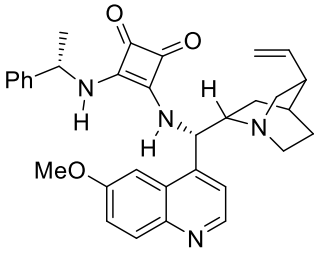
39% conv., 29% *ee*



<10% conv.



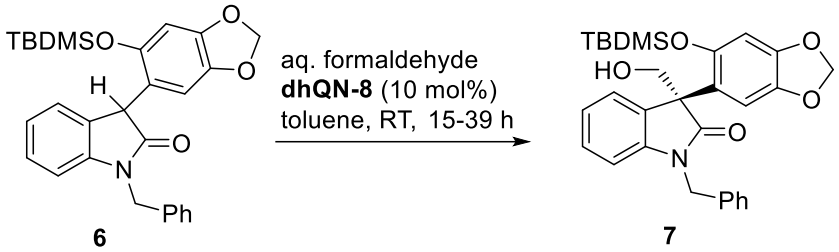
>90% conv., 5% *ee*



64% conv., 35% *ee*

This screening confirmed the *N*-aryl squaramide **dhQN-2** as the lead catalytic scaffold.

2. Screening of additives in the aldol reaction of model substrate 6 in toluene

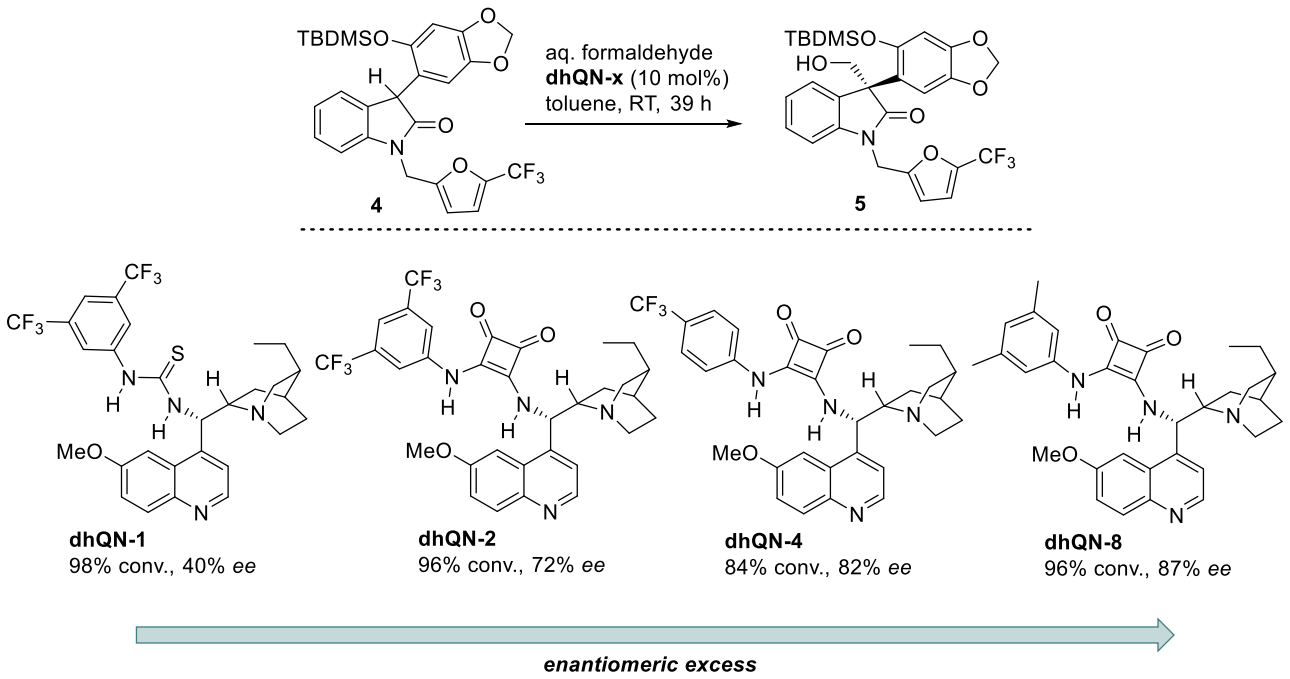


6 **7**

additive	conversion	*ee*	comments
none	79%	90%	"starting" conditions (main text, Table 1, entry 18)
H_2O (30 μL)	44%	92%	lower conversion
brine (30 μL)	54%	93%	lower conversion
$MeCONMe_2$ (DMA, 4.6 μL)	77%	90%	no effect
3 Å MS	61%	89%	lower conversion
4-nitrophenol (10 mol%)	66%	94%	less clean reaction

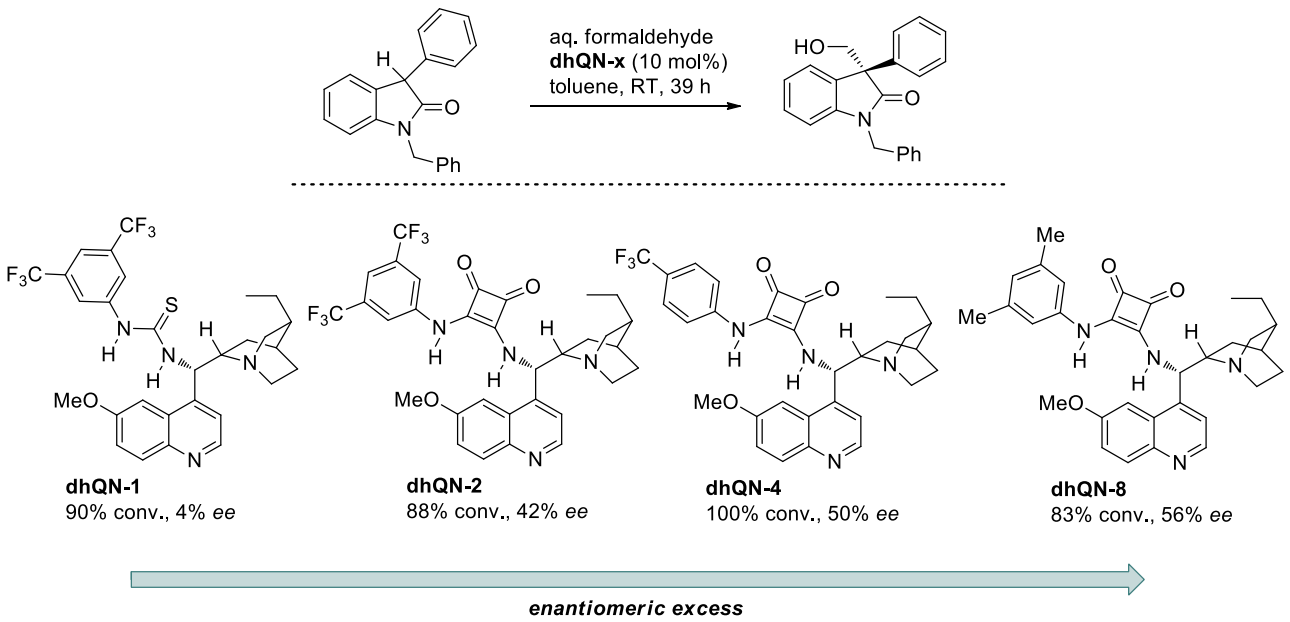
None of the additives provided clear improvements over the “standard” reaction conditions, although in some cases some increase of the enantiomeric excess was observed.

3. Screening of representative squaramide catalysts in the aldol reaction of substrate 4 in toluene



The enantiomeric excess values provided by these catalysts in the reaction with **4** follow the same trend of the enantioselectivities observed with model substrate **6**.

4. Screening of representative squaramide catalysts in the aldol reaction of 1-benzyl-3-phenyl oxindole



While the enantiomeric excess values follow the same trend of the reactions with substrates **4** and **6**, in this case, unfortunately, even the best catalyst **dhQN-8** gave only a less satisfactory 56% *ee*.

5. Experimental section

5.1. General methods and materials

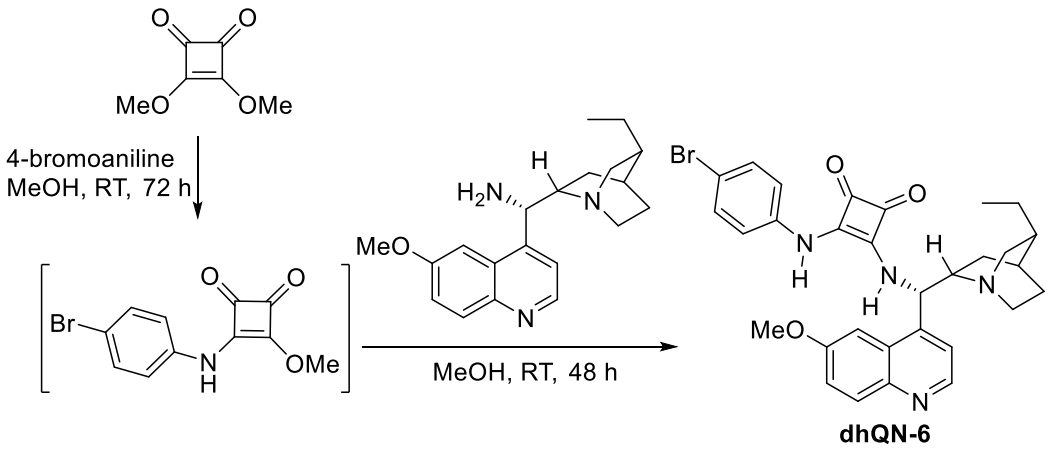
^{1}H, ^{19}F, and ^{13}C-APT NMR spectra were recorded on a Varian Mercury 400 or on a Bruker AVANCE–II spectrometer at 300 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvents signals for ^{1}H and ^{13}C NMR,[1] and using $CF_3C_6H_5$ as external reference calibrated at -63.72 ppm for ^{19}F NMR. ^{13}C NMR were acquired with ^{1}H broad-band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. High Resolution Mass Spectra (HRMS) were recorded on a Waters Xevo Q-TOF or on a MicroTof-Q Bruker mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter provided with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\,^{\circ}C}$ (c = g/100 mL in solvent). Infrared (ATR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer equipped with an ATR probe. Melting points (uncorrected) were determined with a Stuart Scientific SMP3 apparatus. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralcel OD-H), using a UV detector operating at 254 nm.

Analytical grade solvents and commercially available reagents were used as received, unless otherwise noted. Dichloromethane was filtered through basic alumina before use. THF was dried by treatment with KOH pellets, filtration through basic alumina, and distillation from Na/benzophenone. Substrate **4** was prepared from isatin by adapting the reported procedure, as outlined below.[2] 9-Amino-9-deoxy *epi*-dihydroquinine used to synthesize the dhQN catalysts was prepared[3] and purified as tri-hydrochloride salt[4] following the literature procedures. Racemic samples for HPLC reference were obtained using Et_3N as catalyst.

5.2. Preparation and characterization of new squaramide catalysts dhQN-5-8

The one-pot procedure[5] was successful for the synthesis of the 3,5-bis(trifluoromethyl)phenyl derivative **dhQN-2**, and for the new 4-bromo derivative **dhQN-6**. A two-step sequence, involving the isolation of the mono-amine squaramide intermediate, was preferred for the remaining catalysts, as it rendered purer material.

5.2.1. One pot synthesis of 3-((4-bromophenyl)amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethyl-quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-6)



To a stirred solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (35.5 mg, 0.25 mmol, 1 equiv.) in MeOH (0.6 mL), 4-bromoaniline (43 mg, 0.25 mmol, 1 equiv.) was added. The resulting mixture was stirred at room temperature for 72 h and then, a solution of ***epi*-amino-dhQN** (81.4 mg, 0.25 mmol, 1 equiv.) in MeOH (2.2 mL) was added. The reaction mixture was stirred at room temperature for further 48 h. The mixture was then filtered and washed with MeOHto obtain catalyst **dhQN-6** as a pale yellow solid (62 mg, 43% yield).

m.p. 199 °C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.80 (d, J = 4.6 Hz, 1H), 8.17 (s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 2.7 Hz, 1H), 7.66 (d, J = 4.6 Hz, 1H), 7.57 – 7.39 (m, 3H), 7.37 – 7.28 (m, 2H), 5.99 (s, 1H), 3.93 (s, 3H), 3.54- 3.42 (m, 1H) partially overlapped with residual water, 3.15 (dd, J = 13.4, 9.0 Hz, 1H), 2.71 – 2.55 (m, 1H), partially overlapped with residual DMSO, 2.47 – 2.36 (m, 1H) partially overlapped with residual DMSO, 1.49 – 1.19 (m, 8H), 0.81 (t, J = 7.1 Hz, 3H), 0.62 (s, 1H).

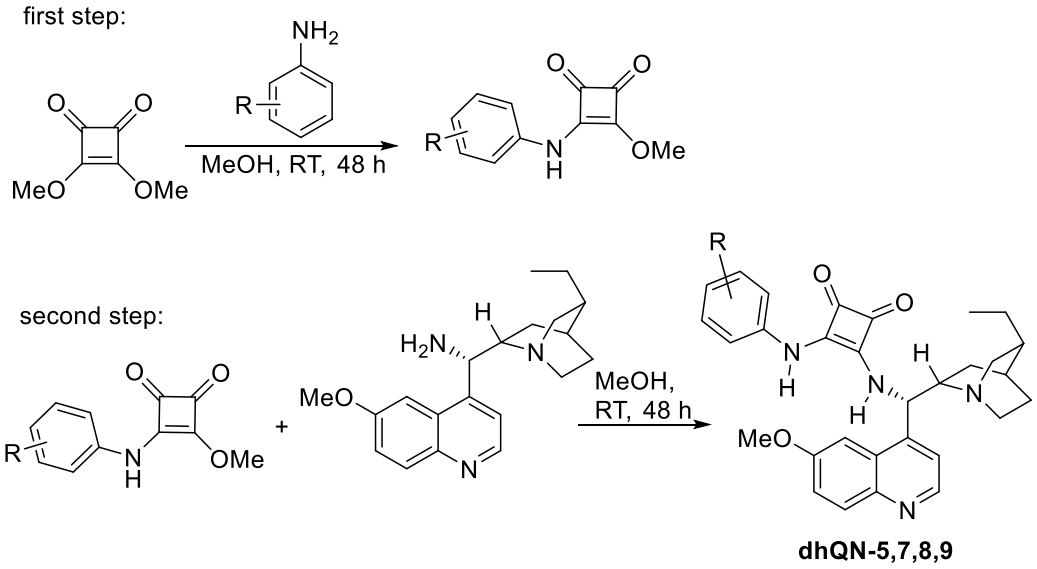
^{13}C-APT NMR (75 MHz, DMSO-d_6) δ 184.1, 179.8, 168.1, 163.3, 157.9, 147.8, 144.3, 143.1, 138.2, 132.1, 131.5, 127.5, 121.9, 120.2, 114.7, 101.5, 58.7, 57.2, 55.7, 40.3, 36.7, 28.0, 26.9, 25.9, 25.0, 12.0.

IR (ATR) ν˜ 3241 (br m), 3222 (br m), 2957 (m), 2939 (m), 2868 (m), 1797 (m), 1667 (s), 1597 (m), 1569 (vs), 1529 (vs), 1428 (vs), 1271 (s), 1047 (m), 817 (s) cm^{-1}.

HRMS (ESI+) calculated for [$C_{30}H_{32}BrN_4O_3$ + H^+] 575.1652; found 575.1633.

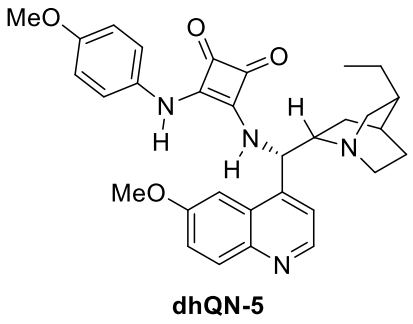
$[\alpha]_D^{RT}$ = -106 ° (c = 0.10, DMSO).

5.2.2. General procedure for the two-step synthesis of catalysts dhQN-5,7-9 [6,7]



To a stirred solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (71 mg, 0.5 mmol, 1 equiv.) in MeOH (2 mL) the corresponding aniline (0.5 mmol, 1 equiv.) was added. The resulting mixture was stirred at room temperature for 48 h and then the precipitated solid was filtered. A portion of the resulting solid (0.25 mmol, 1 equiv.) was subsequently added to a solution of ***epi*-amino-dhQN** (81.4 mg, 0.25 mmol, 1 equiv.) in MeOH (2 mL). The mixture was stirred for 48 h at room temperature. The resulting suspension was filtered and the solid was washed with MeOH, affording the catalysts **dhQN-5,7-9** in pure form.

3-(((1*S*)-((1*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)-4-((4-methoxyphenyl) amino)cyclobut-3-ene-1,2-dione (dhQN-5)



Following the general procedure with 4-methoxyaniline, but performing the first step for 6 h, catalyst **dhQN-5** was obtained in 41% yield as a white solid.

m.p. 252 °C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.81 (d, *J* = 4.5 Hz, 1H), 8.07 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 2.7 Hz, 1H), 7.66 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.34 – 7.24 (m, 2H), 6.92 – 6.85 (m, 2H), 5.99 (s, 1H), 3.94 (s, 3H), 3.71 (s, 3H), 3.50 – 3.36 (m, 1H), 3.15 (dd, *J* = 13.5, 8.8 Hz, 1H), 2.74 – 2.52 (m, 1H), 2.44 (d, *J* = 13.7 Hz, 1H), 1.62 – 1.17 (m, 8H), 0.82 (t, *J* = 7.1 Hz, 3H), 0.62 (d, *J* = 11.1 Hz, 1H).

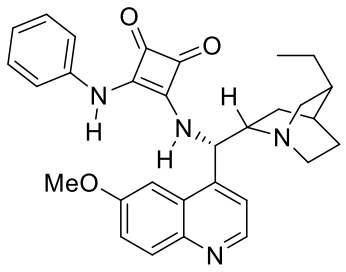
^{13}C-APT NMR (75 MHz, DMSO-d_6) δ 183.2, 167.6, 163.6, 157.8, 155.3, 147.8, 144.3, 143.4, 131.9, 131.5, 127.5, 121.9, 120.1, 119.7, 114.5, 101.6, 58.7, 57.3, 55.7, 55.31, 55.25, 40.2, 36.8, 28.1, 26.9, 26.0, 25.0, 12.0.

IR (ATR) $\tilde{\nu}$ 3249 (br m), 2931 (m), 2963 (m), 1792 (m), 1699 (w), 1662 (s), 1601 (s), 1574 (vs), 1511 (vs), 1441 (vs), 1246 (s), 1033 (vs), 854 (s), 822 (s) cm^{-1}.

HRMS (ESI+) calculated for [$C_{31}H_{35}N_4O_4$ + H^+] 527.2653; found 527.2647.

$[\alpha]_D^{RT}$ = -85 ° (c = 0.11, DMSO).

3-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)-4-(phenylamino) cyclobut-3-ene-1,2-dione (dhQN-7)



dhQN-7

Following the general procedure with aniline, catalyst **dhQN-7** was obtained in 62% yield as a pale yellow solid.

m.p. 195 °C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.81 (d, *J* = 4.5 Hz, 1H), 8.20 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 2.7 Hz, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.34 –

7.26 (m, 2H), 7.04 – 6.97 (m, 1H), 6.00 (s, 1H), 4.12 – 4.05 (m, 1H), 3.94 (s, 3H), 3.42 (d, *J* = 9.3 Hz, 1H), 2.69 – 2.54 (m, 1H), 2.44 – 2.38 (m, 1H), 1.63 – 1.15 (m, 8H), 0.82 (t, *J* = 7.1 Hz, 3H), 0.61 (s, 1H).

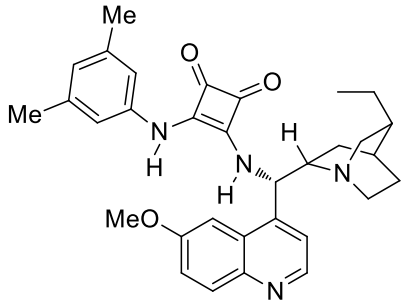
^{13}C-APT NMR (75 MHz, DMSO-d_6) δ 183.9, 179.7, 168.0, 163.6, 157.8, 147.8, 144.3, 143.3, 138.7, 131.5, 129.4, 129.3, 127.5, 122.8, 121.9, 118. 1, 101.5, 57.3, 55.7, 40.2, 36.8, 28.1, 26.9, 26.0, 25.0, 12.1.

IR (ATR) $\tilde{\nu}$ 3247 (br w), 2930 (br m), 1796 (w), 1670 (s), 1575 (vs), 1543 (vs), 1432 (vs), 1230 (s), 1037 (s), 849 (s), 751 (vs), 689 (vs), 632 (vs) cm^{-1}.

HRMS (ESI+) calculated for [$C_{30}H_{33}N_4O_3$ + H^+] 497.2547; found 497.2543.

$[\alpha]_D^{RT}$ = -67 ° (c = 0.12, DMSO).

3-((3,5-Dimethylphenyl)amino)-4-(((1*S*)-((1*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl) methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-8)



dhQN-8

A modified procedure for the synthesis of the intermediate was followed: to a stirred solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (71 mg, 0.5 mmol, 1 equiv.) in MeOH (2 mL), 3,5-dimethylaniline (69 μL, 0.5 mmol, 1 equiv.) was added. The resulting mixture was stirred at room temperature for 48 h and then the precipitated solid was filtered. In this case, the solid contained mostly the product derived from a double substitution of the methoxy by two anilines. The desired intermediate was instead obtained by purifying the mother liquors by a short plug on silica gel using first *n*-hexane and then Et_2O as eluent, and loading the product by dissolving it in a mixture of EtOAc/MeOH (87% yield). Catalyst **dhQN-8** was then obtained in 40% overall yield as a pale white solid following the general procedure for the second step.

m.p. 266 °C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.80 (d, *J* = 4.6 Hz, 1H), 8.10 (s, 1H) partially overlapped with 7.97 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 2.7 Hz, 1H), 7.66 (d, *J* = 4.6 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.68 – 6.62 (m, 1H), 6.01 (s, 1H), 3.94 (s, 3H), 3.41 (d, *J* = 9.5 Hz, 1H) partially overlapped

with residual water, 3.21 – 3.07 (m, 1H), 2.67 – 2.52 (m, 1H), 2.43 (d, *J* = 13.6 Hz, 1H), 2.20 (s, 6H), 1.60 – 1.19 (m, 8H), 0.81 (t, *J* = 7.0 Hz, 3H), 0.60 (s, 1H).

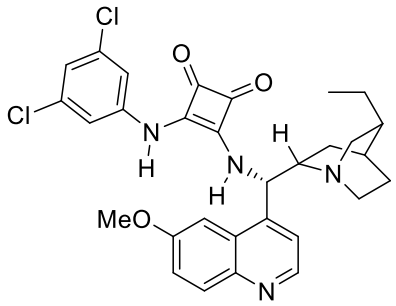
^{13}C NMR (75 MHz, DMSO-d_6) δ = 183.9, 179.9, 167.8, 163.6, 157.8, 147.8, 144.3, 143.4, 138.4, 131.5, 127.5, 124.5, 121.8, 115.9, 101.5, 58.6, 57.2, 55.7, 40.2, 36.8, 28.1, 26.9, 26.0, 25.0, 21.0, 12.0.

IR (ATR) ν˜ 3176 (br w), 3138 (br w), 2954 (br s), 1792 (m), 1654 (s), 1619 (s), 1571 (vs), 1547 (vs), 1458 (br vs), 1265 (s), 1243 (s), 1223 (s), 1085 (m), 1040 (s), 1027 (s), 861 (s), 845 (s), 696 (s), 622 (s) cm^{-1}.

HRMS (ESI+) calculated for [$C_{32}H_{36}N_4O_3$ + H^+] 525.2860; found 525.2879.

$[\alpha]_D^{RT}$ = -85 ° (c = 0.09, DMSO).

3-((3,5-Dichlorophenyl)amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-9)



dhQN-9

Following the general procedure with 3,5-dichloroaniline, but performing the first step for 96 h, catalyst **dhQN-9** was obtained in 65% yield as a beige solid.

m.p. 224 °C (dec.)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 1H) 8.80 (d, *J* = 4.5 Hz, 1H), 8.28 (s, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.85 – 7.62 (m, 2H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 2H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.00 (s, 1H), 3.94 (s, 3H), 3.32 – 3.27 (m, 2H) partially overlapped with residual water, 2.75 – 2.54 (m, 1H) partially overlapped with residual DMSO, 2.47 – 2.42 (m, 1H) partially overlapped with residual DMSO, 1.46 – 1.25 (m, 8H), 0.80 (t, *J* = 7.0 Hz, 3H), 0.60 (s, 1H).

^{13}C-APT NMR (75 MHz, DMSO-d_6) δ = 195.8, 184.7, 168.4, 162.7, 157.8, 147.8, 144.3, 143.1, 141.2, 134.6, 131.5, 127.5, 121.9, 121.6, 116.7, 101.5, 58.7, 57.2, 55.7, 48.6, 40.3, 36.8, 28.0, 26.9, 25.8, 25.0, 11.9.

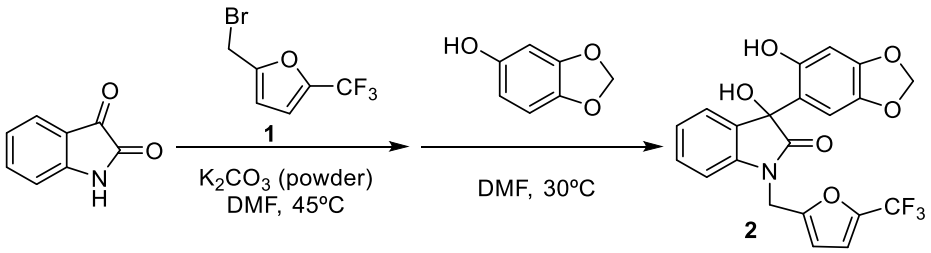
IR (ATR) $\tilde{\nu}$ 3178 (br m), 3084 (m), 2944 (br m), 2872 (m), 1796 (m), 1657 (s), 1626 (m), 1592 (vs), 1554 (vs), 1540 (vs), 1515 (vs), 1434 (br vs), 1266 (s), 1179 (m), 1043 (s), 862 (s), 851 (s), 843 (s) cm^{-1}.

HRMS (ESI+) calculated for [$C_{30}H_{31}Cl_2N_4O_3 + H^+$] 565.1768; found 565.1742.

$[\alpha]_D^{RT}$ = -76 ° (c = 0.10, DMSO).

5.3. Preparation of substrate 4[2]

5.3.1. Synthesis of furyl *N*-protected intermediate 2



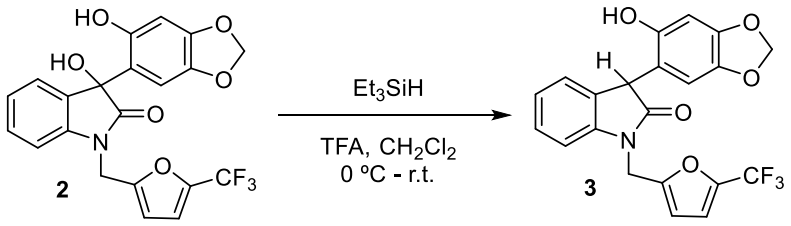
2 mL of DMF is added to a solid mixture of isatin (563.0 mg, 3.75 mmol, 1.0 equiv.) and finely powdered K_2CO_3 (1.036 mg, 7.5 mmol, 2 equiv) in a round flask, which is then sealed by a septum. The reaction mixture is stirred at 45 °C during 20 min. After this time, the furyl-derived alkylating reagent **1** (911.4 mg, 3.86 mmol, 1.03 equiv) is added slowly (30 min) to the mixture, kept at 45 °C. After the addition, the reaction mixture is stirred 18 h at 45 °C. After this time, the first step is complete (observed by TLC, Hx/AcOEt 6:4; revealed with cesium molybdate or iodine), and the reaction mixture is stirred at 30-35 °C. At this temperature, sesamol (580.7 mg, 4.12 mmol, 1.10 equiv) is added slowly during 20 min as solid. After the addition, the reaction mixture is stirred 5 h at 30-35 °C, and additional 1.5 h at 40 °C, being the reaction essentially complete after this time (observed by TLC, *n*-hexane/AcOEt 6:4; revealed with cesium molybdate or iodine).

Work-up

4 mL of *i*PrOH is added to the reaction mixture, which is then stirred at 54 ºC during 30 min. After this time, 14 mL of distilled water is added slowly during 1 h at the same temperature. Later, a solution of acetic acid (220 μL, 3.50 mmol, 0.93 equiv) in 8 mL of distilled water is added slowly during 1 h at the same temperature. After this time, the mixture is left cooling to room temperature during 1 h without stirring. $CHCl_3$ (10 mL) is added, and the organic phase is washed with water (3 x 4 mL). The organic phase is dried with $MgSO_4$, filtered and the solvent removed by rotary evaporation. Finally, after a column chromatography (hexane:AcOEt 9:1 to 5:5), 1.696 g of brown oil is obtained as the product **2** (94% yield).

Spectroscopic ^{1}H NMR data were consistent with those previously reported in the literature.[2]

5.3.2. Reduction of furyl derivative 2: preparation of synthetic intermediate 3



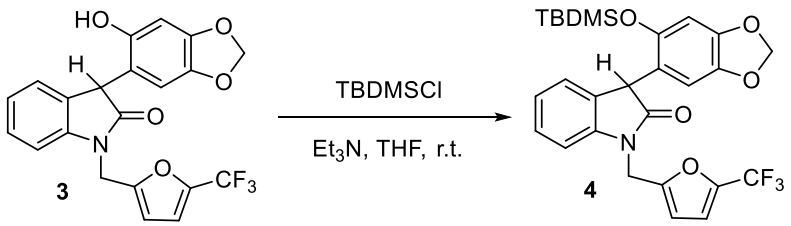
10 mL of CH_2Cl_2 are added to the synthetic intermediate **2** (1.117 mg, 2.32 mmol, 1.00 equiv) in a round flask, which is then sealed by a septum. The mixture is stirred 10 min at 0 °C. After this time, Et_3SiH (492 µL, 3.02 mmol, 1.30 equiv) is added. The reaction mixture is stirred at 0 °C during 1 hour. After this time, TFA (1.077 µL, 13.92 mmol, 6.00 equiv) is added slowly during 1 h at 0 °C. Once the TFA is added, the ice bath is removed, and the reaction mixture is stirred at room temperature 1.5-2 h until observing the reaction complete by TLC (*n*-hexane/AcOEt 6:4; revealed with cesium molybdate).

Work-up

The organic phase (10 mL of CH_2Cl_2 with the reaction mixture) is washed with 10 mL of water two times, and a last time with brine. Then, the organic phase is dried with $MgSO_4$, filtered and the solvent is removed by rotary evaporation. 2 mL CH_2Cl_2 are added to the residue obtained and the mixture is gently heated to form an almost clear solution. Then, 8 mL of *n*-hexane are added to precipitate a white solid (product). The white solid is filtered and washed with a cold mixture (-20 °C) of CH_2Cl_2/hexane 8:2 to give 0.6332 g of pure product **3** (66% yield).

Spectroscopic ^1H NMR data were consistent with those previously reported in the literature.[2]

5.3.3. Protection of furyl derivative 3: preparation of substrate 4



3 mL of THF are added to a solid mixture of TBDMSCl (281.5 mg, 1.83 mmol, 1.30 equiv) and intermediate **3** (588.5 mg, 1.41 mmol, 1.00 equiv) in a round flask, which is then sealed by a septum. The mixture is stirred 10 min at room temperature to obtain a clear solution. After this time, Et_3N (436 μL, 3.10 mmol, 2.20 equiv) is added slowly during 15 min at room temperature. After the addition of Et_3N, the reaction mixture is stirred 20 h at room temperature. After this time, the reaction is complete (observed by TLC, Hx/AcOEt 8:2; revealed with cesium molybdate or iodine).

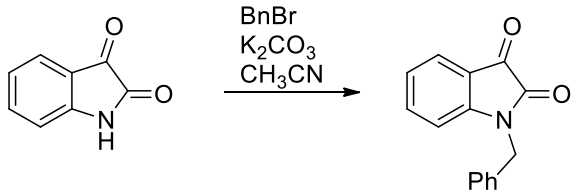
Work up

3 mL of brine are added to the reaction mixture. The biphasic clear mixture obtained is transferred to a separating funnel. 2 x 2 mL of THF are used to wash the flask, and these washing are transferred to the funnel too. Several drops of an aqueous solution of HCl (37%) are added slowly to the biphasic system, stirring and controlling the pH of the aqueous phase (bottom layer) using pH indicator. At pH = 1, the aqueous layer is discarded, and the organic layer (upper layer) is transferred to a new flask. The THF and traces of water present in the mixture are removed by rotary evaporation (bath T = 50 °C, 13-14 mbar). The residue obtained is purified by column chromatography using a mixture of petroleum ether/AcOEt 85:15 as eluent. Finally, 498 mg of a colorless oil, which solidifies when stored at -20 ºC to afford a white solid, are obtained (67% yield).

Spectroscopic ^1H NMR data were consistent with those previously reported in the literature.[2]

5.4. Preparation of model substrate 6

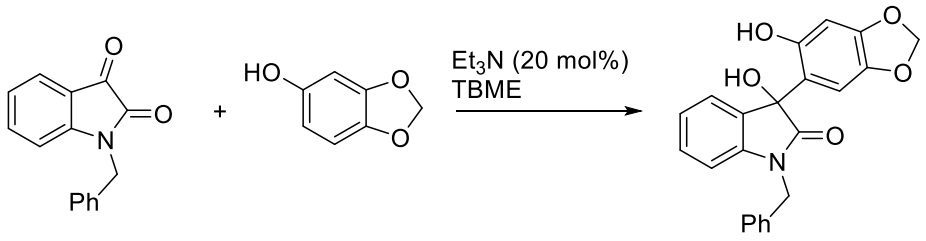
5.4.1. *N*-benzylation of isatin: synthesis of 1-benzylindoline-2,3-dione[8]



Isatin (5.00 g, 34.0 mmol) and finely ground K_2CO_3 (14.10 g, 102 mmol) were added to a 250 mL round bottom flask equipped with a stirring bar and a condenser. The solids were suspended in CH_3CN (untreated, 100 mL), and treated with benzyl bromide (4.05 mL, 34.0 mmol). The mixture was stirred overnight at 50 °C. The solvent was then evaporated, the residue taken with CH_2Cl_2 (ca. 80 mL) and washed with H_2O (80 mL). The aqueous phase was extracted with two portions of CH_2Cl_2 (50 mL each). The combined organic phases were dried with $MgSO_4$, filtered and evaporated. Crystallization from ethanol afforded the title compound as orange needles in 60-70% yield.

Spectroscopic ^{1}H NMR data were consistent with the literature.[8]

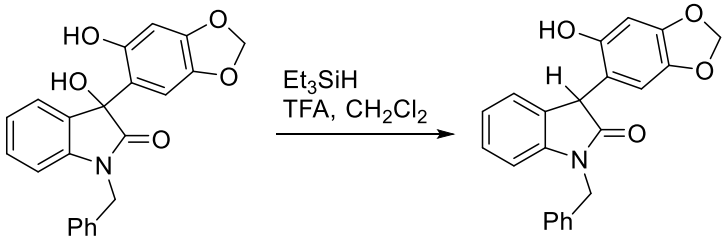
5.4.2. Addition of sesamol to *N*-benzyl isatin: synthesis of 1-benzyl-3-hydroxy-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)indolin-2-one[9]



N-benzyl isatin (3.559 g, 15.0 mmol), TBME (untreated, 35 mL), sesamol (2.486 g, 18.0 mmol), and Et_3N (416 μL, 3.0 mmol) were sequentially added to a round bottom flask equipped with a magnetic stirring bar. After 24 h stirring at RT, the solvent was removed under reduced pressure, and the residue purified by chromatography on silica gel (petroleum ether/EtOAc 6.5:3.5 → 6:4 → 4:6). The title 3-hydroxy oxindole adduct was obtained as a pale pink solid in 77% yield (4.368 g).

Spectroscopic ^{1}H NMR data were consistent with the literature.[9]

5.4.3. Reductive dehydroxylation of the *N*-benzyl 3-hydroxyoxindole: synthesis of 1-benzyl-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)indolin-2-one[2]



Under a nitrogen atmosphere, the 3-hydroxyoxindole (3.754 g, 10.0 mmol) was added to a 250 mL round bottom flask equipped with a magnetic stirring bar, and dissolved in CH_2Cl_2 (48 mL). The solution was cooled to 0 °C by an ice bath, and treated with Et_3SiH (4.88 mL, 30.0 mmol), and TFA (2.31 mL, 30.0 mmol). The ice bath was then removed, and the mixture stirred at RT. After 1 h, H_2O (40 mL) was added, the phases separated, and the organic phase further washed with an additional H_2O portion (40 mL), and brine (40 mL). The organic phase was dried with $MgSO_4$ and filtered. Volatiles were removed under reduced pressure, and the thus obtained residue suspended in toluene containing a small amount of Et_2O. Filtration of the thus obtained slurry, and washing the filter cake with pre-cooled petroleum ether (0 °C), afforded the title compound as a pale pink solid in 63% yield (2.280 g).

m.p. 178 °C (dec.)

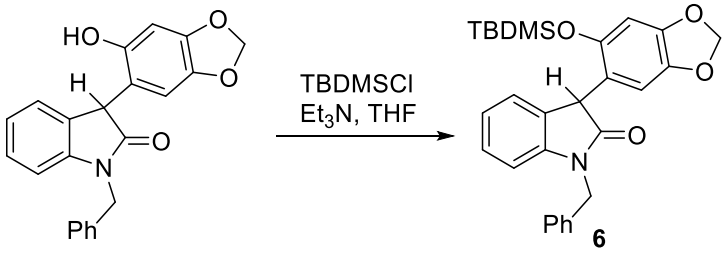
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.35 – 7.23 (m, 7H), 7.14 (td, *J* = 7.5, 0.9 Hz, 1H), 6.84 (br d, *J* = 7.7 Hz, 1H), 6.62 (br s, 1H), 6.39 (d, *J* = 0.7 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 5.14 (s, 1H), 4.96 (d, *J* = 15.6 Hz, 1H), 4.90 (d, *J* = 15.6 Hz, 1H).

^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 179.0, 151.1, 147.7, 143.6, 141.6, 135.1, 128.9, 128.6, 127.8, 127.2, 126.5, 126.0, 123.3, 115.1, 110.0, 106.7, 101.3, 101.2, 47.4, 44.1.

IR (ATR) $\tilde{\nu}$ 3251 (br m), 2956 (w), 2934 (w), 2897 (w), 2863 (w), 1671 (vs), 1608 (s), 1499 (s), 1487 (vs), 1462 (vs), 1443 (vs), 1284 (s), 1201 (s), 1177 (vs), 1164 (vs), 1037 (vs), 939 (s), 838 (vs), 756 (vs), 739 (s), 695 (s), 671 (s) cm^{-1}.

HRMS calculated for [$C_{22}H_{17}NO_4$ - H^+] 358.1085; found 358.1079.

5.4.4. Silylation of the phenolic oxygen: synthesis of 1-benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)indolin-2-one (6)



6

Under a nitrogen atmosphere, the oxindole substrate (1.797 g, 5.0 mmol) was added to a 100 mL round bottom flask equipped with a magnetic stirring bar, and dissolved in THF (12 mL). TBDMSCl (0.904 g, 6.0 mmol) and Et_3N (1.53 mL, 11.0 mmol) were added to the obtained solution, and the resulting mixture stirred at RT overnight (ca. 18 h). The mixture was then filtered on Celite, and the volatiles removed by evaporation. The residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (2 x 10 mL) and then with brine (10 mL). The organic phase was dried with $MgSO_4$, filtered and evaporated. Chromatographic purification (*n*-hexane/EtOAc 95:5 → 8:2) afforded compound **6** in 87% yield (2.07 g) as a white solid.

m.p. 121-123 °C

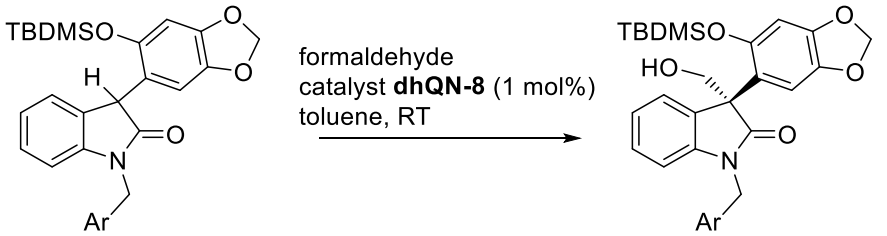
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.29 – 7.24 (m, 1H), 7.15 (tt, *J* = 7.8, 1.1 Hz, 1H), 7.11 (br d, *J* = 7.2 Hz, 1H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.75 (br d, *J* = 7.8 Hz, 1H), 6.50 (br s, 1H), 6.19 (br s, 1H), 5.86 (br s, 2H), 5.26–4.77 (br m, 3H), 1.00 (br s, 9H), 0.31 (br s, 6H).

^{13}C NMR not recorded: in line with the furyl substrate **4**,[2] the occurrence of rotamers interconverting slowly on the NMR time scale, evidenced by several broad signals in the ^{1}H NMR spectrum, hampered the straightforward obtainment of a well-defined ^{13}C NMR spectrum.

IR (ATR) ν̃ 3051 (w), 2934 (w), 2902 (w), 2860 (w), 1699 (vs), 1608 (m), 1501 (s), 1483 (vs), 1461 (s), 1425 (s), 1341 (s), 1174 (vs), 1162 (s), 1036 (s), 902 (s), 842 (vs), 788 (s), 758 (s) cm^{-1}.

HRMS calculated for [$C_{28}H_{31}NO_4Si$ + H^+] 474.2095; found 474.2094.

5.5. Optimized procedure for the catalytic enantioselective aldol reactions

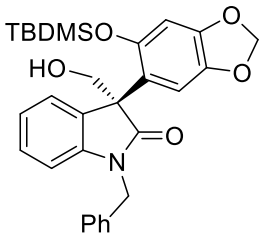


6: Ar = Ph
4: Ar = 2-(5-CF_3)-furyl

7: Ar = Ph
5: Ar = 2-(5-CF_3)-furyl

To a test tube, equipped with a magnetic stirring bar, were sequentially added the substrate **6** (94.7 mg, 0.20 mmol) or **4** (106.3 mg, 0.20 mmol), catalyst **dhQN-8** (1.00 mg, 0.0020 mmol, 1.0 mol%), toluene (0.40 mL) and aqueous formaldehyde (37% w/w, 30 μL, 0.40 mmol). The resulting mixture was stirred gently for 42 h at RT (ca. 30 °C), then directly purified by chromatography on silica gel, affording compound **7** or **5** as a white solid.

(*S*)-1-Benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one (7)



Following the optimized procedure, the title compound was obtained as a white solid in 83% yield (84.2 mg), after column chromatography on silica gel (*n*-hexane/EtOAc 8:2 → 75:25). The enantiomeric excess of **7** (89% ee) was determined by CSP HPLC (Chiralcel OD-H; flow: 0.75 mL/min; *n*-hexane/*i*-PrOH 90:10; UV detector: 254 nm): t_{maj} = 18.3 min; t_{min} = 14.4 min.

m.p. 157-159 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4H), 7.29-7.24 (m, 2H), 7.16-7.11 (m, 1H), 6.95-6.90 (m, 2H), 6.77 (dt, *J* = 7.8, 0.7 Hz, 1H), 6.39 (s, 1H), 5.95 (d, *J* = 1.6 Hz, 1H), 5.92 (d, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 15.3 Hz, 1H), 4.39 (d, *J* = 15.4 Hz, 1H), 4.27 (dd, *J* = 11.6, 10.2 Hz, 1H), 3.74 (dd, *J* = 11.6, 10.2 Hz, 1H), 2.89 (dd, *J* = 10.1, 2.7 Hz, 1H), 0.72 (s, 9H), 0.06 (s, 3H), -0.02 (s, 3H).

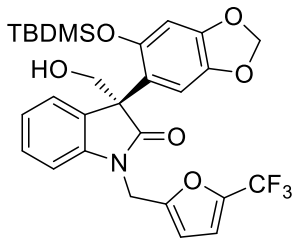
^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 178.9, 149.0, 147.1, 142.5, 141.2, 136.0, 131.3, 128.8, 127.9, 127.7, 127.4, 123.1, 122.7, 118.4, 109.5, 109.1, 101.3, 100.3, 66.5, 55.6, 43.9, 26.2, 19.0, -3.5, -3.6.

IR (ATR) $\tilde{\nu}$ 3478 (br w), 3396 (br w), 2957 (w), 2929 (w), 2901 (w), 2857 (w), 1700 (vs), 1610 (m), 1505 (m), 1486 (s), 1465 (s), 1428 (m), 1361 (s), 1247 (s), 1197 (vs), 1169 (s), 1044 (s), 841 (vs), 786 (vs), 735 (vs), 697 (vs) cm^{-1}.

HRMS calculated for [$C_{29}H_{33}NO_5Si + Na^+$] 526.2020; found 526.2020.

$[\alpha]_D^{25°C}$ = -92.2 ° (c = 0.35, CH_2Cl_2).

(*S*)-3-(6-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one (5)



Following the optimized procedure, the title compound was obtained as a white foam in 86% yield (97.1 mg), after chromatography on silica gel (*n*-hexane/EtOAc 75:25). The enantiomeric excess of **5** (85% ee) was determined by CSP HPLC (Chiralcel OD-H; flow: *n*-hexane/*i*-PrOH 90:10; UV detector: 254 nm): t_{maj} = 15.2 min; t_{min} = 10.7 min. Application of the optimized procedure on a 1.00 mmol scale, that is, using 531.6 mg of substrate **4** (1.00 mmol), 5.20 mg of catalyst **dhQN-8** (0.01 mmol, 1 mol%), 1.00 mL of toluene, and 148 μL of aq. formaldehyde (37% w/w, 2.00 mmol), afforded the title compound in 84% yield (474.3 mg) and 85% ee.

m.p. 139-140 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, *J* = 7.6, 1.5 Hz, 1H), 7.19 (br s, 1H), 6.98 (td, *J* = 7.4, 0.9 Hz, 1H), 6.94 (br d, *J* = 7.4 Hz, 1H), 6.90 (br d, *J* = 7.8 Hz, 1H), 6.72-6.69 (m, 1H), 6.38 (s, 1H), 6.36 (br d, *J* = 3.3 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.44 (d, *J* = 16.4 Hz, 1H), 4.54 (d, *J* = 16.3 Hz, 1H), 4.23 (dd, *J* = 11.4, 9.8 Hz, 1H), 3.76 (dd, *J* = 11.4, 3.2 Hz, 1H), 2.61 (dd, *J* = 9.7, 3.1 Hz, 1H), 0.69 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H).

^{13}C-APT NMR (400 MHz, $CDCl_3$) δ 178.4, 152.3 (q, *J* = 1.6 Hz), 148.9, 147.2, 141.9. 141.5 (q, *J* = 42.5 Hz), 141.3, 131.2, 128.1, 123.2, 123.1, 118.8 (q, *J* = 266.0 Hz), 118.2, 112.6 (q, *J* = 2.9 Hz), 109.2, 108.8, 108.6, 101.4, 100.3, 66.6, 55.6, 36.9, 26.1, 18.9, -3.6, -3.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -64.13 (s, 3F).

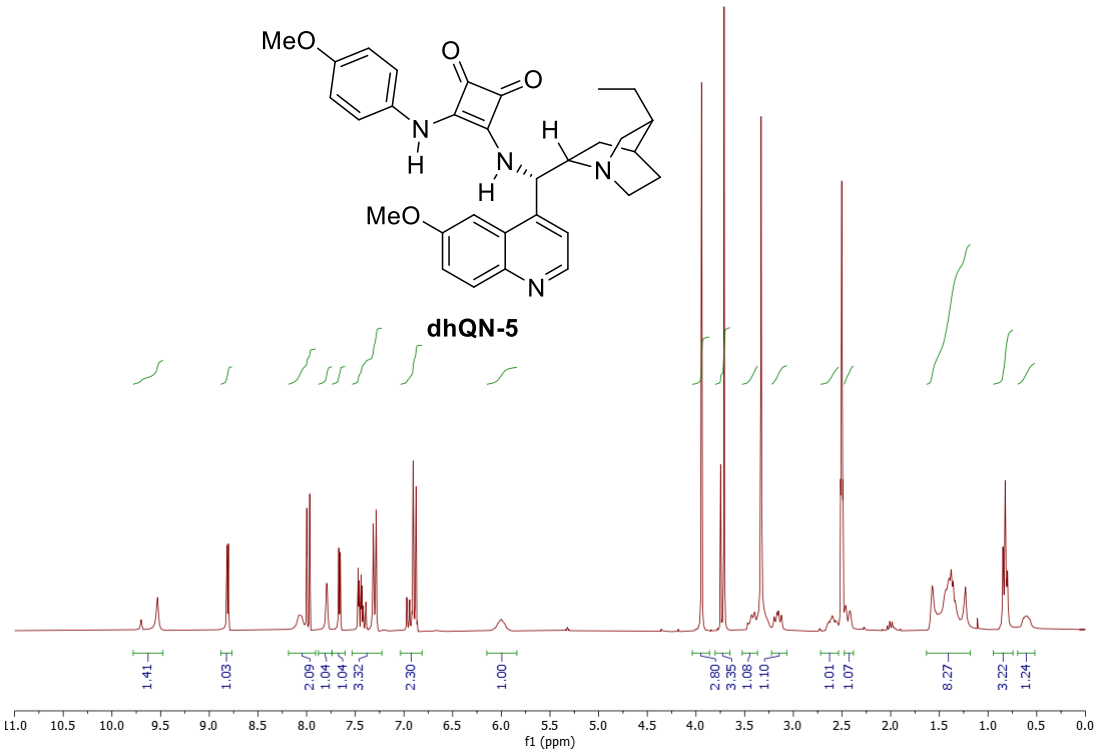
IR (ATR) $\tilde{\nu}$ 3417 (br w), 2956 (w), 2931 (w), 2901 (w), 2884 (w), 2862 (w), 1702 (vs), 1613 (s), 1490 (vs), 1464 (s), 1426 (m), 1362 (s), 1318 (s), 1194 (vs), 1166 (vs), 1134 (br vs), 1102 (vs), 1036 (vs), 860 (vs), 837 (vs), 821 (vs), 785 (vs), 753 (vs), 741 (vs), 699 (m), 678 (m) cm^{-1}.

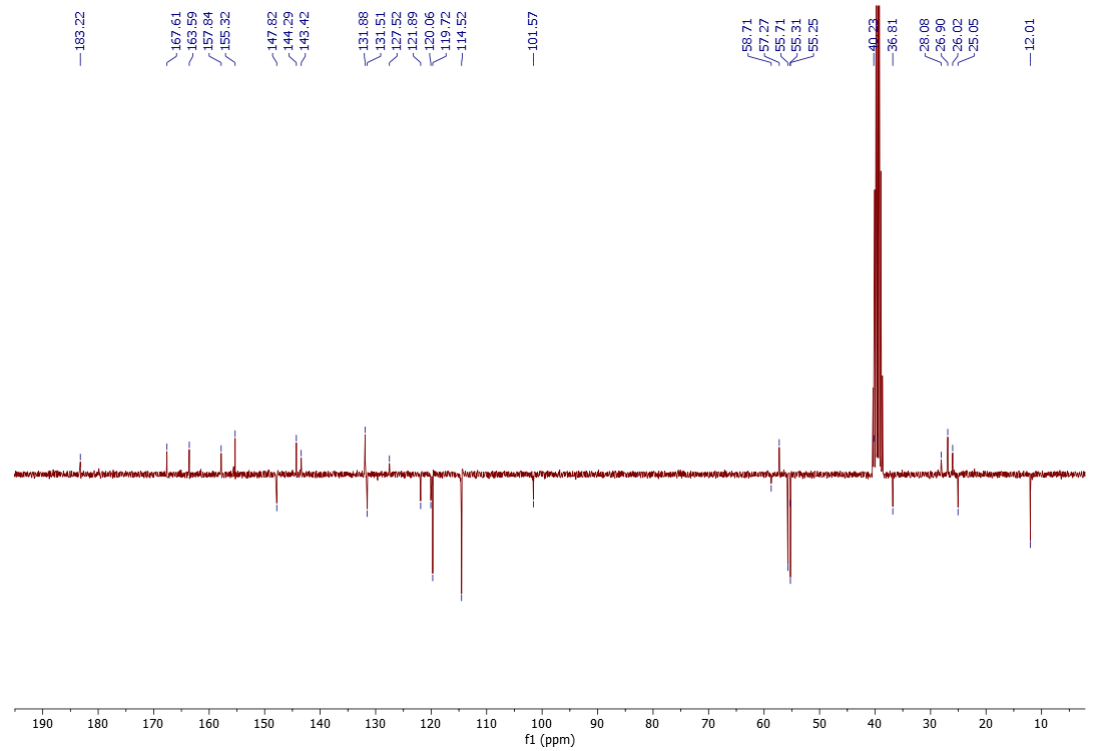
HRMS calculated for [$C_{28}H_{30}F_3NO_6Si + Na^+$] 584.1687; found 584.1697.

$[\alpha]_D^{25°C}$ = -41.5 ° (c = 0.38, CH_2Cl_2).

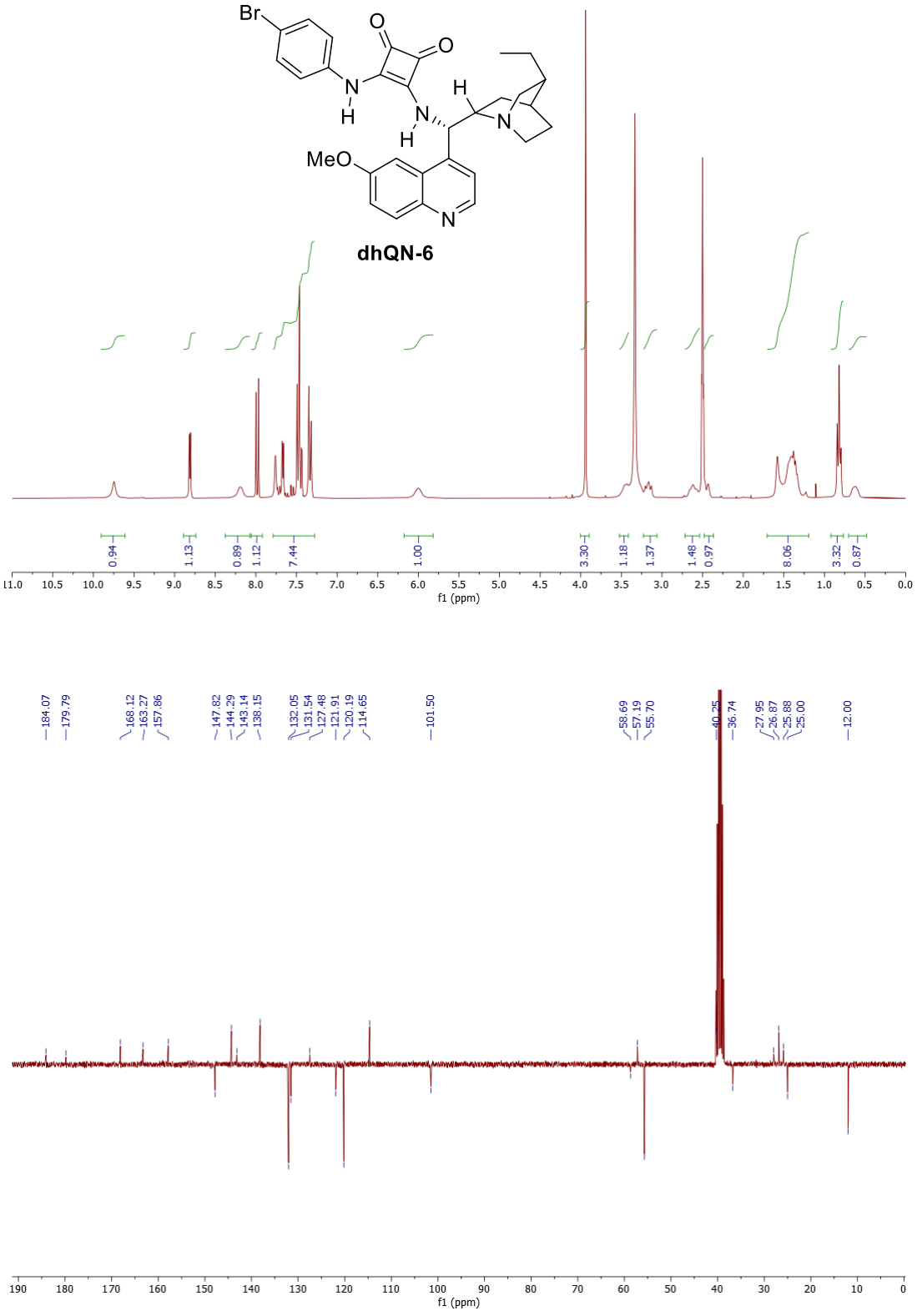
5.6. Copies of NMR spectra for new compounds and HPLC traces

3-(((1*S*)-((1*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)-4-((4-methoxyphenyl) amino)cyclobut-3-ene-1,2-dione (dhQN-5)

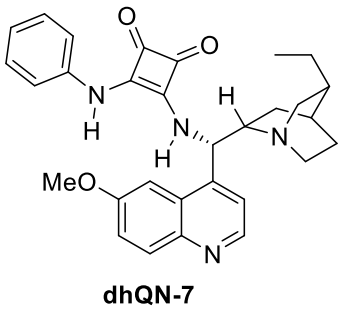




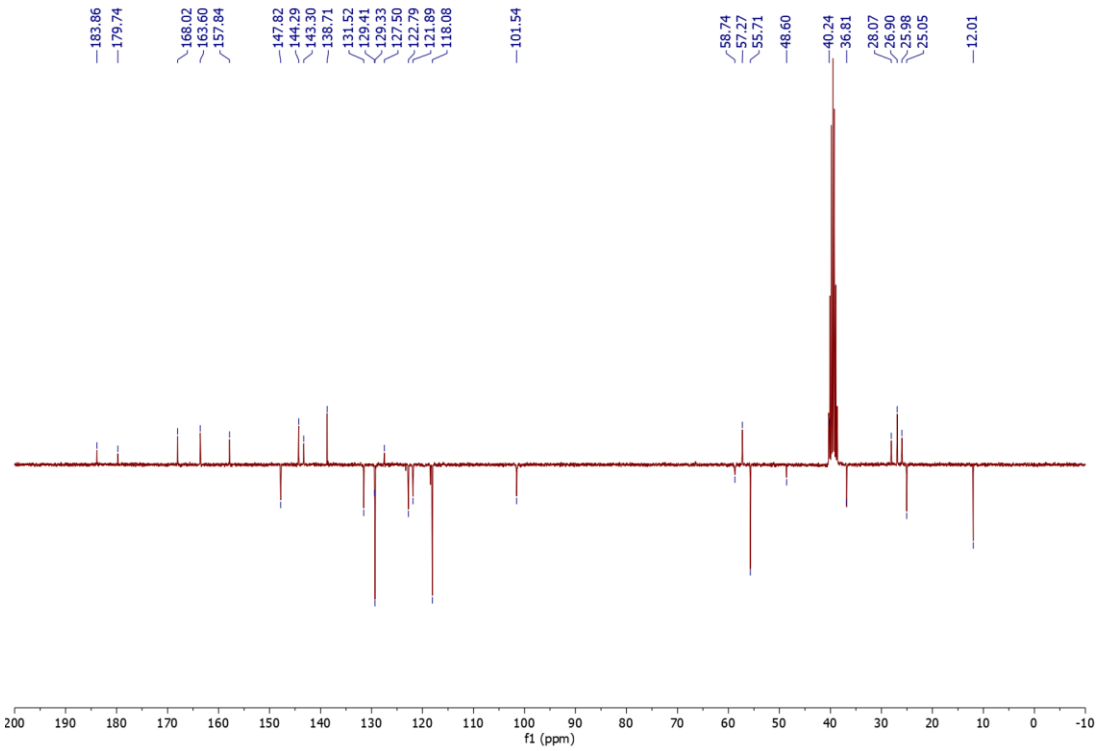
3-((4-Bromophenyl)amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-6)



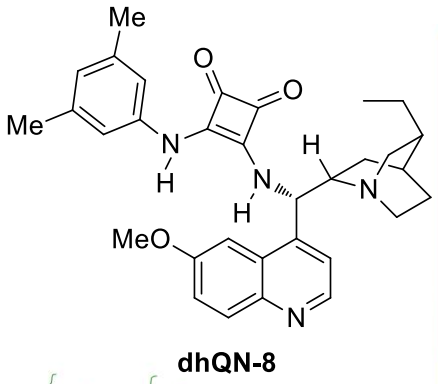
3-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-Ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)-4-(phenylamino) cyclobut-3-ene-1,2-dione (dhQN-7)



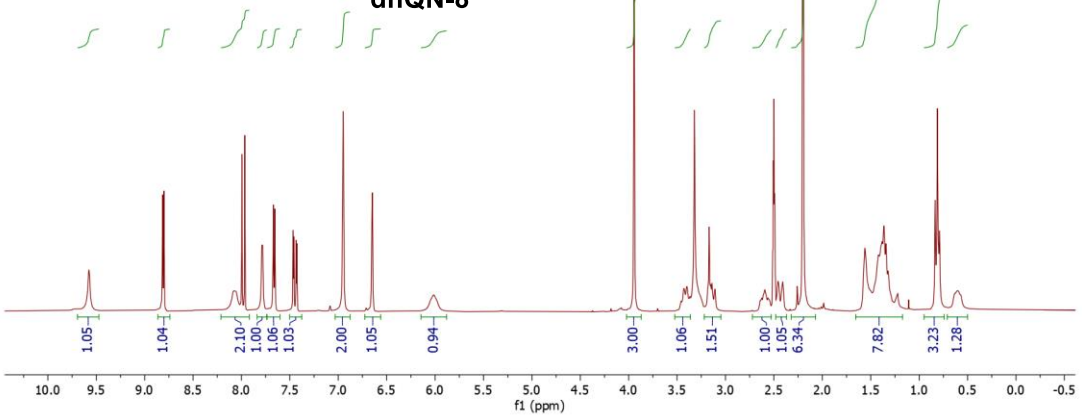
dhQN-7

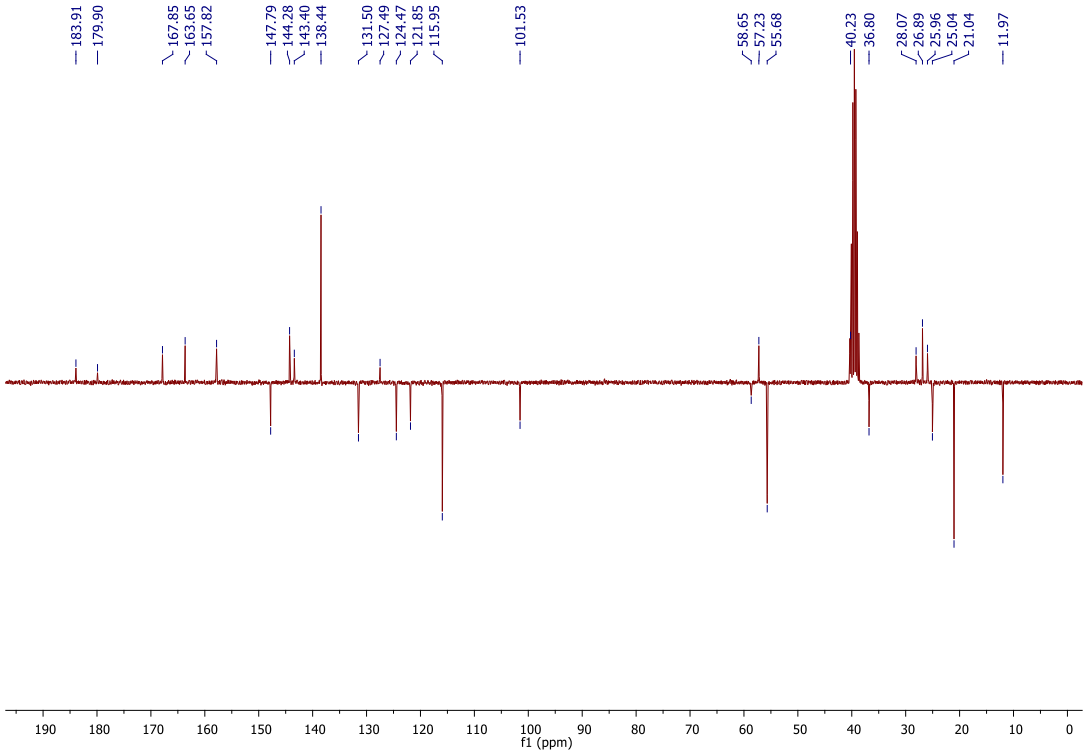


3-((3,5-Dimethylphenyl)amino)-4-(((1*S*)-((1*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl) methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-8)

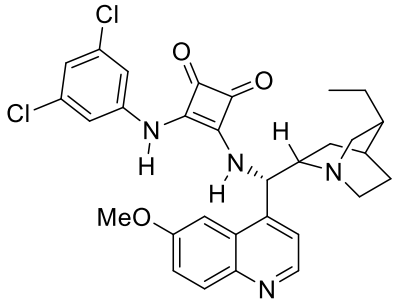


dhQN-8

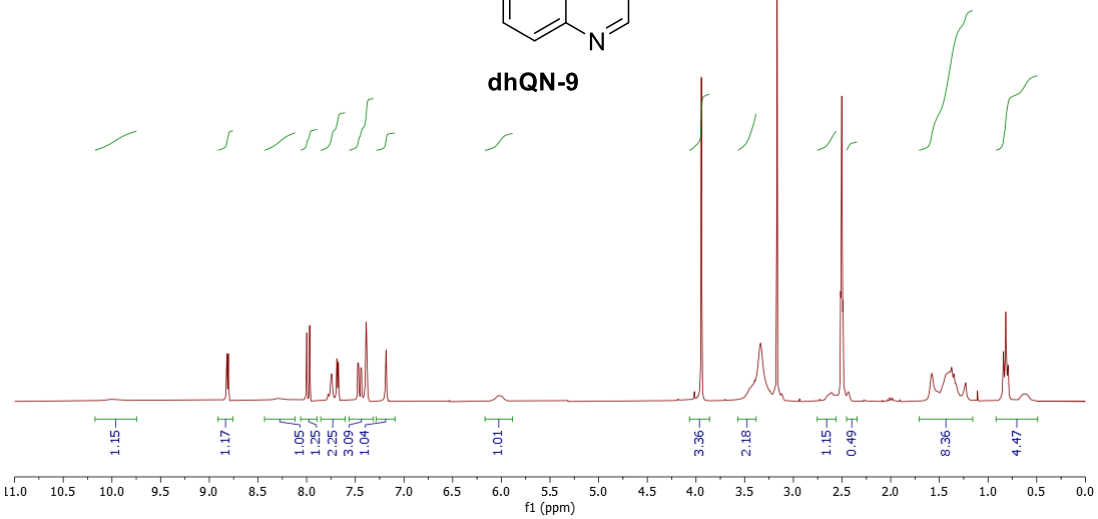


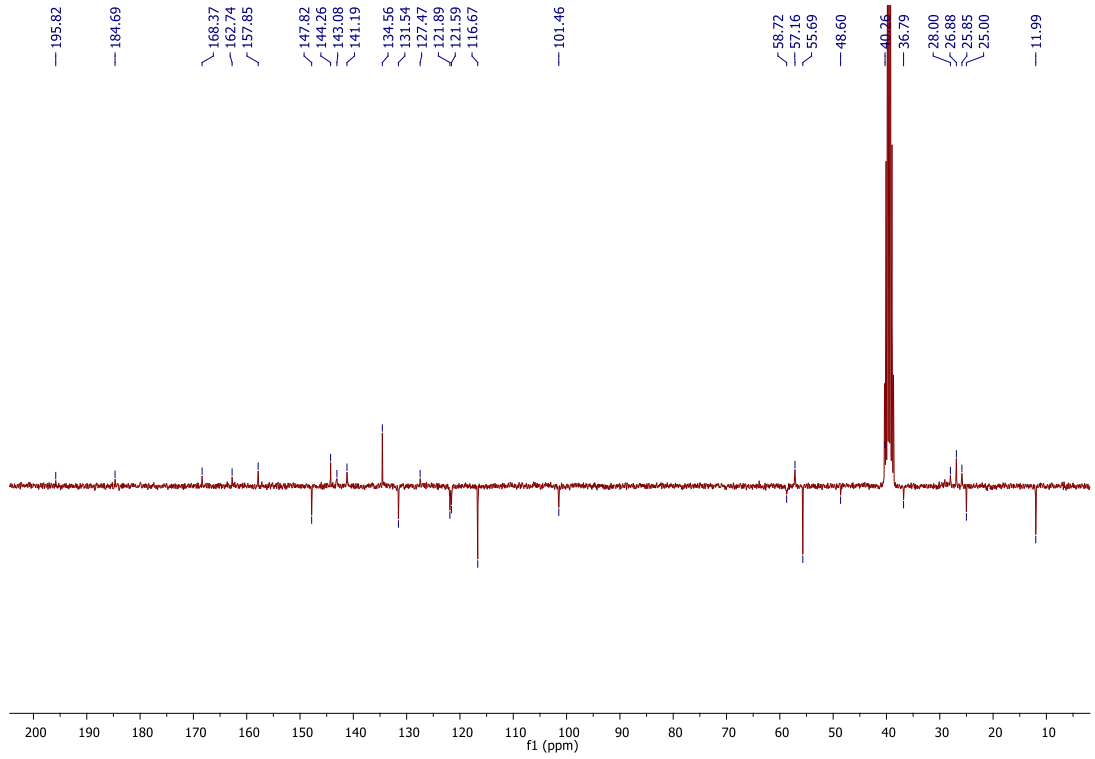


3-((3,5-Dichlorophenyl)amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (dhQN-9)

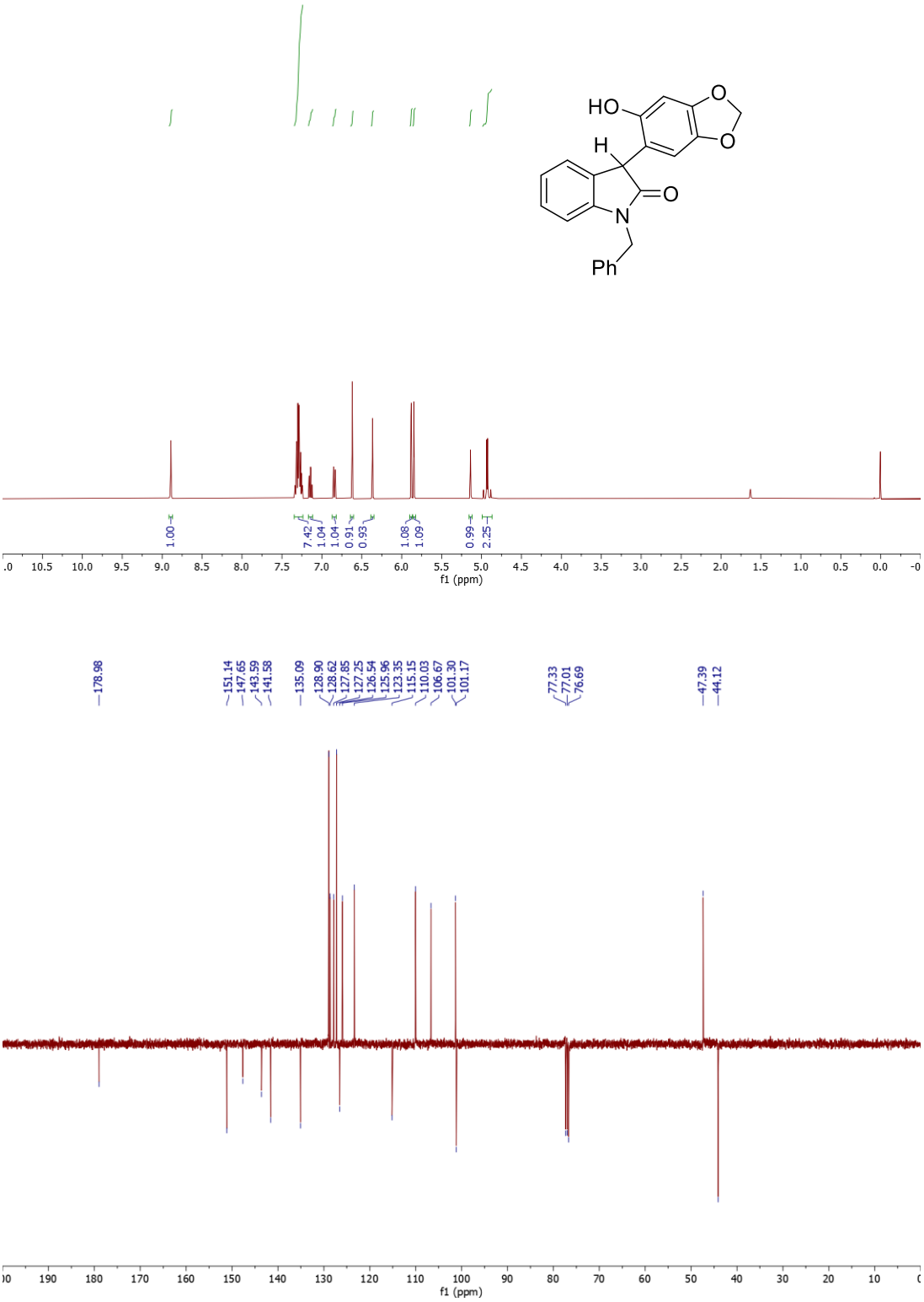


dhQN-9

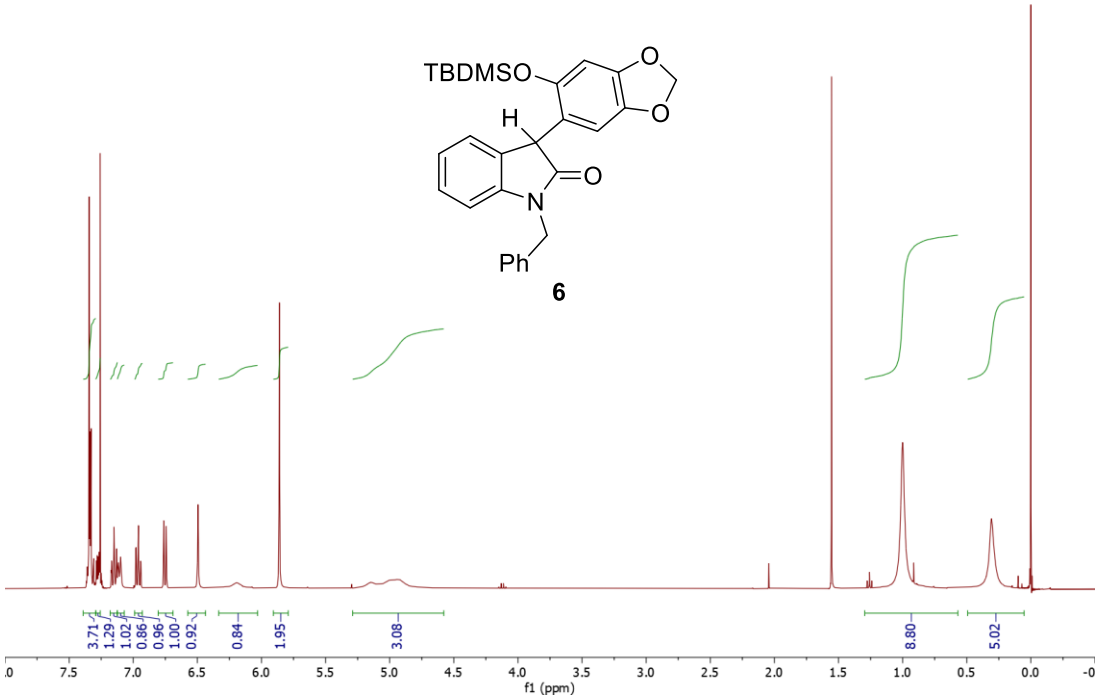




1-Benzyl-3-(6-hydroxybenzo[*d*][1,3]dioxol-5-yl)indolin-2-one

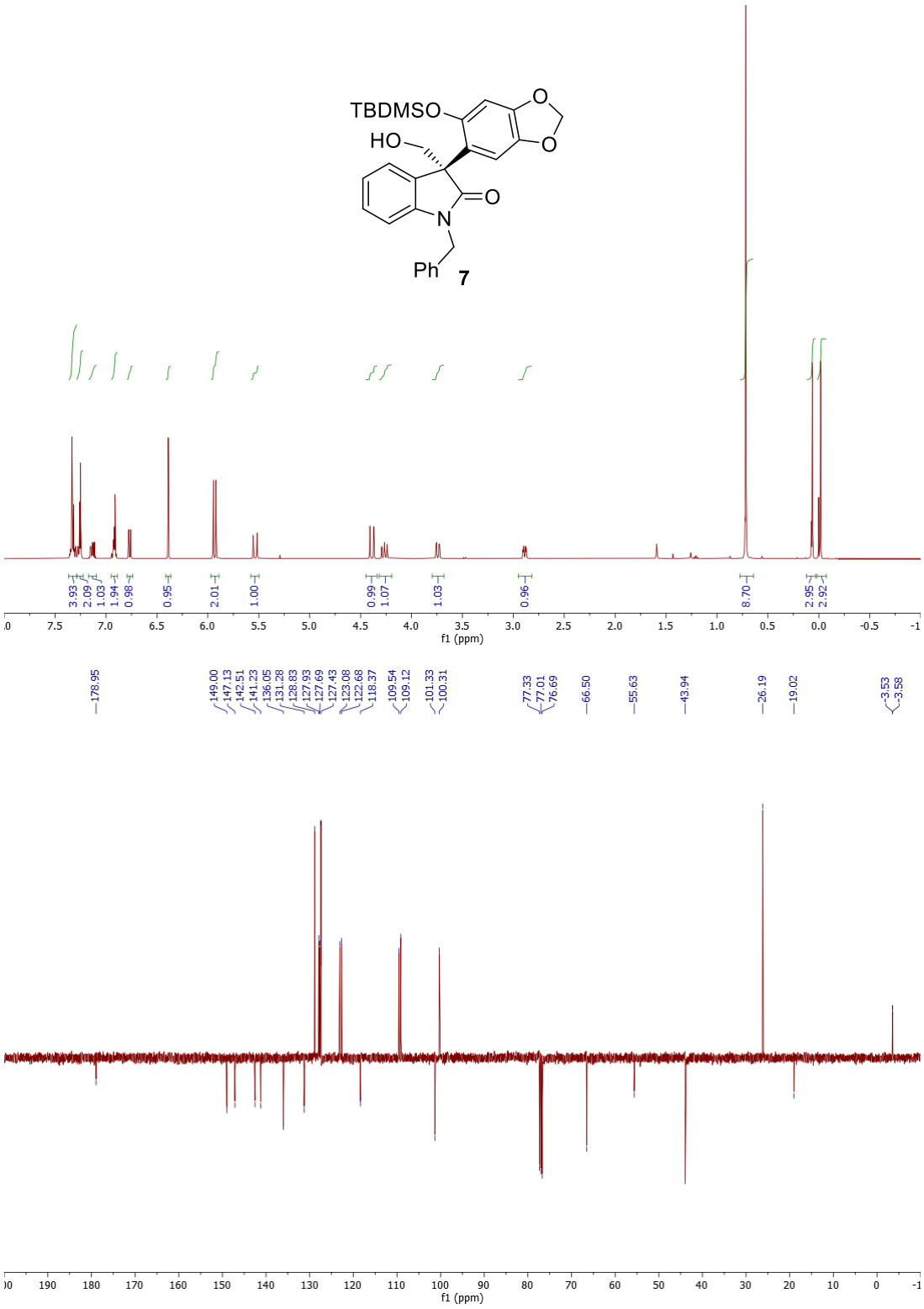


1-Benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)indolin-2-one (6)

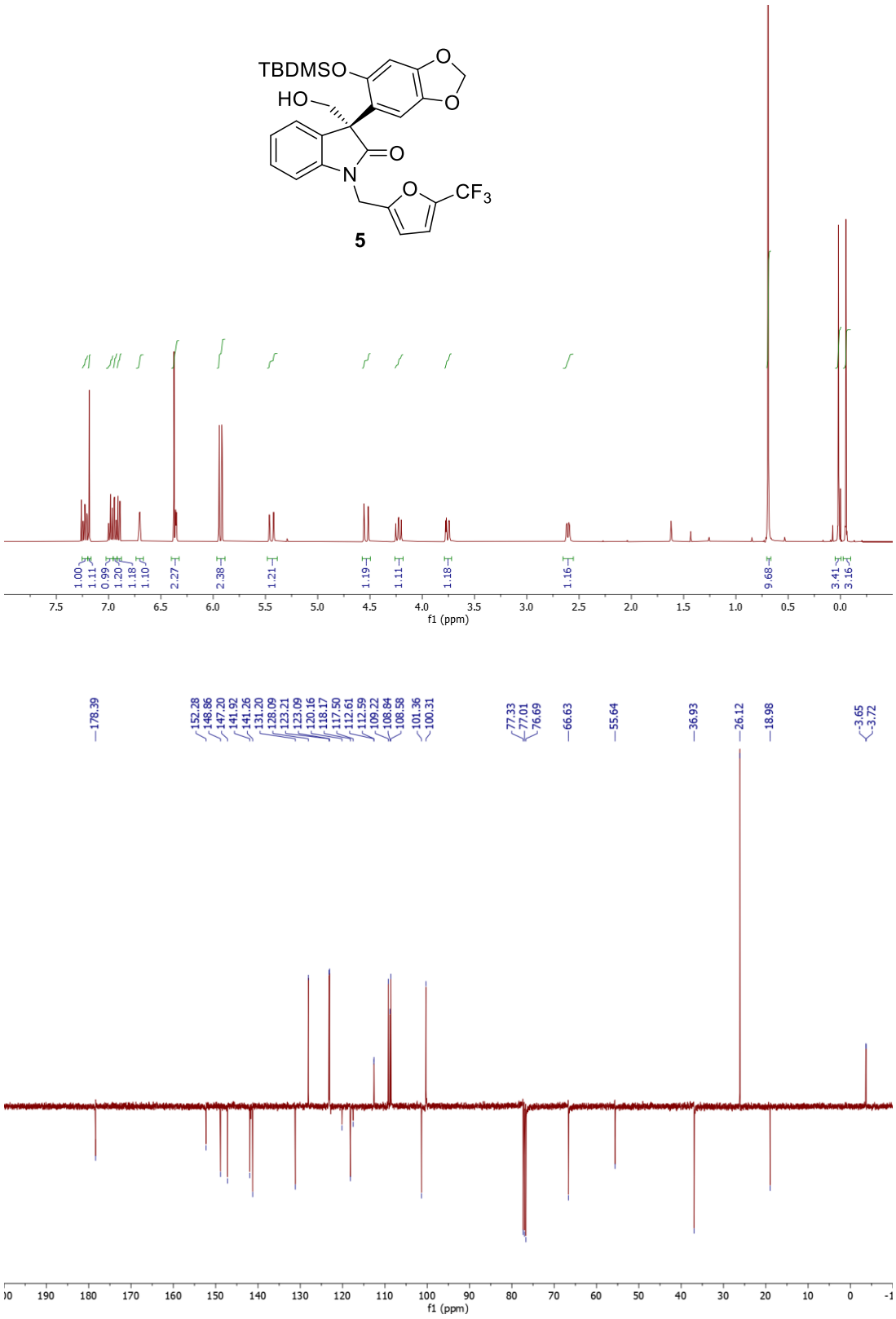


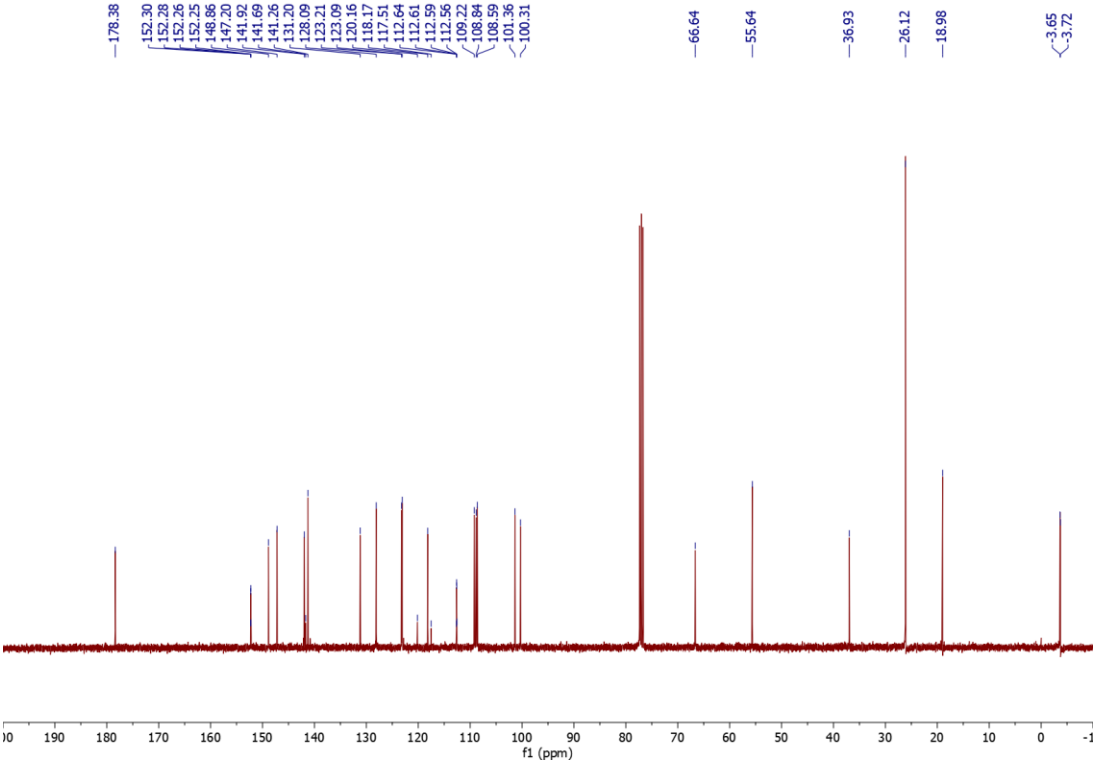
^{13}C NMR not recorded: in line with the furyl substrate **4**,[2] the occurrence of rotamers interconverting slowly on the NMR time scale, evidenced by several broad signals in the ^{1}H NMR spectrum, hampered the straightforward obtainment of a well-defined ^{13}C NMR spectrum.

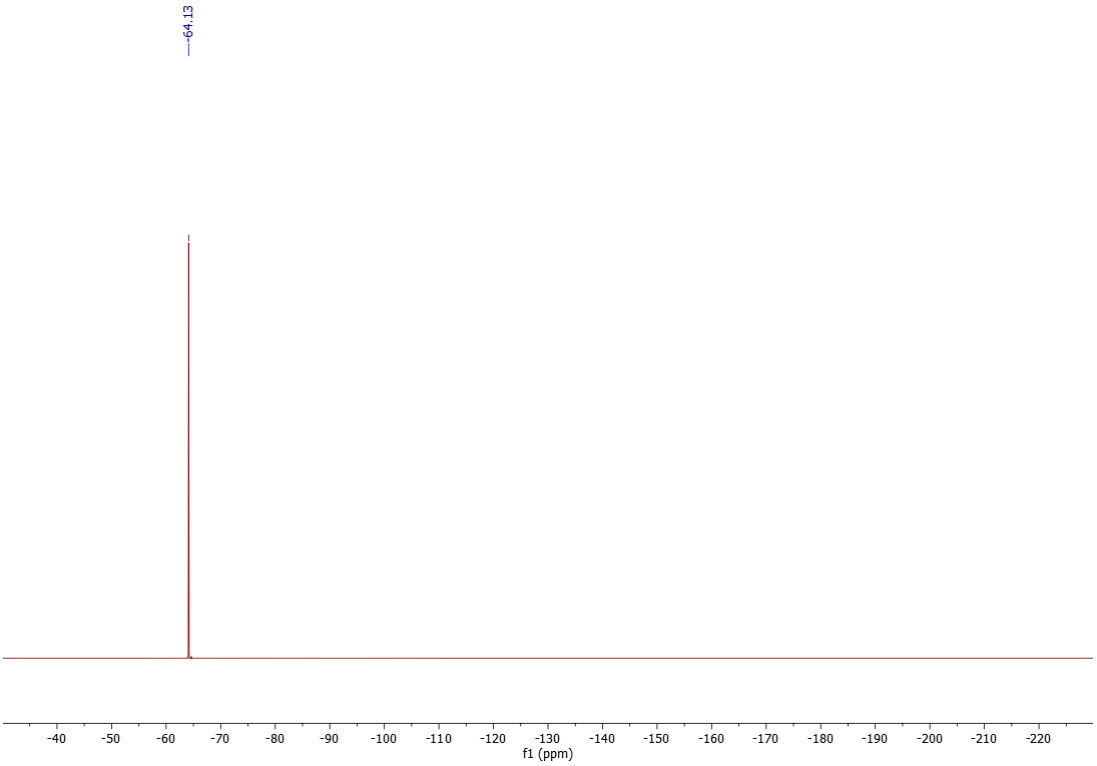
(*S*)-1-Benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one (7)



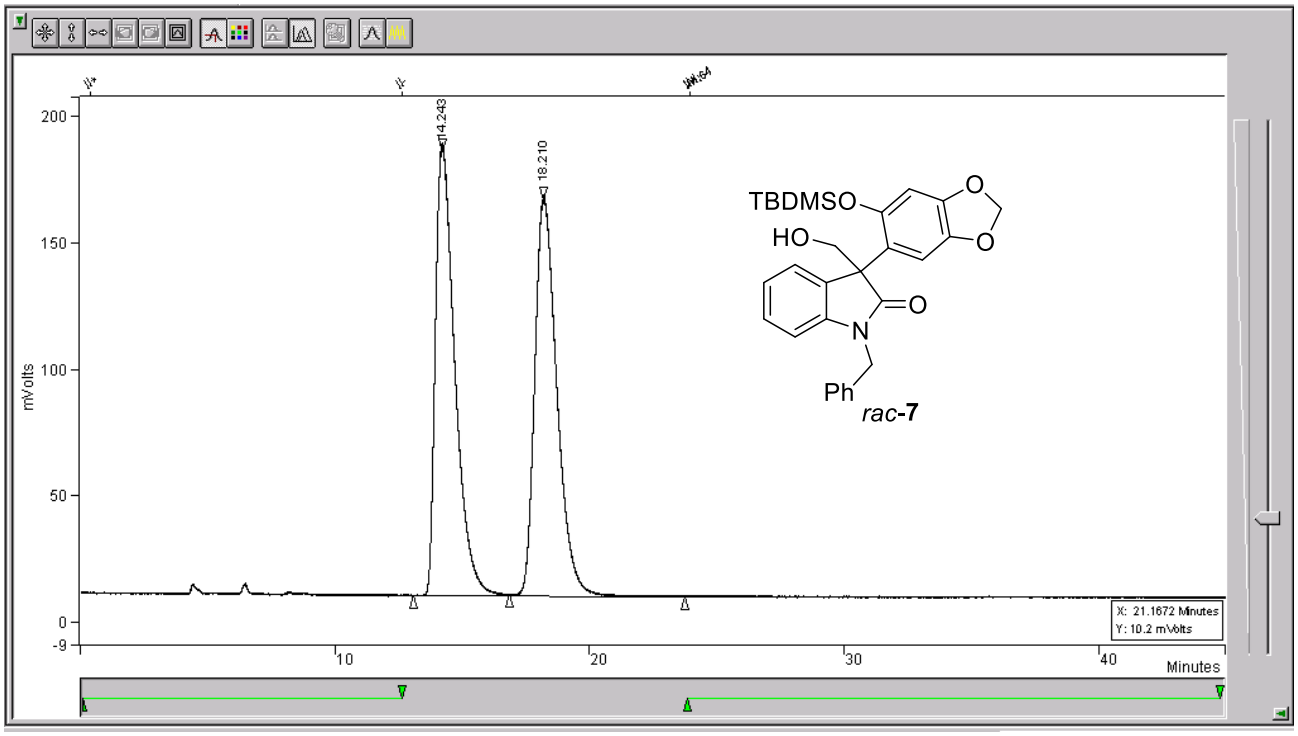
(*S*)-3-(6-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one (5)



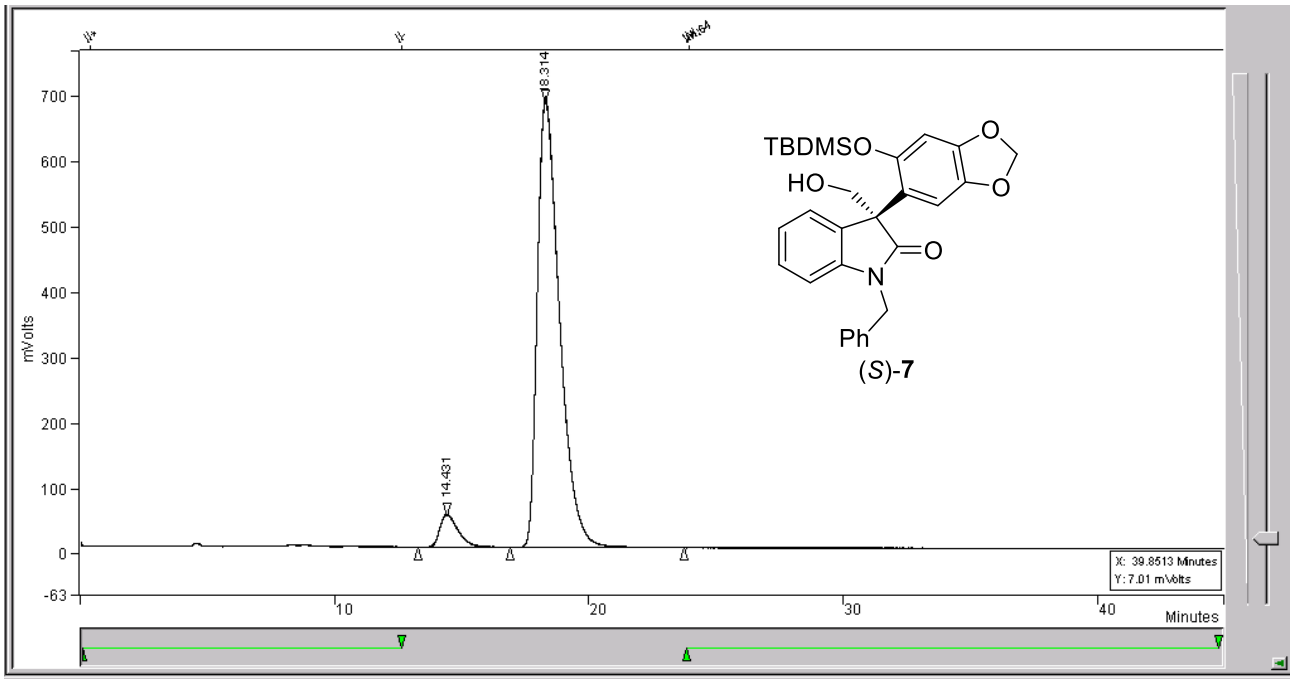

178.38
152.30
152.28
152.26
152.25
148.86
147.20
141.92
141.69
141.26
131.20
128.09
123.21
123.09
120.16
118.17
117.51
112.64
112.61
112.59
112.56
109.22
108.84
108.59
101.36
100.31
66.64
55.64
36.93
26.12
18.98
3.65
3.72
f1 (ppm)


64.13
f1 (ppm)

(*S*)-1-Benzyl-3-(6-((*tert*-butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)indolin-2-one (7)

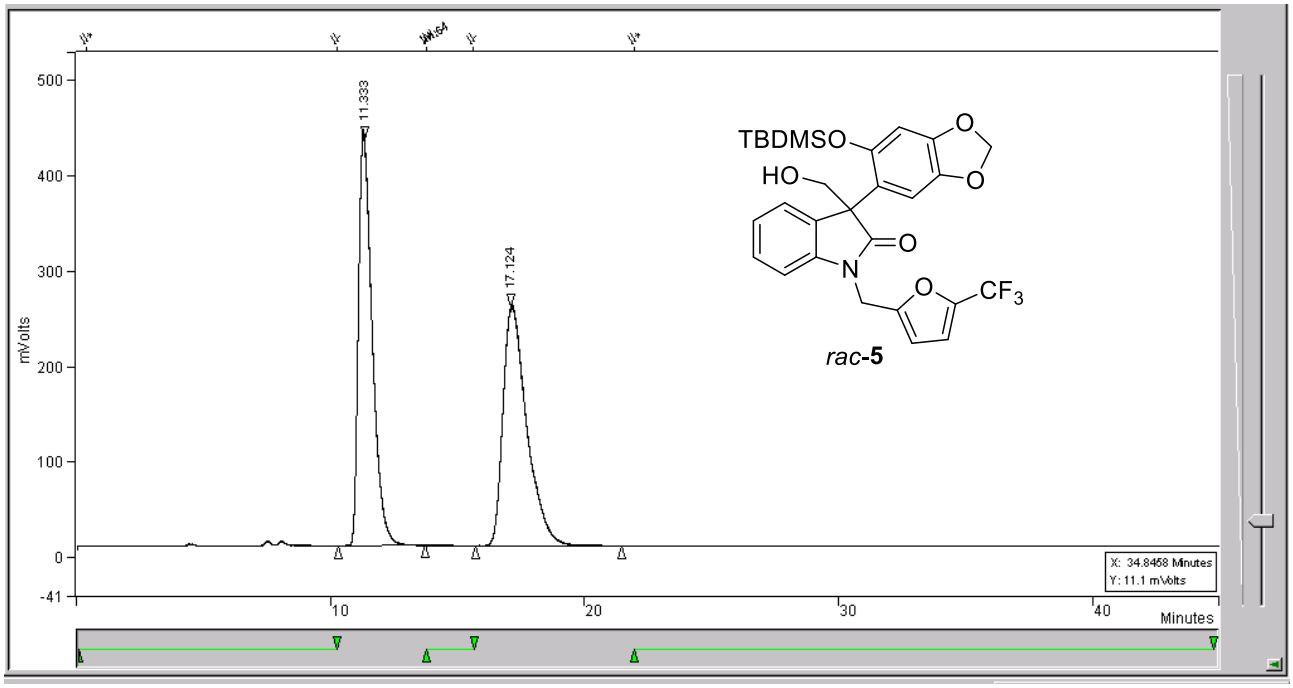


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.8704	14.243	0.000	9472618	BV	48.7	
2		50.1296	18.210	0.000	9521852	VB	55.3	
	Totals:	100.0000		0.000	18994470			

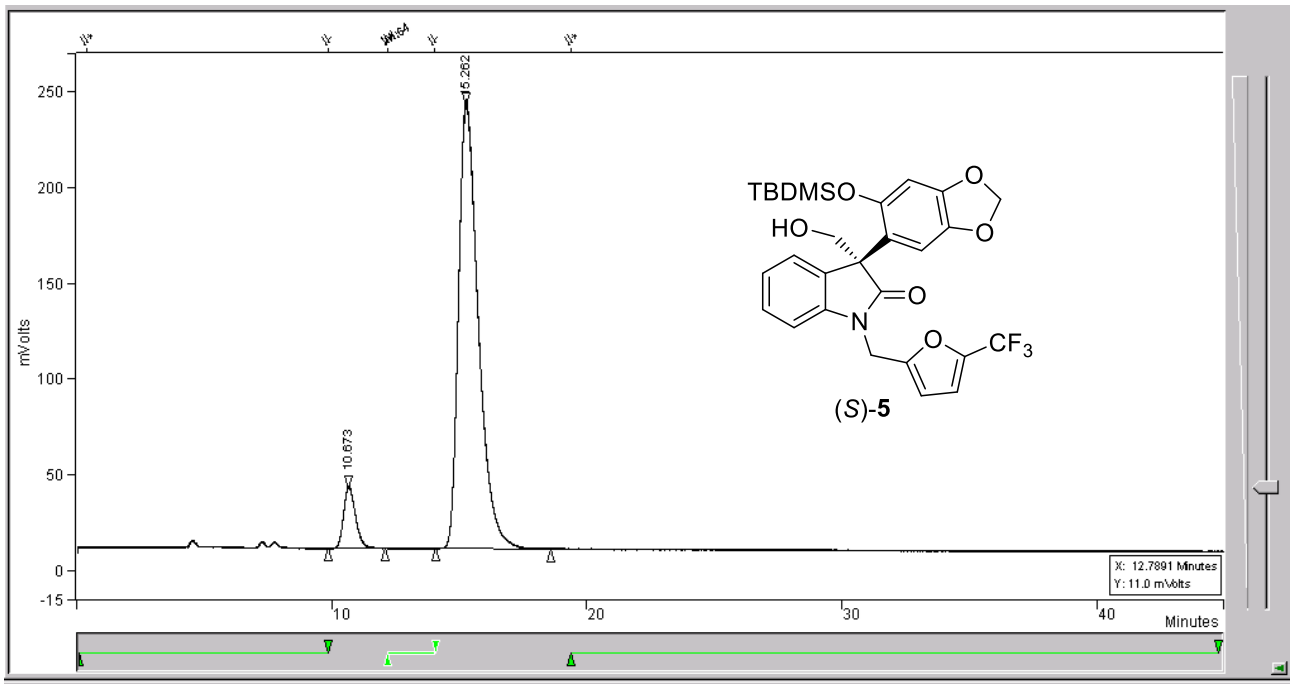


Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		5.7037	14.431	0.000	2510521	BV	46.3	
2		94.2963	18.314	0.000	41505056	VB	55.5	
	Totals:	100.0000		0.000	44015577			

(*S*)-3-(6-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*][1,3]dioxol-5-yl)-3-(hydroxymethyl)-1-((5-(trifluoromethyl)furan-2-yl)methyl)indolin-2-one (5)



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.7741	11.333	0.000	16279130	BB	34.8	
2		50.2259	17.124	0.000	16426918	BB	58.2	
	Totals:	100.0000		0.000	32706048			



Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		7.6445	10.673	0.000	1040403	BB	30.5	
2		92.3555	15.262	0.000	12569454	BB	48.8	
	Totals:	100.0000		0.000	13609857			

6. References

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[8] Procedure adapted from: C. S. Marques, P. McArdle, A. Erxleben, A. J. Burke, *Eur. J. Org. Chem.* **2020**, 3622.

[9] Procedure adapted from: A. Kumar, J. Kaur, P. Chauhan, S. S. Chimni, *Chem. Asian J.* **2014**, *9*, 1305.